

An Integrated Regulatory Approach to Extractables and Leachables

Extractables and Leachables (E&L) are critical in pharmaceutical development, manufacturing, and lifecycle management, as drug products interact with materials such as equipment, container closure systems, and delivery devices. Chemical substances may migrate from these materials into the product, potentially impacting its quality, safety, and efficacy. Extractables are released under exaggerated conditions, while leachables occur under normal storage and use. Their presence may affect product stability, therapeutic performance, and physical properties, and can pose toxicological risks. Regulatory agencies therefore require a science- and risk-based approach, including analytical screening and toxicological evaluation. Comprehensive E&L studies help ensure patient safety, regulatory compliance, and product reliability. With increasing formulation and system complexity, robust E&L assessment remains essential to modern pharmaceutical quality assurance.

Impurity Control in Pharmaceutical Development

Managing impurities is essential to ensure the safety, quality, and efficacy of pharmaceutical products. Traditional regulatory focus has addressed:

- Process-related impurities in Drug Substances (DS)
- Degradation products in Drug Products (DP).

However, increasing regulatory attention has shifted toward **extractables and leachables (E&L)** arising from packaging, manufacturing systems, and delivery devices. However, The chemical diversity of pharmaceutical packaging materials and direct-contact medical devices creates significant challenges in designing comprehensive and effective Extractables and Leachables studies.



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Background-Risk Control^[1]

Risk control is a component of the broader risk management process. A strong high-level conceptual framework and detailed explanation of quality risk management are provided in the ICH Q9 guideline^[2]. Key elements of



this framework are highlighted in the main introductory paper, *Introduction: Concepts in Leachables Risk Management*. Collecting information and prior knowledge during material selection—either from suppliers or from internally generated historical data on similar products—is a key factor in risk assessment.

If the available knowledge is inadequate to establish a low risk level, or if the hazard appraisal is high (based on the hazard appraisal matrix described in the materials selection paper), additional activities may be required. These activities involve collecting further information to help the pharmaceutical manufacturer determine how the risk can be reduced and whether it is acceptable. In general, the purpose of this information is to address and minimize the specific risks identified during the risk assessment process.

As illustrated, the information obtained can contribute to risk reduction. For instance, if a material is considered to pose an unacceptable risk to drug product safety or quality, it may be possible to replace it with an alternative material that presents a lower risk, such as one that does not contain substances of concern or is known to have lower leaching potential.

Regulatory Landscape for E & L^[3-8]

Overview of Key Guidance

- USP (1663) – Extractables
- USP (1664) – Leachables
- USP (1665) – Manufacturing Systems
- ICH Q3E (Emerging guidance)
- PQRI recommendations

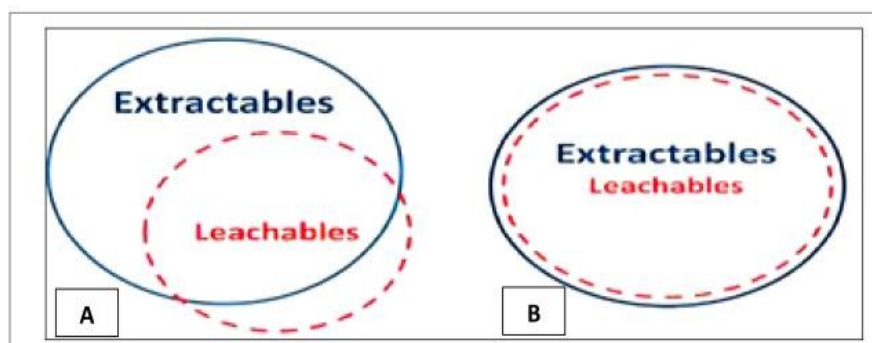


Fig. 1: Conceptual relationship between extractables and leachables
(A) Traditional view: Leachables & Extractables; (B) Modern risk-based view: Strong but context-dependent correlation.

- BPOG protocols.

USP (1663): Scientific Framework for Extractables Studies^[3]

Scope and Purpose

USP (1663) provides a **scientific framework**, not prescriptive test methods. It emphasizes risk-based design and lifecycle management. Applications include:

- Material qualification
- Packaging system development
- Worst-case leachables prediction
- Investigation of contamination issues
- Support of combination products.

