PDA Training Course Extractables & Leachables

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United States Pharmacopeia:
USP Chapters Addressing Extractables/Leachables from Packaging and Manufacturing Systems

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Trainer

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- 30 + years of experience in chemical characterization (E&L) of pharmaceutical packaging, manufacturing systems and medical devices, largely spent at Baxter Healthcare.
- Nearly 170 journal articles, numerous book chapters and one book on the topics of analytical chemistry, ion chromatography, theory and practice of chemical characterization.
- If there is something that you do not like about an E&L Standard, Monograph or Recommendation, then chances I am probably to blame.

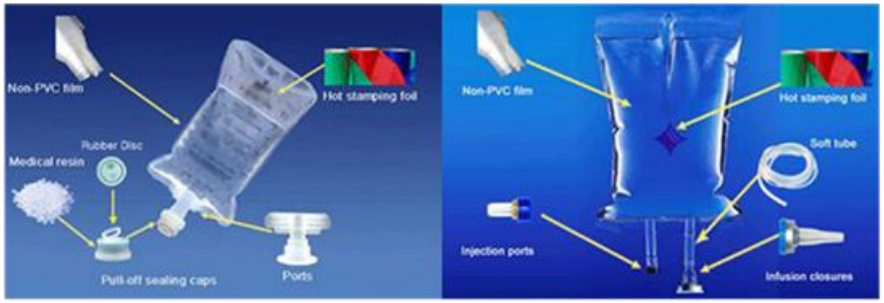
Training Outline

1. The USP Approach to Pharmaceutical Materials.
2. Chapters <381>, <1381>, <382> and <1382> for *Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems.*
3. Chapter <383> for *Cured Silicone Elastomers for Pharmaceutical Packaging and Manufacturing Components.*
4. Chapters <660> and <1660> for *Containers-Glass*.
5. Chapters <661.1> and <1661> for *Plastic Materials of Construction**.
6. Chapter <661.2> and <1661> for *Plastic Packaging Systems for Pharmaceutical Use.*
7. Chapters <1663> and <1664>, *Extractables and Leachables*.
8. Chapter <662> and <1662> for *Metallic Packaging Systems and their Materials and Components of Construction.*
9. Chapters <665> and <1665> for *Polymeric Materials, Components and Systems used in the Manufacturing ….*
10. Biocompatibility Chapters <87>, <88> <1031>.
11. System Suitability Mixtures.

1. The USP Approach to Pharmaceutical Materials

Ingredients → Extractables → Leachables

Materials → Systems → Packaged Products



The Universe of USP E&L Chapters

<1663>, Extractables

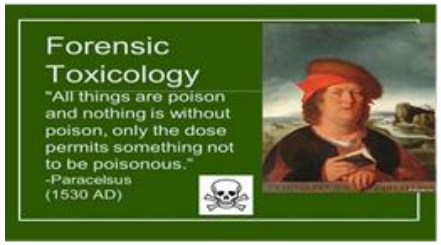
<1664>, Leachables

- 1664.1 OINDP
- 1664.X Other Dosage Forms

USP <383>

USP <381>

Biological Assessment:
USP <87>, <88>, <1031>



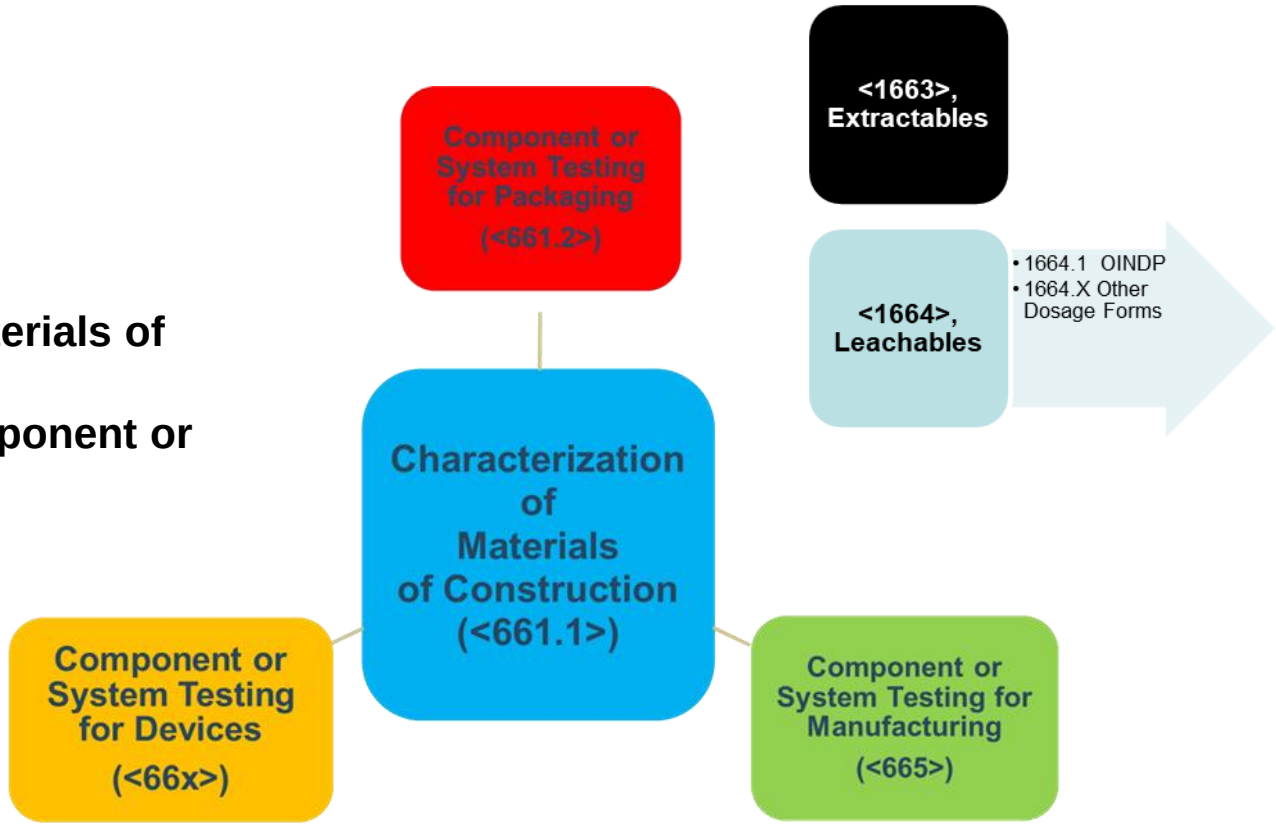
USP <661>

USP <662>

USP <660>

The USP Approach to Plastics

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



Underlying Principles

- **Risk-based approach** – amount and degree of testing reflects the level of risk.
- **Low risk is not no risk**.
- **"Aim for the Middle"** – information generated is directly applicable in many situations and appropriately applicable in extreme situations.
- **"Minimum Standard"** – the "minimum standard" established by the USP is a baseline applicable for all situations which may need to be augmented in "special cases".
- **Relevant information drives good decisions making**.
- **Materials of construction are tested** for the purpose of **selection.**
- **Components are tested for selection and/or qualification.**
- **Testing for selection and testing for qualification are different by necessity and purpose.**

2. Elastomeric Components

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

Contents of <381>

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

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

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

4. If components comply with the <381>requirements, studies should then be designed to determine safety and compatibility as recommended in <1663⟩ and ⟨1664⟩.

5. Closures must conform to the requirements of either the USP in vitro <87> or the in vivo < 88> biological reactivity tests.

6. Tests are always conducted on the components after surface modifications.

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

Physicochemical Tests in <381>

Determination of turbidity (opalescence): a nonspecific test for all the extractable species in a rubber formulation that are not soluble in an aqueous solution. A high turbidity is the indication of a high extractable potential.

Acidity/alkalinity: a nonspecific test indicative of the acidic, basic, or buffering power of the aqueous extractables from the rubber formulation. High values in the acidity/alkalinity test may need to be evaluated in conjunction with drug product's pH.

Color: a nonspecific test indicative of the presence of extractable species in a rubber formulation that have the capacity of attributing color to an aqueous solution.

Absorbance: The UV spectrum of an aqueous extract from a rubber formulation is indicative of the unsaturated or aromatic character of the chemical species extracted such as antioxidants, preservatives, and curing or dying agents.

Reducing substances: a nonspecific test for extracted species from a rubber formulation with potential reducing power (polymer, curing system, preservatives, antioxidants, etc.).

Ammonium and Volatile Sulfides: specific tests for curing-related extractables. Ammonium ions can be generated during the curing process. Sulfur and sulfur precursors are often used as components of curing systems.