Packaging Hierarchy

- **Packaging system:** All materials / components that contain and protect the product.
- **Primary packaging:** Direct contact with product.
- **Secondary / tertiary packaging:** Indirect contact but potential sources of migrants.
- **Delivery System:** Components transferring product to the patient.

Chemical Terminology

- **Extractables:** Substances released under laboratory extraction conditions.

- **Leachables:** Substances that migrate into the drug product under normal storage / use.
- **Migrants:** Substances crossing barriers from non-contact materials.

Threshold Concepts

- **Safety Concern Threshold (SCT):** Exposure level with negligible safety risk.
- **Analytical Evaluation Threshold (AET):** Level at which compounds must be reported and assessed.

Extractables Study Design^[1]

Extractables are organic and inorganic chemical entities that can be extracted from a material or component under laboratory conditions through studies commonly referred to as extractables studies.

Such studies are described using various terms that reflect different design approaches intended to accelerate, exaggerate, or simulate the leaching process. They are also associated with purpose-based descriptors such as scouting, discovery, identification, and quantification.



Design considerations include

- Extraction type
- Extraction solvent
- Extraction temperature and/or pressure
- Extraction time
- Preparation method from material (cutting, milling, flushing etc.)
- Surface area of material or component to extraction solvent volume ratio.

The primary objective of conducting an extractables study is to generate an extractables profile that provides information on the identity and quantity of the extractables observed from a material. This profile aims to cover a broad range of potential extractables by using multiple orthogonal analytical techniques capable of detecting different classes of compounds, such as volatile, semi-volatile, and non-volatile extractables, including elemental impurities.

Alternatively, extraction studies

may be designed to simulate drug product leaching conditions and, in some instances, may serve as a substitute for leachables studies; these are commonly referred to as 'simulation studies'.

For polymeric single-use systems used in biopharmaceutical manufacturing, the BioPhorum Operations Group (BPOG), has provided an analytical protocol for suppliers and others to use when measuring extractables in these materials.

Simulation Studies^[1]

A valuable and informative study design is the 'simulation study'. This type of study, along with considerations for when it can be applied and justified, is described in several pharmacopoeial chapters and industry case studies.

The objective of simulation studies is to generate results that closely resemble those that would be obtained from leachables studies. There are several situations in which leachables studies may be

difficult to perform, including:

- **Complex drug product formulations** that make accurate determination of leachables difficult (e.g., creams, ointments, formulations containing interfering excipients, or highly concentrated protein solutions).
- **Unsuitable leachables samples**, such as those from early-stage development or formulations involving cell-based or biological materials.

A key challenge in predicting leachables from extractables studies arises from differences in solvents, as extractables testing uses various extraction media while leachables studies involve the actual drug product formulation. Variations in polarity, pH, and ionic strength influence leaching behaviour based on the principle of '*like dissolves like*', creating a gap between the two approaches. This gap is more pronounced in complex formulations such as biopharmaceuticals, where proteins and excipients-including buffers, surfactants, preservatives, and isotonic agents-create a unique chemical environment unlike typical extraction solvents. Simulation studies can help bridge this gap by providing more accurate predictions of potential leachables. When the drug product itself is used as the extraction medium, such studies also serve as an early risk mitigation tool by assessing possible interactions between leachables, the active pharmaceutical ingredient (API), and other formulation components, particularly protein-related interactions that