3. <383> Cured Silicone Elastomers for Pharmaceutical Packaging and Manufacturing Components

Scope: The scope of the chapter includes elastomeric closures for pharmaceutical packaging and manufacturing components such as tubing, gaskets, and O-rings.

Contents:

- Biological reactivity, Class VI except for manufacturing components
- Identity
- Physicochemical Tests;
  - Acidity or Alkalinity
  - Reducing Substances
  - Substances soluble in hexane
  - Phenylated Compounds
  - Mineral Oils
  - Volatile Matter
  - Residual Peroxides
  - Platinum

Status of Elastomers Chapters

1. <381>: Official as of 1-Dec-2020
2. <382>: Published in USP43/NF38, 2nd Supplement. To be official 1-Dec-2025
3. <1381> and <1382>: Official as of 1-Dec-2020
4. <383>: Commenting period closed, in final revision and internal USP balloting

4. Glass Packaging

USP <660>, CONTAINERS—GLASS

Per PF 49(2): 01-Mar-2023 to 31-May-2023

The General Chapters—Packaging and Distribution Expert Committee is proposing to revise this chapter to address a recent FDA request (FDA letter) to update the Type I definition from one that is composition-based to performance-based. The request highlighted the FDA's concern about global issues regarding glass production and resulting drug shortages. The FDA is supportive of the use of new glass compositions that are not currently outlined in the USP if they demonstrate equivalency or superior performance to Type I borosilicate glass. The current USP definition is impeding the adoption of new glass compositions and delaying drug approvals.

FDA Letter, 11-22-002-AB, November 01, 2022

This letter reiterates FDA's recommendations on pharmaceutical glass type classification. In 2017, FDA provided USP a recommendation to revise the definition of Type I glass from composition-based characteristics to performance-based characteristics to allow for innovation in the manufacturing of glass intended for parenteral packaging. We shared published information to support this recommendation and noted that a performance-based classification instead of a chemical composition-based classification would be beneficial for public health.1 Over the last two years, there have been reported global shortages of glass vials, potentially creating a bottleneck for the delivery of the COVID-19 vaccine and threatening the availability of some existing parenteral products.

Current status: A new composition-based classification is being developed based on non-destructive testing (major elements) of the glass article.

Glass Packaging

USP <660>, CONTAINERS—GLASS

Current Status

- A new composition-based classification is being developed based on non-destructive testing (major elements) of the glass article.
- Extractables elements testing

Note that <1660> contains a useful review of glass delamination.

USP Plastic Packaging Chapters

USP <661>, Current

PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION

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

Official as of 1-Nov-2020

Plastic Packaging and Materials

USP <661> (and related), Future

<661> Plastic Packaging Systems and their Materials of Construction

<661.1>
Plastic Materials of Construction

(Materials Characterization)

- Identification
- Biological Activity
- Physicochemical Tests
- Extractable Metals (as appropriate)
- Plastic Additives

<661.2>
Plastic Packaging Systems for Pharmaceutical Use

(Systems Characterization)

- Biological Activity
- Physicochemical Tests
- Safety Assessment (Extractables/Leachables)

Future

Official as of 1-Dec-2025 with early adoption option

6

Plastics Chapters in 2025

- **Monograph <661>** is an introductory Monograph that establishes the Scope of the Packaging Monographs, and their inter-relationships. The <661> Monograph also establishes the relationship between the packaging Monographs and other USP chapters such as <1663> and <1664>.
- **Monograph <661.1>** provides test methods and specifications for **Plastic Materials of Construction**.
- **Monograph <661.2>** provides test methods and specifications for **Plastic Packaging Systems for Pharmaceutical Use**.
- **Monograph <1661>** provides insights into the science and technology of <661.1> and <661.2> and serves as a **"user's manual"** for both <661.1> and <661.2>.
- **Monographs <1663>** and **<1664>** provide insights and **recommended practices** on how to design and perform **E&L** studies.

All these Chapters are open for review and likely revision.

Essential Principles

- Informed Selection of Materials of Construction leads to the development of components that are suitable for their intended use.
- Informed Selection of Components leads to the development of systems that are suitable for their intended use.
- Proper Assessment of Systems, simplified via the use of intentionally selected materials and components, establishes that the systems are suited for their intended use.

Characterization, Hazard Identification; USP <661.1>

Qualification, Risk Assessment; USP 661.2

5. Plastic Materials – USP <661.1>

Objective: Material Characterization (Hazard Identification)

Purpose: Enable material selection

Value: Material characterization data drives selection

Contents

- Identity
- Biocompatibility[1]
- Physicochemical testing (water extracts)
- Extractable Metals (as appropriate)
- Polymer Additives[1]

[1]The specific tests and specifications for these parameters vary in terms of the dosage form and the material.

Application of Tests, <661.1>

Table 1. Application of Tests		
Test Parameter	**Oral and Topical Dosage Forms[a]**	**All Other Dosage Forms**
Identification	X	X
Physicochemical		
UV Absorbance	X	X
Acidity/Alkalinity	X	X
Total Organic Carbon (TOC)	X	X
Extractable Elements	---[b]	---[b]
Plastic Additives	---[c]	X
Biological Reactivity		
In vitro per *Biological Reactivity Tests, In Vitro ⟨87⟩*[d]	---	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 Plastic additives tests.
[b] As deemed necessary and appropriate by end-user. See USP ⟨1661⟩ for additional information.
[c] Provide 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) provides baseline information and will often not be sufficient to assess the final suitability for use expectations of regulatory authorities.

Two Important Points about <661.1>

EXTRACTABLE ELEMENTS: 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.

BIOLOGICAL REACTIVITY TESTING in support of plastic packaging materials used for final pharmaceutical product packaging/delivery systems (drugs and drug/device combination products) 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.

Outcomes of <661.1> Testing

- If a material has been tested per <661.1>, conforms to the reporting requirements in <661.1> and meets the specifications contained in <661.1>, then the material is well-characterized.
- Armed with the test results, a potential user of the material can make and justify the decision whether to use the material in a specific application.
- <661.1> provides information from which suitability for use can be inferred.
- **A material is not qualified by <661.1> testing, the material is characterized by the user's interpretation of the <661.1> data.**

Selection: The action of carefully choosing someone or something as being the best or most suitable.

Qualification: The action of proving and documenting that a system is suited for its intended use.

Materials Covered by <661.1>

- **Polyvinyl Chloride, plasticized**
- **Polyethylene**
- **Cyclic Olefins**
- **Polypropylene**
- **Polyethylene Terephthalate**
- **Polyethylene Terephthalate G**
- Polybutylene terephthalate
- **Polyamide (Nylon)**
- Polyurethane
- **Polyethylene vinyl acetate (EVA)**
- Acrylonitrile butadiene styrene
- Polytetrafluoroethylene
- **Polycarbonate**
- Polystyrene
- Poly(methyl methacrylate)
- Polysulfone
- Poly(vinylidene chloride)
- **Polyvinyl chloride, unplasticized**

Bold = published in current Chapter.

Double Jeopardy?

Individual plastic materials of construction are deemed to be well characterized and appropriate for use if:

1. They meet the requirements in this chapter, or
2. **They are used in a packaging system that meets the requirements in *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩.**

6. Plastic Packaging, USP <661.2>

Objective: System Qualification (Risk Assessment)

Purpose: Secure regulatory approval of the packaging system or packaged product.

Value: Regulatory approval requires system qualification

Contents

- Characterized materials (per <661.1)>
- Biocompatibility
- Physicochemical testing (water extracts)
- Extractable (and/or leachables) profiling followed by toxicological assessment.

<661.2> Testing

Table 1. Application of Tests		
Test Parameter	**Oral and Topical Dosage Forms[a]**	**All Other Dosage Forms**
Physicochemical		
UV Absorbance	X	X
Acidity/Alkalinity	X[b]	X[b]
Total Organic Carbon (TOC)	X	X
Appearance of Solution	X	X
Total terephthaloyl moieties	PET and PETG only[c]	PET and PETG only[c]
Ethylene glycol	PET and PETG only[c]	PET and PETG only[c]
Biological Reactivity		
Biological Reactivity Tests, In Vitro (87)[d]	---	X
Chemical Suitability for Use		
Assessment	Risk-based testing	Risk-based testing
Functionality		
Spectral Transmission	If light protection is necessary	If light protection is necessary

[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] Polyethylene terephthalate (PET) and polyethylene terephthalate G (PETG).

[d] Biological reactivity testing in support of plastic packaging components and systems used for final pharmaceutical product packaging/delivery systems provides baseline information and will often not be sufficient to assess the final suitability for use expectations of regulatory authorities.

Extractables and Leachables in <661.2>

- An appropriate and rigorous suitability for use assessment may include extractables testing of the packaging component/system and leachables testing of the packaged drug product.
- The design of the extractables and leachables study should be based on sound and justifiable scientific principles, and the studies themselves should be consistent with
  - the nature of both the packaging system and packaged drug product,
  - the clinical use of the packaged drug product, and
  - the perceived safety risk associated with the packaging system and dosage form.
- The nature and degree of testing should be dosage form-dependent and consistent with a risk-based approach.
- General essential principles and demonstrated best-practices recommendations for extractable and leachable studies can be found in:
  - Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems ⟨1663⟩,
  - Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems ⟨1664⟩.

Recent Modifications to <661.2>

- A new extraction process has been added (50 ± 2°C for 72 hr) for cases where “heating at 70° leads to the deterioration of the container”.
- The TOC acceptance criteria have been changed to conform with requirements for *Purified Water*:
  - For containers ≤ 5 mL, TOC NMT 32 mg/L,
  - For containers between 5 and 100 mL, TOC NMT 24 mg/L,
  - For containers > 100 mL, TOC NMT 8 mg/L

Outcomes: <661.1> & <661.2> Testing

The packaging component or system is chemically suited for its intended use if:

- The packaging component or system is constructed from well-characterized materials as defined in ⟨661.1⟩.
- The packaging component’s or system's general physicochemical properties have been established.
- The packaging component’s or system's biocompatibility (biological reactivity) has been appropriately established.
- The packaging component or system has been established to be suitable by means of the appropriate chemical suitability for use assessment.

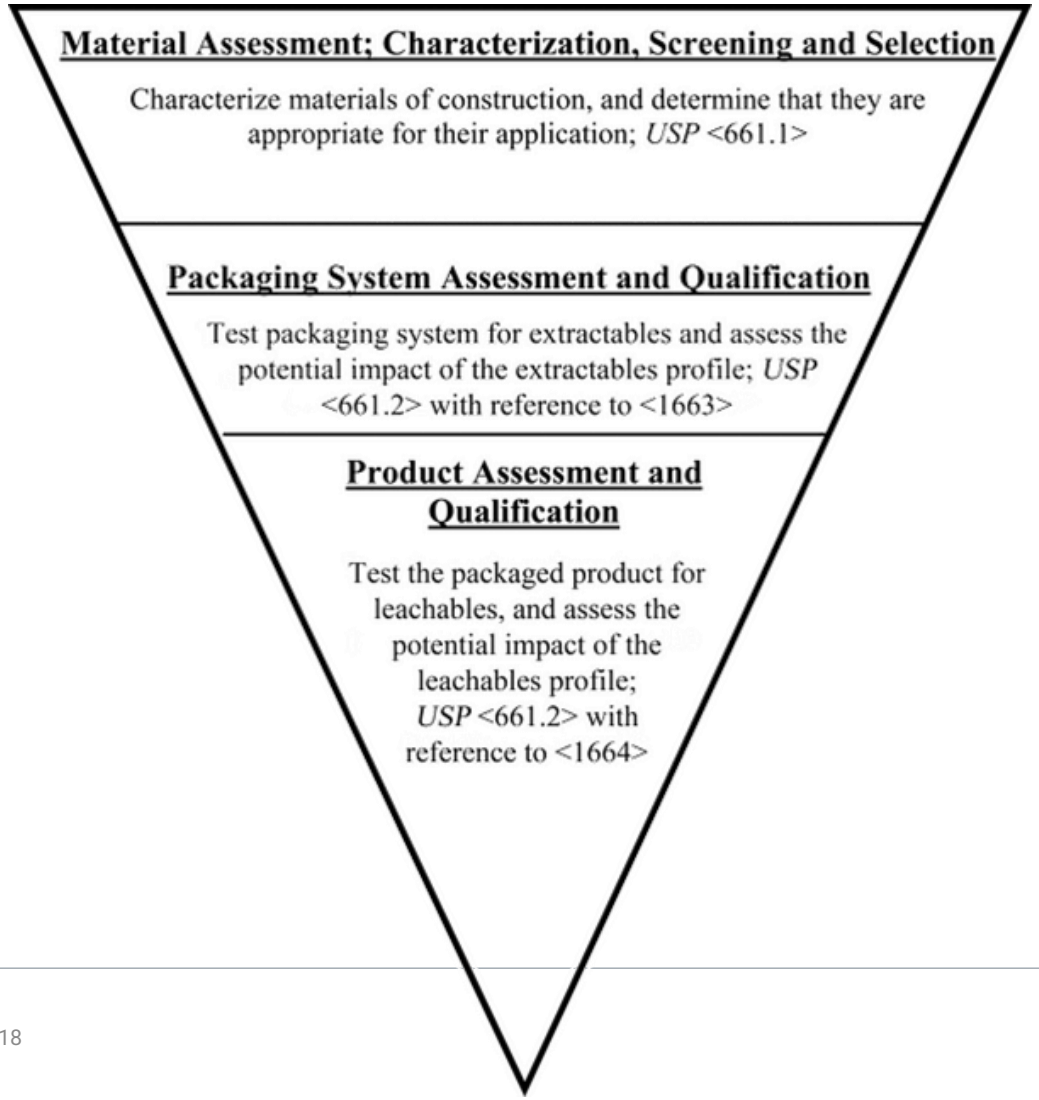
The “User’s Manual”, <1661>

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

1. INTRODUCTION
2. SCOPE
3. GENERAL PRINCIPLES – THE OVERALL ASSESSMENT PROCESS
4. MATERIALS ASSESSMENT: CHARACTERIZATION, SCREENING, AND SELECTION, USP ⟨661.1⟩
5. PACKAGING SYSTEM ASSESSMENT AND QUALIFICATION, USP ⟨661.2⟩
   - 5.1 Extractables and Leachables
6. APPLICABILITY AND APPLICATION OF ⟨661.1⟩
   - 6.1 Applicability
   - 6.2 Application
   - 6.3 Description of Plastics Contained in ⟨661.1⟩
7. APPLICABILITY AND APPLICATION OF ⟨661.2⟩
   - 7.1 Applicability
   - 7.2 Application

Official as of 1-Nov-2020

Three Stage Qualification per <1661>



7. Extractables – USP <1663>

Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems

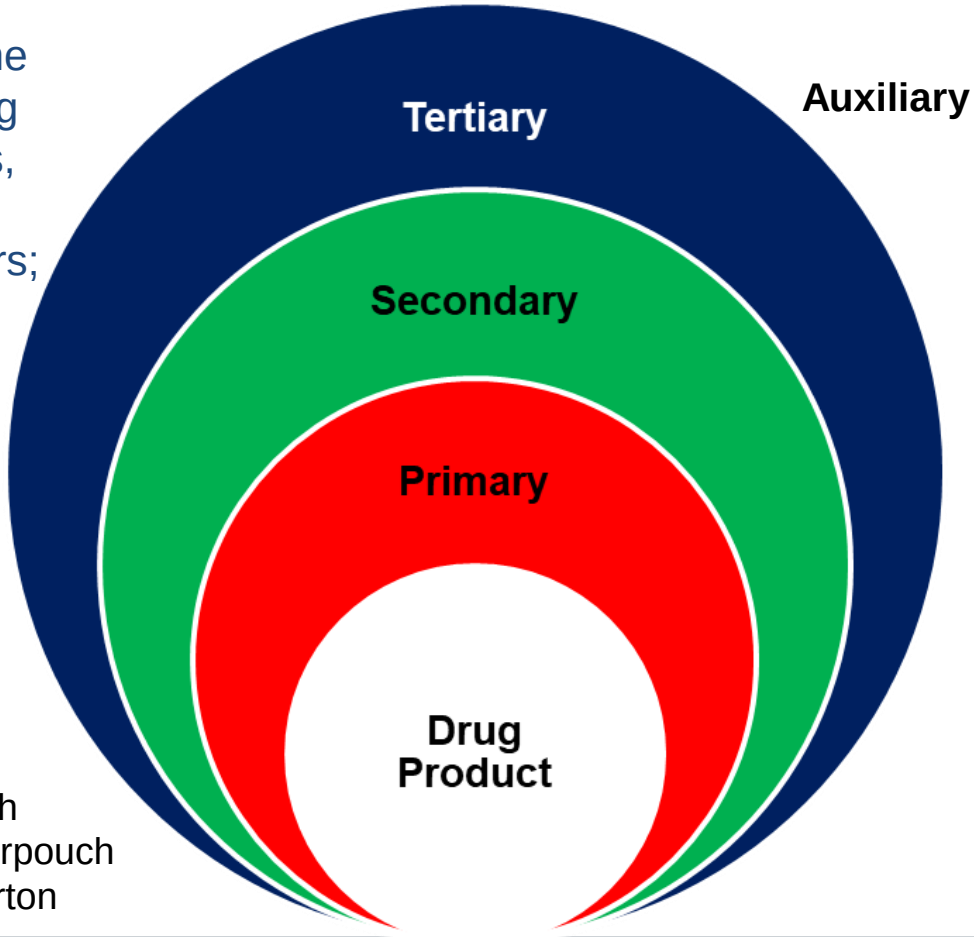
Official as of 1-Dec-2020

Extractables: organic and inorganic chemical entities that are released from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction and **into an extraction solvent under laboratory conditions**. Depending on the specific purpose of the extraction study these laboratory conditions (e.g., solvent, temperature, stoichiometry, etc.) may accelerate or exaggerate the normal conditions of storage and use for a packaged dosage form. Extractables themselves, or substances derived from extractables, have the potential to leach into a drug product under normal conditions of storage and use and thus become leachables.