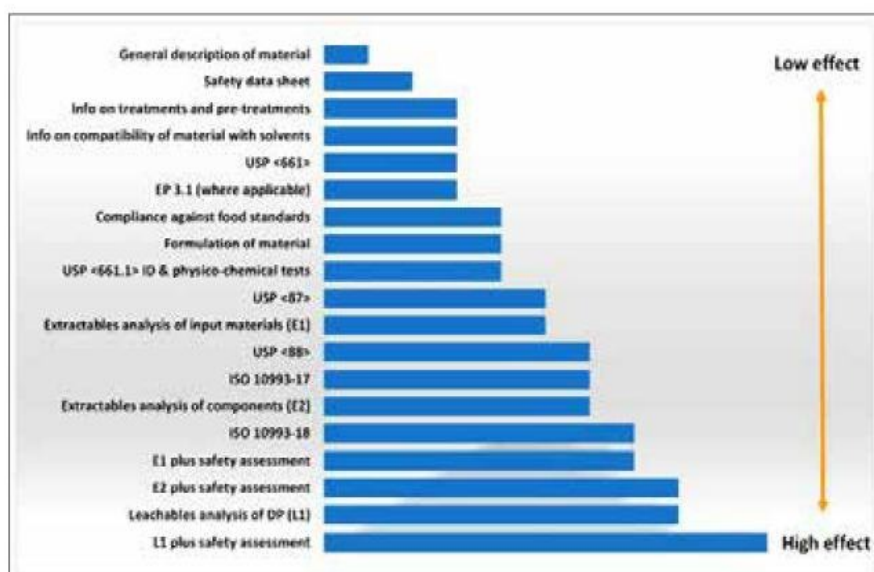


Fig. 2: Examples of information that can influence risk control and their potential impact include: **E1** – extractables analysis of input materials; **E2** – extractables analysis of components; and **L1** – leachables analysis of the drug product (DP). As noted below, extractables and leachables studies may be conducted in accordance with pharmacopoeial guidelines or other recognized best-practice resources.



may affect product quality and patient safety.

Extractable Study- Current Challenges

- No single analytical technique detects all extractables
- Reference standards may be unavailable
- Matrix effects complicate analysis.

Therefore, extractables characterization is an exercise in scientific due diligence rather than absolute completeness.

Leachable Study Design⁽¹⁾

Leachables studies provide critical insight into substances that may be present in the final drug product and to which patients may be exposed. The data, combined with safety assessments, help manufacturers evaluate risks and make informed decisions, often supporting risk management tools such as Failure Mode and Effects Analysis (FMEA) by refining probability estimates. Simulation studies may offer similar benefits depending on product characteristics and risk assessment outcomes. A leachables study is an analytical investigation that identifies and quantifies substances released from packaging, delivery, or manufacturing systems over the product's shelf life. These studies are essential for safety evaluation, especially for high-risk routes of administration or where interactions with packaging are likely. They also support the establishment of specifications and acceptance criteria before regulatory submission. Study design is case-specific and relies on information such as extractables profiles, material composition, manufacturing processes, and

Systemic Toxicity Thresholds				
Exposure Duration	Oral		Parenteral, Dermal/Transdermal, Inhalation	
	TTC	QT	TTC	QT
> 10 years	1.5 µg/day	48 µg/day	1.5 µg/day	12 µg/day
> 1 to 10 Years	10 µg/day		10 µg/day	
> 1 Month to 1 Year	20 µg/day		20 µg/day	
≤ 1 Month	120 µg/day	136 µg/day	120 µg/day	26 µg/day
Local Toxicity Thresholds				
Topical Ophthalmic	Subcutaneous and Intradermal	Dermal and Transdermal	Intracerebral, Intrathecal, Epidural and Intraocular	Inhalation
20 ppm	50 ppm	500 ppm	Compound-specific evaluation (see Section 6.4)	5 µg/day

Table 1: Systemic and Local Toxicity Thresholds Q3E guideline⁽⁶⁾

clinical usage conditions.

Thus, the design of a leachables study for the packaging or delivery system may consider the following factors:

- Leachables assessment should be conducted using the final drug product formulation (e.g., liquids, suspensions, lyophilized powders) along with the complete packaging and delivery system, including primary and secondary components.
- Study conditions should reflect real manufacturing, storage, and clinical use environments, considering factors such as sterilization, temperature, contact time, and exposure conditions (static or dynamic).
- Auxiliary components used during administration (e.g., infusion systems) should be included where applicable.
- Both accelerated and long-term stability studies may be performed to support leachables data generation.
- Assessments typically involve multiple formulation batches with replicates; however,

bracketing or worst-case approaches may be used for products with multiple strengths.

- Testing should be carried out on components as used in actual production, although direct sampling may be limited by sterility and operational constraints.
- Simulation studies are often preferred, especially for complex systems, as they allow better control, flexibility, and identification of leachable sources.
- Safety evaluations should account for cumulative exposure to leachables resulting from repeated or prolonged use of components..

Importance of Leachables Assessment

Leachables are critical because they may:

- Cause toxicological risk to patients
- Interact with the formulation
- Affect drug stability or quality.

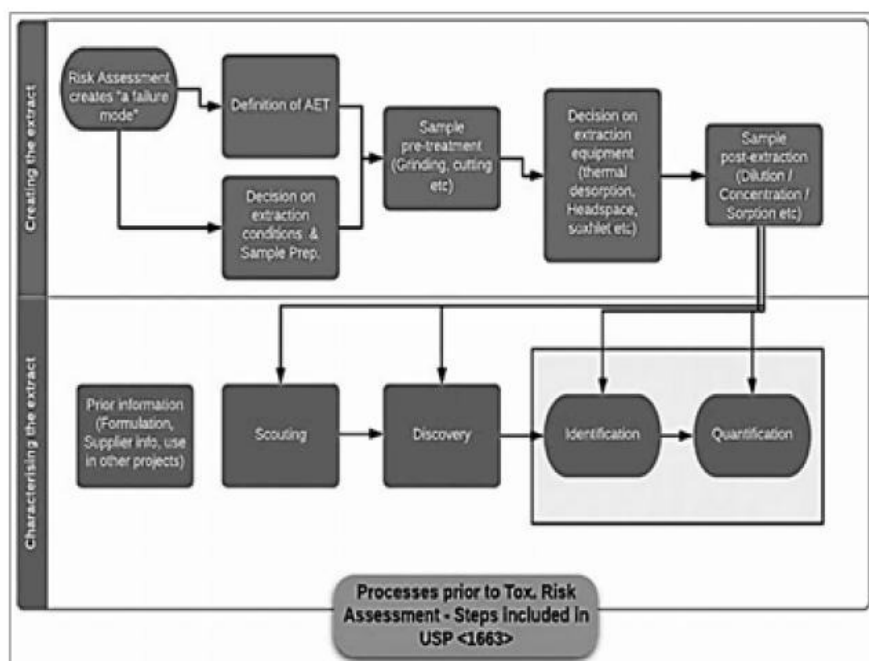


Fig. 3: Example process steps for extractables studies used in risk control, based on USP <1663>^[1 & 3].

Regulatory agencies require evaluation especially for high-risk dosage forms.

Risk-Based Approach (Dosage Forms)

However, even low-risk products can have leachables issues.

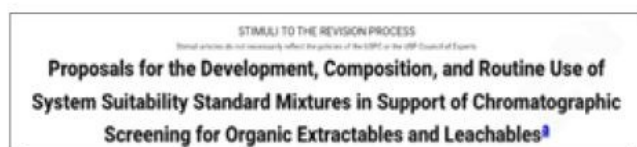
Extractables – Leachables Correlation^[4]

A correlation is established when leachables detected in the drug product can be linked to extractables from packaging materials which helps in:

- Identify the source of contamination
- Justify extractables testing as a control strategy
- Support lifecycle management.

Recent USP Updates on E & L:

Background: Stimuli article published USP-PF 49(4), July 2023.



New Chapter Proposals for different drug products:

- <1664.1> Orally Inhaled and Nasal Drug Products
- <1664.2> Parenteral Drug Products (intramuscular, intravenous, and subcutaneous)
- <1664.3> Assessment of Leachables in Topical Ophthalmic Drug Products
- <1664.4> Assessment of Leachables in Topical and Transdermal Drug Products.

Guideline for E & L Q3E^[6].

The guideline provides a risk-based framework to assess and control leachables to protect the Patient safety, quality and efficacy.

Key Concepts of Q3E is Risk Assessment and Control. Each product requires an E&L risk management process including Risk assessment, Risk control, Lifecycle management.

Classification of Leachables as *Class 1* – High Concern like Mutagenic carcinogens, highly potent toxic compounds must be avoided or strictly controlled; *Class 2* – Moderate Concern are most typical leachables which requires Toxicological evaluation, Exposure assessment; *Class 3* – Low Concern i.e. Compounds with low toxicity. If exposure is <1 mg/day, no additional qualification is needed.

Safety Assessment Workflow for leachables above AET:

- Identify chemical structure
- Estimate patient exposure
- Evaluate mutagenicity
- Evaluate systemic toxicity
- Assess local toxicity if relevant
- Compare with safety thresholds

Possible outcomes:

- Acceptable exposure
- Need for mitigation
- Additional toxicology studies.

Examples-Formula for AET calculations^[6].