Leachables: foreign organic and inorganic **chemical entities** that are **present in a packaged drug product because they have leached** into the packaged drug product from a packaging/delivery system, packaging component, or packaging material of construction **under normal conditions of storage and use or during accelerated drug product stability studies**.

A Hierarchy of Packaging

Packaging Component: any single part of the package or container–closure system including the container (e.g., ampules, prefilled syringes, vials, bottles); closures (e.g., screw caps, stoppers); ferrules and overseals; closure liners; inner seals; administration ports; overwraps; administration accessories; labels; cardboard boxes; and shrink wrap.



Examples:

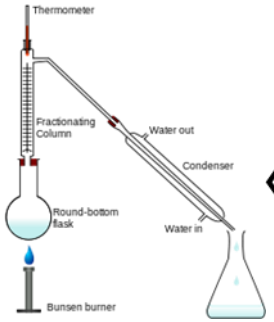
Primary = Bag
Secondary = Overpouch
Tertiary = Label on Overpouch
Auxiliary = Shipping carton

Extraction Studies - Purposes

The extraction study should be designed so that it fulfills the study's purpose!

- Compositionally characterize packaging systems, packaging components, and/or materials of construction
- Assisting in the selection of components and materials of construction
- Establish the affects of various manufacturing processes (e.g., sterilization) on composition
- **Establish the worst-case potential leachables profile**
- Establish the actual leachables profile when it is not scientifically possible to establish actual leachables
- Facilitate qualitative and quantitative leachables–extractables correlations
- Facilitate the development of extractables specifications and acceptance criteria
- Facilitate investigations into the origin(s) of identified leachables

Two Elements of an Extraction Study



Generating the Extract

Testing the Extract

Generating the Extract

The means by which an extraction process is accomplished are reflected in the juxtaposition of several experimental parameters including:

- The chemical nature of the extracting media
- The time duration of the extraction process
- The temperature and pressure at which the extraction is performed
- The stoichiometry of the extraction process (extracted surface area per unit volume of extracting solution)
- The mechanism or process by which the extraction is accomplished

Extraction processes should allow completion in a reasonable time frame but should not be so aggressive that they alter the qualitative and/or quantitative nature of the resulting extractables profile.

Extraction Techniques

- ***Maceration (solvent soaking)***—the test article is allowed to soak for a period of tie in an organic or aqueous extracting solvent at temperatures below the solvent's boiling point. Analysts can also fill packaging system units with extracting solvent and store them at relevant temperatures.
- ***Reflux***—the test article is immersed in boiling solvent for a period of time.
- ***Soxhlet***—the test article is placed in the “thimble” of a Soxhlet extraction apparatus that is slowly filled with redistilled solvent from a boiling flask/condenser system; and periodically, the extracting solvent (containing extractables) is siphoned back into the boiling flask and the process begins again (for as many times as required to attain equilibrium).
- ***Sealed vessel***—the test article and extracting solvent are sealed inside a container and heated for a period of time.
- ***Instrument-based solvent extraction***—the test article is placed inside a sealed apparatus and extracted in an automated cycle; examples include pressurized fluid extraction, microwave-assisted extraction, and supercritical fluid extraction.
- ***Sonication***—the test article and extracting solvent are placed into an extraction vessel and immersed in solvent inside an ultrasonic bath.

[1]R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 368.

Testing the Extract

1. **Scouting:** analytical techniques that provide information regarding bulk chemical properties of organic and/or inorganic chemical entities present in an extract which can be used to guide extractables discovery, identification, and quantitation For example; TOC, UV, delta pH, NVR.
2. **Discovery:** testing an extract to produce analytical results (signals) that are attributable to individual extractables
3. **Identification:** the process by which the molecular structure of an unknown analyte is elucidated from compound-specific analytical data.
   - Unknown
   - Partial
   - Tentative
   - Confident
   - Confirmed
4. **Quantitation:** the process of establishing (estimating) the concentration of an extractable in an extract.
   - Qualitative (estimate)
   - Semi-quantitative
   - Quantitative

General Recommendations per <1663>

- **Generation of extracts should be accomplished with:**
  - Multiple solvents or extracting media with varying extracting power based on the known extracting power of the drug product vehicle;
  - Multiple and complementary extraction techniques, including those with the capability for volatiles analysis;
  - Extraction conditions that allow equilibrium to be achieved.
- **Characterization of extracts should use:**
  - Multiple and complementary analytical techniques;
  - Careful sample preparation, keeping the analytical technique(s) in mind;
  - A systematic process for identification and quantitation of extractables.

Leachables – USP <1664>

ASSESSMENT OF DRUG PRODUCT LEACHABLES ASSOCIATED WITH PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS

Official as of 1-Dec-2020

This chapter covers various important concepts, including:

1) the requirement for leachables studies;
2) fundamental concepts for leachables studies;
3) thresholds for leachables and their application;
4) The design and implementation of leachables studies;
5) leachables method development and validation;
6) Extractables/leachables correlations
7) leachables specifications, including acceptance criteria.

Leachables Studies

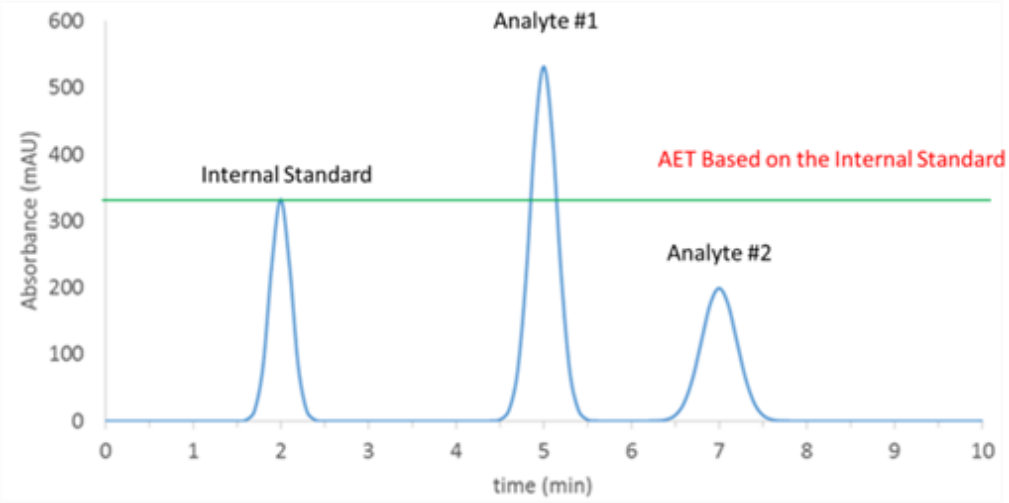
- A leachables study is a laboratory investigation (to establish) qualitative and quantitative leachables profile(s) over the proposed shelf-life.
- The purpose of a leachables study is to systematically and rationally identify and quantify drug product leachables to the extent practicable, and within certain defined analytical threshold parameters.
- The results of leachables studies are used to understand the impact of leachables on patient safety and drug product quality and stability.

Safety Thresholds

Safety thresholds are important in leachables assessment because reporting and risk assessing every individual leachable at the limits of current analytical technology is neither necessary, from a toxicological perspective, nor feasible.

Safety thresholds allow for a science- and risk-based determination of acceptable levels of leachables.

The analytical evaluation threshold (AET) establishes which leachables should be reported for safety evaluation and qualification.



R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 370.

Validation of Quantitative Methods

The extent of validation required depends on the goals of the leachables study in which the analytical method is being used.

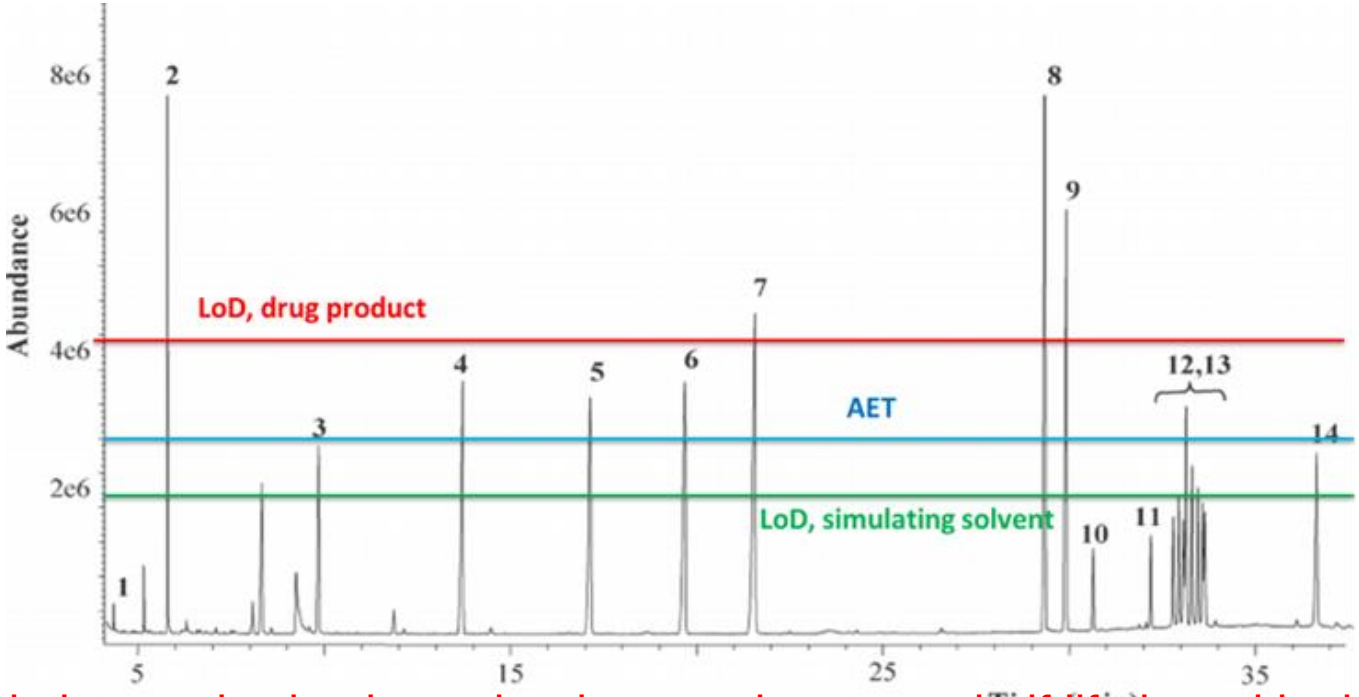
Validation parameters may include:

- accuracy,
- precision (repeatability, intermediate precision),
- specificity,
- limit-of-detection, limit-of-quantitation,
- linearity and range, and
- robustness.

System suitability tests and criteria should also be developed for each leachables method.

The Simulation Study

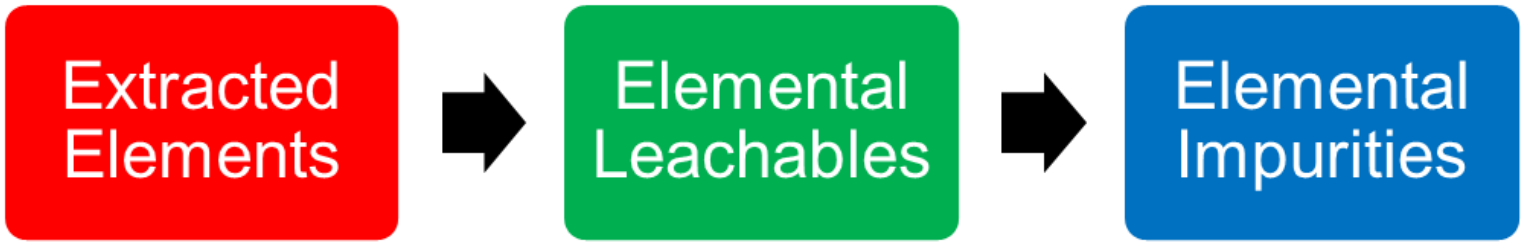
It is possible that in cases of very low thresholds (e.g., AETs), quantitation of drug product leachables might still not be analytically feasible, even with high sensitivity target compound analytical methods.



A simulation study simulates the drug product over shelf life but with simulating extraction solvent(s) that are easier to test than the drug product itself.

Elemental Leachables

The results of extractables testing of plastic packaging systems should be used to establish those elemental impurities that should be monitored as targeted elemental leachables in the drug product.



8. <662> Metallic Packaging Systems

USP <662> METALLIC PACKAGING SYSTEMS AND THEIR MATERIALS AND COMPONENTS OF CONSTRUCTION

In Scope:

- Metallic primary packaging components including:
  - canisters for inhaled drug products
  - cans for topical aerosols
  - soft aluminum tubes for topical dosage forms
  - blister packs for solid oral dosage forms
  - aluminum foil backing for some transdermal devices
- Metal components used for secondary packaging
  - pouches
  - overwraps

Out of Scope:

- Metal components that are a part of drug delivery systems
  - a spring for auto-injectors,
  - metering valves for metered dose inhalers or
  - staked needles for prefilled syringes
- Metal cylinders for medical gasses
- Metallic manufacturing components

<662> Metallic Packaging Systems

Requirement

A metal material of construction is **well characterized for its intended use** if the construction materials or components have been **subjected to functional and chemical analysis** and the **tests results meet** relevant and defined **acceptance criteria**.

<662> Metallic Packaging Systems

Functional Analysis

Table 1. Functional Tests for Coated Aluminum Inhalation Canisters, Aerosol Cans, Soft Tubes and Foil, and Uncoated Aluminum and Stainless Steel Inhalation Canisters

Test Parameter	Coated Aluminum Inhalation Canisters, Aerosol Cans, Soft Tubes and Foil	Uncoated Aluminum and Stainless Steel Inhalation Canisters
a. Pressure Test	X[a]	X[a]
a. Coating Adhesion	X	
a. Coating Continuity/Porosity	X	
a. Coating Surface Wettability	X	
a. Coating Thickness	X	
a. Particulate Matter	X	X
a. Pinholes	X[b]	

[a]Aluminum and Stainless Steel Inhalation Canisters and Aluminum Aerosol Cans
[b]Aluminum Foil

<662> Metallic Packaging Systems

Chemical Analysis: Table 3. Selection of Extraction Solvents for Metallic Packaging Materials and Components

Packaging Systems	Physical State of the Dosage Form	Dosage Form	Extraction Solvents	
			Organic Extractables[1]	Extracted Elements[2]
Uncoated Stainless Steel and Aluminum	Liquid - Aqueous	• Inhalation	Not required	C1. pH 3
Coated Aluminum	Liquid - Aqueous	• Inhalation	C1. pH 3 C2. pH 10	
	Liquid – Organic Solvent	• Inhalation	C3. Ethyl Alcohol[3] **OR** C4. n-Hexane[3]	
	Semi-solid	• Topical Creams and Ointments • Transdermal • Suppositories	C3. Ethyl Alcohol[3] **OR** C4. n-Hexane[3]	
	Solid	• Inhalation Powders • Topical Powders	*Thermal Extraction.* See 3d.	
		• Oral Solids and Powders	FCR[4]	FCR[4]

<662> Metallic Packaging Systems

Chemical Analysis: Table 5. Extracted Elements to be Targeted from Primary Metallic Packaging Containers and Foil and Metallic Secondary Packaging Foil According to ICH Q3D(R2) Classification.