AET for extractables from a filter used in a liquid drug product manufacturing process.



Examples of Packaging Concerns for Common Classes of Drug Products			
Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component - Dosage Form Interaction		
	High	Medium	Low
Highest	Inhalation Aerosols and Sprays	Injections and Injectable Suspensions; Inhalation Solutions	Sterile Powders and Powders for Injection; Inhalation Powders
High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays	-
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions		Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders

Table 2. Modified FDA/CDER/CBER Risk-based approach to consideration of Leachables⁴⁹.

$$AET(\mu\text{g}/\text{filter}) = \frac{SCT(\mu\text{g}/\text{day}) \times UF \times \text{Doses per batch}}{\text{Filters/batch}}$$

Then convert to concentration in the filter material:

$$AET(\mu\text{g}/\text{g filter}) = \frac{AET(\mu\text{g}/\text{filter})}{\text{Weight of filter(g)}}$$

Further calculate,

1. $AET(\mu\text{g}/\text{mL extraction solvent}) = AET(\mu\text{g}/\text{filter}) \div \text{Extraction solvent (mL)/filter.}$

2. $AET(\mu\text{g}/\text{cm}^2) = AET(\mu\text{g}/\text{filter}) \div \text{Contact surface area (cm}^2\text{)/filter.}$

Leachables for manufacturing equipment for liquid drug product

Formula 1 – Total per Batch

$$AET(\mu\text{g}/\text{batch}) = SCT(\mu\text{g}/\text{day}) \times UF \times \text{Doses per batch}$$

Formula 2 – Concentration in Drug Product

$$AET(\mu\text{g}/\text{mL}) = \frac{SCT(\mu\text{g}/\text{day}) \times UF}{\text{Maximum daily dose (mL)}}$$

Formula 3:

$AET(\mu\text{g}/\text{mL extraction solvent}) = AET(\mu\text{g}/\text{stopper}) \div \text{Extraction solvent (mL)/Stopper.}$

Formula 4:

$AET(\mu\text{g}/\text{mL extraction solvent}) = AET(\mu\text{g}/\text{g stopper}) \div \text{Extraction solvent (mL)/gram of Stopper.}$

Leachables for a prefilled syringe (PFS)

Step 1 – Calculate concentration in drug product

$$AET(\mu\text{g}/\text{mL}) = \frac{SCT \times UF}{\text{Maximum daily dose}}$$

Step 2 – Convert to amount per syringe

$$AET(\mu\text{g}/\text{PFS}) = AET(\mu\text{g}/\text{mL}) \times \text{Volume per PFS}$$

Analytical Uncertainty Factor^[6]

According to ICH Q3E, when applying an Analytical Evaluation Threshold (AET) with semi-quantitative methods, an uncertainty factor (UF) is used to address differences in detector response between

analytes and reference standards. These differences may lead to underestimation, especially for unknown compounds quantified using surrogate standards. The UF ensures that all potentially significant extractables or leachables are identified and assessed for safety. A default UF of ≤ 0.5 is recommended, though it may also be statistically derived from response factor data.

Lifecycle Management

E&L assessments must be revisited when changes occur, such as

- Formulation changes
- New packaging materials
- Manufacturing process modifications
- Changes in dosing regimen
- New toxicology information.

Conclusion

Extractables and Leachables (E&L) studies play a critical role in ensuring the safety, quality, and efficacy of pharmaceutical products by assessing interactions between drug formulations and packaging materials. Regulatory frameworks such as USP <1663>, USP <1664>, PQRI, and ICH Q3E promote a risk-based approach for identifying and controlling these compounds. Despite analytical advancements, challenges remain in detecting trace-level and unknown compounds and evaluating their toxicological risks. Ongoing collaboration and improved analytical tools will strengthen E&L strategies and enhance patient safety.

References

- ICH Q9, Quality Risk Management. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Step 4, November 2005.
- USP Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems. United States Pharmacopoeia.
- Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery systems. United States Pharmacopoeia.
- Safety thresholds and best practices for extractables and leachables in orally inhaled and nasal drug products. Product Quality Research Institute. September 2006.
- International Council for Harmonisation (ICH). ICH Q3E: Impurities: Guideline for Extractables and Leachables (Step 2 Draft). Geneva: ICH; 2025.