Pharmaceutical Packaging	ICH Q3D(R2) Classification			
	Class 1	Class 2A	Class 3	Other Elements
Stainless Steel				
Inhalation Canisters	As, Cd, Hg, Pb	Co, Ni, V	Cr, Cu, Mo	Fe
Aluminum				
Inhalation Canisters	As, Cd, Hg, Pb	Co, Ni, V	Cr, Cu	Al, Fe, Mn, Mg, Zn
Aerosols Cans				
Soft Tubes				
Primary Packaging Foil				
Secondary Packaging Foil				

<662> Metallic Packaging Systems

Current Status

- Both <662> and <1662> are currently under development at USP.
- Both Chapters must be approved for publication in the *Pharmacopeial Forum (PF)* . Not likely to occur until early-mid 2024.
- Publication in *PF* starts a 3-month public comment period.
- Comments received are reviewed and changes to the chapters are made. End of 2024
- Assuming few comments and largely editorial revisions, inclusion in the USP at end of 2025.
- If there are many comments requiring major revisions, then the revised chapter goes back into the *PF* for another comment cycle, likely adding another year.
- <662> is likely to have a delayed implementation.

9. Items Used in Pharma Manufacturing

USP <665> PLASTIC COMPONENTS AND SYSTEMS USED TO MANUFACTURE PHARMACEUTICAL DRUG PRODUCTS AND BIOPHARMACEUTICAL DRUG SUBSTANCES AND PRODUCTS

USP <1665> Characterization of Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products

Current Status

- USP<1665> is official as of 1-May-2022.
- USP <665> was published in USP/NF 2022 but is not official until 01-May-2026.

- Both chapters are likely to be modified somewhat as a result of ICH Q3E.

<665> - Scope

In Scope:

- Biological Drug Substances and Biological and Non-biological Drug Products
- (“Traditional”) Pharmaceuticals, “Small Molecule” Drug Products, Biologics (pharmaceuticals produced by a biological process such as recombinant proteins expressed in cell culture, antibody-drug conjugates (ADCs) and products used in cell and gene therapy)
- Single-Use Systems and Multi-Use Systems

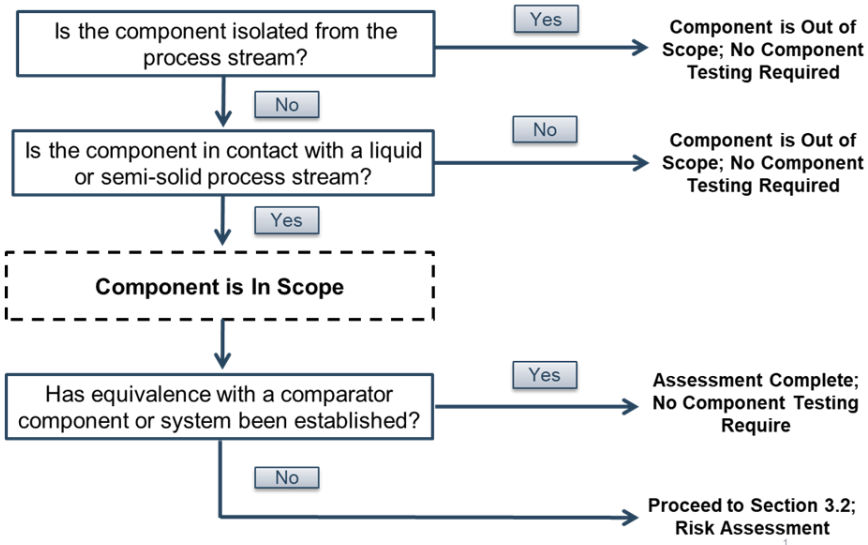
Out of Scope:

- Non-biological Drug Substances
- Auxiliary items (Scoops, funnels, pipettes, graduated cylinders, weighing dishes, beakers, etc.)
- Solid or gaseous process streams
- Rubber (elastomeric) components

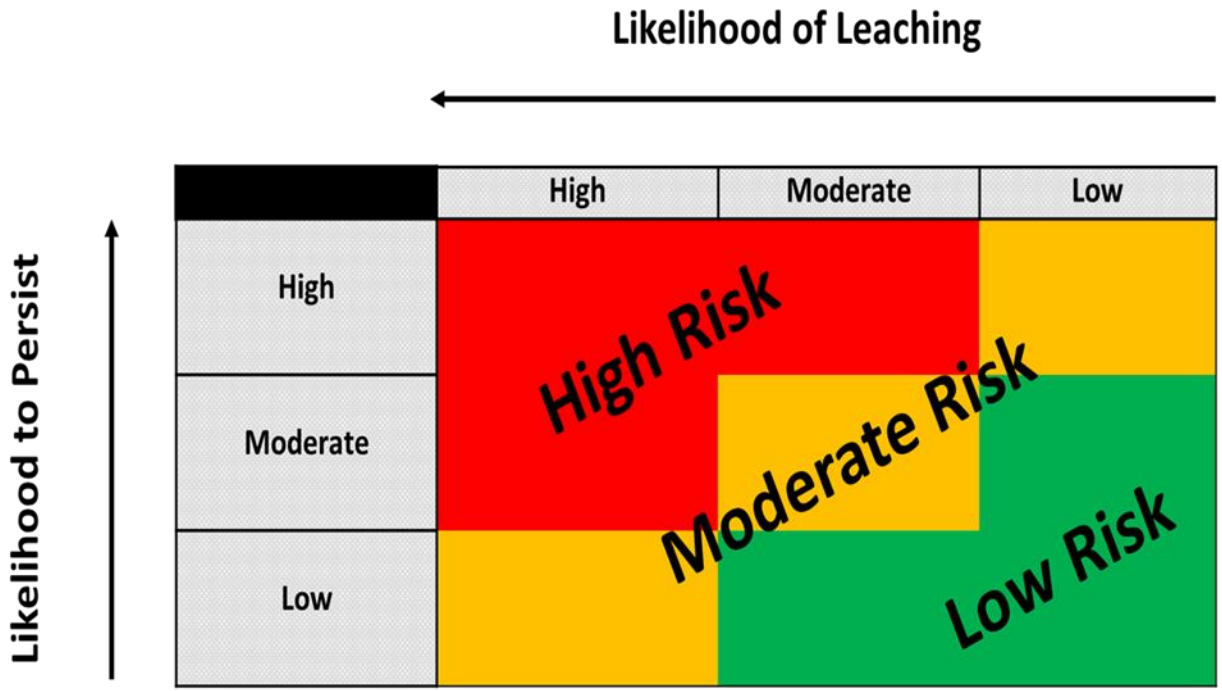
<665> Decision Process

Is testing required? **What is the leachables risk?** **What testing is required?**

Initial Assessment:



<665> Risk Assessment



<665> does not specify a mandatory Risk Evaluation Matrix. Rather, **it is the responsibility of the sponsors to establish and justify their own Matrices.** An example Matrix is contained in USP <1665>.

Required Risk Dimensions

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.

The outcome of any risk assessment process (including the use of a Risk Evaluation Matrix) must be one of three risk categories, **low** risk, **moderate** risk and **high** risk.

Required Testing per <665>

Table 2. Guidelines for Application of Chemical Component Tests as Established by Risk

Risk Level	Extraction Solutions for Chemical Testing[a]	Chemical Testing of Extracts
Low	*Solution C1*	• Non-volatile residue • UV absorbance
Moderate	*Solution C1*	• Organic extractables profiling
High	*Solution C1* *Solution C2* *Solution C3*	• Organic extractables profiling • Extracted elements (as necessary and appropriate)[b]

Solution Composition:

C1 = 50/50 Ethanol/water
C2 = Salt solution, pH 3.0
C3 = Phosphate buffer, pH 10

Extraction Conditions per <665>

Component	Extraction Solutions	Extraction Conditions at 40°C			
		1 Day	7 Days	21 Days	70 Days
Containers intended for storage	All	X		X	X
Containers not intended for storage[b]	All	X		X	
Tubing attached to containers not used for storage	All				
Tubing attached to containers used for storage	All	X		X	X
Tubing for fluid transport[c]	All	X		X	
Connector/Disconnector[a]	All	X		X	
Aseptic Connector/Disconnector	All	X	X		
Small components (o-rings, gaskets, check valves, diaphragms, septa, polymer pump surfaces, sensors	All	X			
Ports on container not used for storage	All	X		X	
Ports on containers used for storage	All	X		X	X
Closures (e.g., molded stoppers) for storage containers	All	X		X	X
Filters (process, sterilizing and virus)	All	X	X		
Filtration Cassettes (Tangential Flow)	All	X			
Tangential flow modules for perfusion or continuous processing	All	X	X	X	
Impellers and molded parts for bioreactors and mixers [b]	All	X		X	
Filling Needle	All	X			
Chromatography column housing	All	X			

Red = USP <665> X = BPOG protocol

Footnotes a, b and c talk to circumstances where longer or shorter extractions may be appropriate.

Acceptance Criteria

A low risk component that is deemed to be qualified for use 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 whether the risk classification is corroborated or not.

A moderate or high risk component is deemed to be qualified for use if:

- The extractables profile has been toxicologically safety risk assessed.
- The toxicological safety risk assessment concludes that the probable risk posed by all extractables is within acceptable parameters.

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.

Alternate extractions are allowed when extraction conditions:

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

10. Biocompatibility Chapters, <87>

⟨87⟩ Biological Reactivity Tests, In vitro.

The objective of this proposed revision is to:

- reduce the amount of redundant testing,
- refine the type of testing performed to align with the potential risk, and
- replace in vivo testing with in vitro testing or utilize other information using a risk-based approach focused on the knowledge of the material and pharmaceutical application.

The key changes proposed are as follows:

- Reorganize the chapter into six distinct sections, 1. Scope, 2. Preparation of Extracts, 3. Cytotoxicity Tests, 4. Skin Irritation Test, 5. Genotoxicity Tests, and Appendices.
- Remove the Agar Diffusion Test from the list of 3. Cytotoxicity Tests and add the 3.5 Neutral Red Uptake (NRU) Test.
- Add 4. Skin Irritation Test.
- Add the following genotoxicity tests: 5.2 Ames Bacterial Reverse Mutation Assay, 5.3 Mammalian Cell Genetic Toxicity Tests, *5.3.1 Chromosomal Aberration Test*, *5.3.2 Gene Mutation Test*, and *5.3.3 Micronucleus (MNvit) Test*.

Biocompatibility Chapters, <88>

⟨88⟩ Biological Reactivity Tests, In vivo.

The objective of this proposed revision is to:

- reduce the amount of redundant testing,
- refine the type of testing performed to align with the potential risk, and
- replace in vivo testing with in vitro testing or utilize other information using a risk-based approach focused on the knowledge of the material and pharmaceutical application.

The key changes proposed are as follows:

1.Delete Classification of Plastics because the distinction of plastic materials into six classes (Class I to Class VI) no longer serves a current purpose because in practice only Class VI is now utilized by vendors and end users.
2.Delete Intracutaneous Test.
3.Delete Implantation Test.
4.Delete Safety Tests–Biologicals as the relevant FDA Code of Federal Regulations, 21 CFR §610.11, was revoked on August 3, 2015.
5.In 2.2 Apparatus, add the requirement that the autoclave has the ability to connect to a calibrated resistance thermometer or a calibrated thermocouple and that the autoclave must be calibrated before first use.

Biocompatibility Chapters, <1031>

⟨1031⟩ The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants.

The key changes proposed are as follows:

1.Change the title.
2.Expand the scope of the chapter to encompass plastic materials of construction and plastic and elastomeric components for pharmaceutical packaging/delivery systems and for packaging of combination products.
3.Add an overview of the USP classification of plastics, as described in Biological Reactivity Tests, In Vivo ⟨88⟩, which identified six different classes of plastics (Classes I–VI). The classes were differentiated by the number and types of solvent used for extraction and the biological reactivity tests performed. A review of the utilization of the classification system found **that typically only the most stringent category (Class VI) was used by suppliers** of plastic materials of construction and components, and pharmaceutical manufacturers. This classification system has been replaced by the term "pharmaceutical grade polymeric materials", which is defined as materials that are in compliance with specific in vitro tests.

Biocompatibility Chapters, <1031>

⟨1031⟩ The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants.

The key changes proposed are as follows:

4. Include the following significant additions:

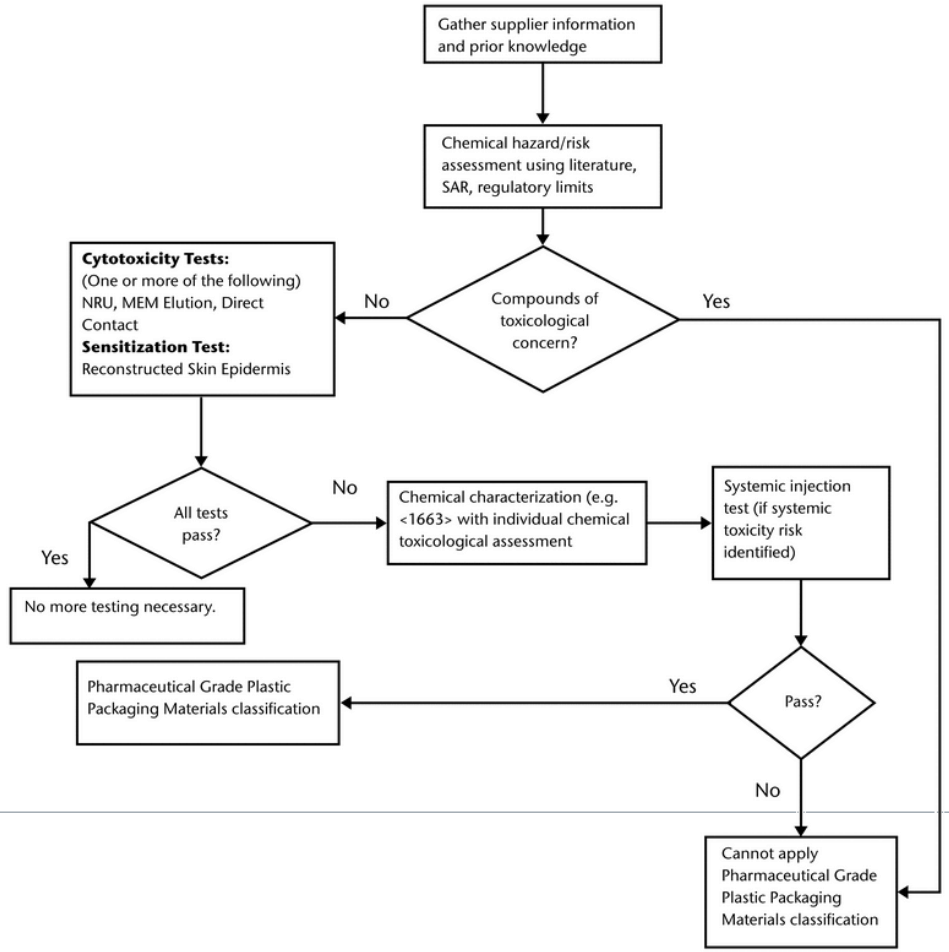
- A risk-based approach to biocompatibility evaluation
- Assessment of test methods
- Chemical characterization as a key part of the overall safety assessment process
- Biological reactivity test failure analysis
- Overall biocompatibility evaluation

5. Add sections for Glossary, Appendix, and References.

Biocompatibility Chapters, <1031>

The term **"Pharmaceutical Grade Plastic Packaging Materials"** replaces the Classification of Plastics Classes I–VI and is designed to facilitate communication among suppliers, users, and manufacturers of plastic materials by summarizing the tests to be performed for prospective plastic packaging materials.

Figure 1. Testing scheme to establish pharmaceutical grade plastic packaging material classification.

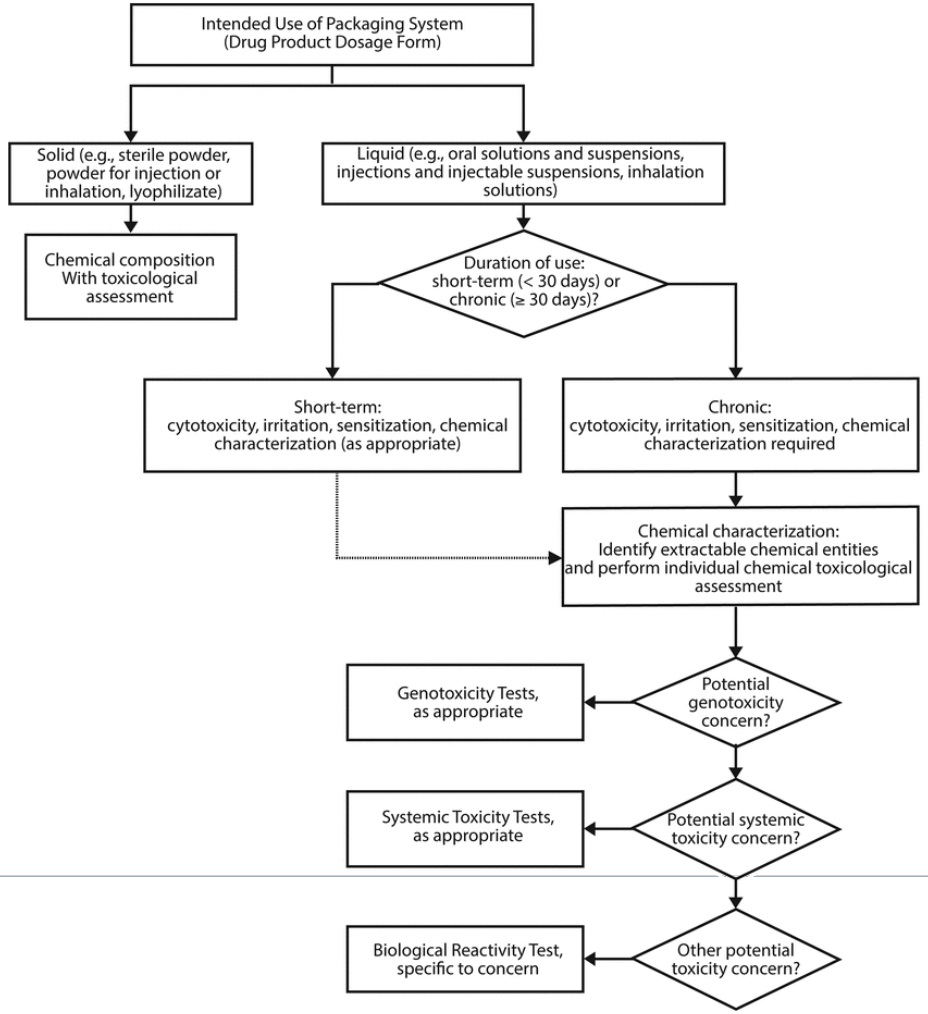


Biocompatibility Chapters, <1031>

What Testing is Required?

To determine which tests may be appropriate, the flow chart in Figure 3 may be used.

Figure 3. Biological reactivity test decision matrix.



11. System Suitability Mixtures

Pharmacopeial Forum, PF 49(4): "Proposals for the Development, Composition, and Routine Use of System Suitability Standard Mixtures in Support of Chromatographic Screening for Organic Extractables and Leachables"

Key Points:

- System suitability testing is performed during each chromatographic run to ensure that at time of use the method was set up and implemented properly.
- System suitability for screening methods (NTA) is established by testing a set of representative compounds as the universe of potential compounds that the methods must address is large and not fully known at the time of testing
- To facilitate consistent analytical performance across laboratories and to standardize system suitability testing, a standardized system suitability mixture is necessary.
- The USP is committed to the concept of efficient and effective system suitability assessment.
- The USP maintains that while extractables and leachables screening methods may vary somewhat in terms of operational details, they all must meet a minimum quality standard that is at least partially established by system suitability testing.
- The USP IS NOT proposing standardized chromatographic screening methods.

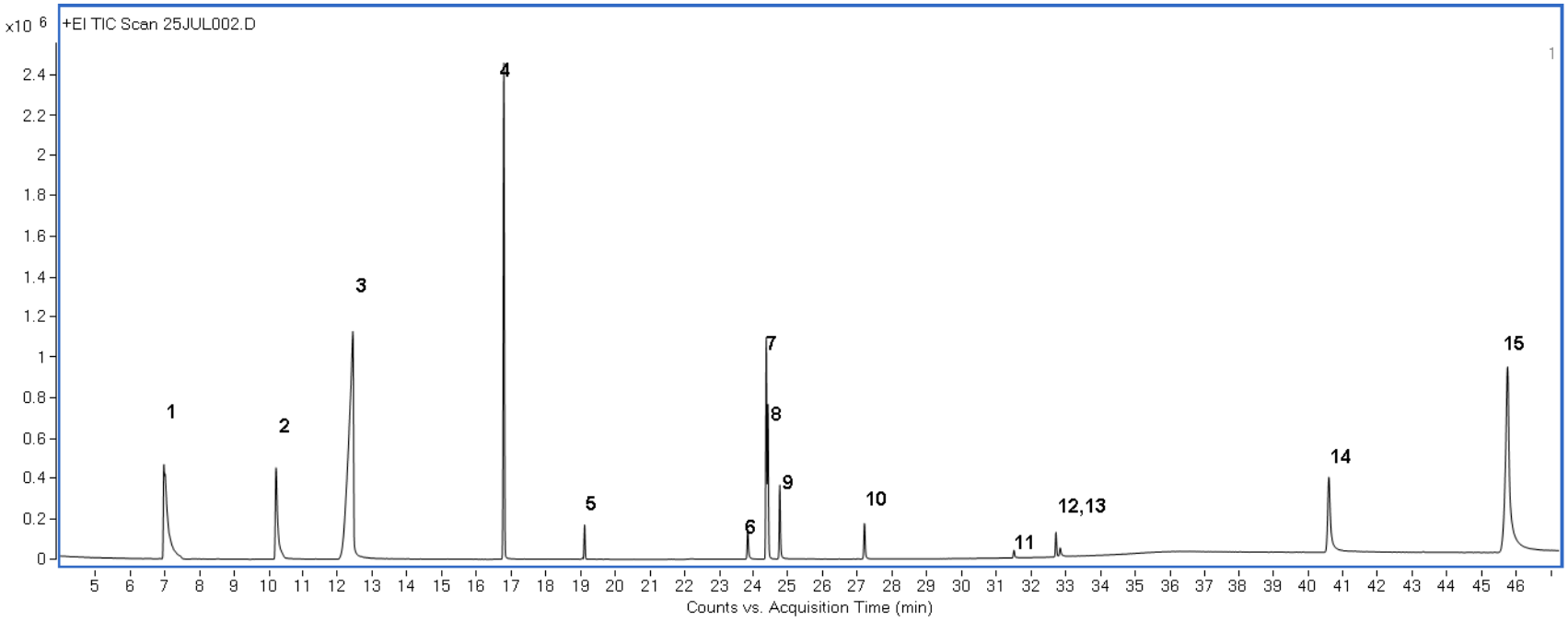
GC/MS System Suitability Mixtures

Table 3. Legend for the Typical Chromatogram, Composition of the GC/MS Suitability Mixture: Solvent = Dichloromethane (DCM)				
Compound	**CAS-number**	**Peak Number**	**Retention Time (min)**	**Concentration (mg/L)**
Cyclohexanone	108-94-1	1	6.99	20
2-Ethyl-1-hexanol	150-13-0	2	10.24	10
2-Ethylhexanoic acid	124-04-9	3	12.46	50
2-Fluorobiphenyl	321-60-8	4	16.82	10
Butylated hydroxytoluene, BHT	128-37-0	5	19.14	1 (1082708)
Caffeine-(trimethyl-$^{13}C_3$)	78072-66-9	6	23.83	2
n-Nonadecane	629-92-5	7	24.37	5
2-Heptadecanone	2922-51-2	8	24.41	5
Tri-n-pentyl phosphate	2528-38-3	9	24.76	5
Pyrene	129-00-0	10	27.20	1
Di-(2-ethylhexyl) phthalate, DEHP	117-81-7	11	31.51	1 (1545056)
Tinuvin 327	3864-99-1	12	32.72	2
n-Heptacosane	593-49-7	13	32.84	1
Irgafos 168	31570-04-4	14	40.55	10 (1544964)
18-Pentatriacontanone	504-53-0	15	45.75	50

Note: The numbers in () refer to the USP catalog number for existing reference standards.

GC/MS System Suitability Mixtures

Figure 4. Typical Chromatogram, GC/MS System Suitability Mixture. See Table 3 for peak labeling.



System Suitability Acceptance Criteria

1. There are recognizable chromatographic peaks for each compound in the mixture (e.g., 12 compounds = 12 peaks).
2. Each compound in the mixture is properly identified.
3. The reported concentration for each compound in the mixture should be within 50% - 200% of the prepared concentration.

Current Status:

The period for public comment closed September 30th and the comments are being collected and collated. Based on the comments, USP may:

- Make revisions to its approach to system suitability mixtures,
- Modify its proposed system suitability mixtures,
- Abandon or significantly modify its commitment to provide system suitability mixtures,
- Develop mixtures for other purposes (e.g., quantification)

Ongoing Work in E&L:

- USP Monographs as noted previously
- ICH Q3E: May see the Draft Standard for Public Comment in Q4 of 2024 [Key project, generating PDEs for many E&L compounds to drive setting proper values for the dose-based threshold (e.g., SCT)]
- ISO 10993:18(2020): Working groups have been established to produce Technical Reports for topics such as:
  - Proper Identification Practices
  - Proper Quantitation Practices
  - Establishing and Managing the AET
  - Recovery Expectations when Extracts are Processed Prior to Instrumental Analysis
  - How to Recognize and Deal with Compromised Extracts
- FDA-sponsored Round Robin studies related to migrations modeling, lab-to-lab variation
- ELSIE Initiatives
- Who knows what other organizations (or people) are doing?

Q&A

Thank you!

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