Extractables & Leachables
in Pharmaceutical Systems.

Regulatory Expectation and Strategic Quality Risk.

CUP contract labs

Dr. Falco Reissig
Head of Analytical Chemistry

Executive Summary

Extractables and Leachables (E&L) represent a critical quality risk for modern pharmaceutical products, particularly for parenteral drugs, combination products, and complex delivery systems. Chemical compounds originating from packaging materials, manufacturing equipment, or device components may migrate into the drug product during manufacturing or storage. Regulatory authorities increasingly require systematic risk assessment and scientifically robust E&L studies in accordance with guidelines such as USP <1663>, USP <1664>, USP <1665> and ICH Q3E. Insufficient evaluation may lead to regulatory delays, additional toxicological investigations, or costly product reformulations.

A structured, risk-based E&L strategy—combining material characterization, advanced analytical screening, and toxicological evaluation—has therefore become an essential element of pharmaceutical quality assurance and regulatory compliance.

Market Context and Regulatory Framework

The increasing complexity of pharmaceutical products has significantly expanded the relevance of Extractables and Leachables investigations.

Modern drug products often involve polymer-based packaging materials, disposable and single-use manufacturing components, and sophisticated drug-device combination systems. These materials may contain additives such as stabilizers, antioxidants, plasticizers, or residual processing agents that can potentially migrate into the drug product.

At the same time, regulatory expectations regarding E&L evaluation are becoming more clearly defined and globally harmonized. Guidance documents such as USP <1663> (Assessment of Extractables) and USP <1664> (Assessment of Leachables), together with the developing ICH Q3E guideline, provide a structured framework for identifying, evaluating, and controlling material-derived impurities.

E&L studies are particularly critical for parenteral formulations, inhalation products, and long-term drug delivery systems, where patient exposure to potential contaminants may be significant. In addition, changes in packaging materials, manufacturing equipment, or suppliers may trigger the need for renewed E&L assessments.

Within this evolving regulatory landscape, companies must implement scientifically robust and risk-based evaluation strategies to ensure both patient safety and efficient regulatory approval processes.

Scientific Background

Extractables and Leachables represent two closely related but scientifically distinct categories of material-derived impurities. Extractables are compounds that can be intentionally extracted from packaging materials or manufacturing components under aggressive laboratory conditions, typically using elevated temperatures, extended contact times, or strong extraction solvents. These studies are designed to identify the potential chemical universe that may migrate from materials into the drug product.

Leachables, in contrast, are the compounds that actually migrate into the pharmaceutical product under normal manufacturing, storage, or clinical use conditions. Their occurrence depends on multiple factors including material composition, formulation chemistry, storage conditions, and duration of product contact with the material.

Regulatory guidelines therefore recommend a risk-based approach that integrates extractables screening with targeted leachables monitoring. Threshold concepts such as the Safety Concern Threshold (SCT), Analytical Evaluation Threshold (AET), and Qualification Threshold (QT) help determine which compounds require identification, quantification, and toxicological assessment.

Advanced analytical technologies play a key role in this process. Comprehensive E&L studies typically combine gas chromatography–mass spectrometry (GC-MS), liquid chromatography–mass spectrometry (LC-MS/MS), and inductively coupled plasma mass spectrometry (ICP-MS) to detect volatile, semi-volatile, non-volatile, and elemental contaminants.

Extractables & Leachables.

Structured, Risk-Based E&L Study Strategy

A robust Extractables and Leachables strategy begins with a structured risk assessment considering product formulation, packaging materials, manufacturing components, and expected patient exposure. Early identification of potential material-related risks allows companies to address compatibility issues long before late-stage development or regulatory submission.

The first step typically involves comprehensive characterization of all product-contact materials. Primary packaging components, secondary packaging elements, and manufacturing equipment surfaces are systematically evaluated. Information on additives, processing aids, and potential degradation products is collected to establish an initial risk profile.

Extractables studies are then performed under controlled worst-case conditions. Materials are exposed to selected solvents, elevated temperatures, and extended contact times to intentionally release potential extractable compounds. The resulting analytical profile defines the possible impurity landscape associated with the material system.

Based on these results, leachables studies are designed to monitor compounds that may migrate into the drug product during storage or use. These investigations are often integrated into stability studies and conducted under real storage conditions across the expected shelf life.

Analytical characterization relies on complementary technologies such as GC-MS, LC-MS/MS, and ICP-MS to detect a broad range of organic and inorganic compounds. Identified substances are subsequently evaluated using toxicological thresholds such as SCT, AET, and QT to determine their potential safety relevance. Through this structured workflow, E&L studies provide a scientifically robust basis for regulatory submissions and long-term product lifecycle management.

E&L Study Workflow

01 Request

02 Technical Questionaire

03 Expert Consultation & Study Design

04 Extractables Studies

05 Analytical Characterization

06 Leachables Studies

07 Toxicological Assessment

08 Study Report & Regulatory Documentation

Industry-Specific Constraints

Extractables and Leachables studies differ fundamentally from traditional impurity analysis because the potential contaminants originate from external material systems rather than the drug substance itself. Their occurrence is influenced by complex interactions between formulation chemistry, packaging materials, storage conditions, and manufacturing processes.

Additional analytical challenges may arise in specialized pharmaceutical environments.

For example, radiopharmaceutical production frequently relies on disposable synthesis cassettes, complex tubing systems, and highly specialized device components. These systems increase the number of potential material contact surfaces and may require adapted analytical workflows.
Nevertheless, the underlying scientific principles remain identical across pharmaceutical modalities: a risk-based evaluation combining extractables screening, proper leachables monitoring, and toxicological assessment.

Our Analytical toolbox:

LC-HRMS
GC-MS
HS-GC-MS
GC-MS after derivatisation
ICP-MS

Detection of volatile, semi-volatile, non-volatile and elemental impurities.

Extractables & Leachables.

Strategic Value

A structured Extractables and Leachables strategy significantly reduces regulatory, operational, and development risks. Early identification of material-derived impurities enables companies to address potential compatibility issues before they impact product approval timelines.
Specialized analytical laboratories equipped with advanced mass spectrometry technologies and regulatory expertise can efficiently perform comprehensive E&L studies and generate regulatory-ready documentation.
Collaborating with an experienced partner such as CUP Contract Labs allows manufacturers to obtain reliable analytical data and toxicological assessments without building extensive in-house capabilities.
In an increasingly complex pharmaceutical landscape, systematic E&L evaluation becomes a strategic element of product quality assurance.

EXPERT VOICES

"I find **high-resolution mass spectrometry** (LC-HRMS) particularly exciting. The measurement results are extremely precise and give us insights down to the molecular formula level. Depending on the product, packaging, or cassettes used, we sometimes find no leachables—in other cases, we find over 100 substances. This diversity makes every project unique."

Sophia Fries
Senior Scientist

Conclusion

As pharmaceutical products become more complex and packaging systems more sophisticated, Extractables and Leachables investigations are becoming a central component of regulatory expectations.

Material-derived impurities must be systematically identified, evaluated, and controlled to ensure patient safety and product quality.

A structured, risk-based E&L strategy—integrating advanced analytics, toxicological evaluation, and regulatory expertise—provides the foundation for reliable product development and sustainable regulatory success.

Expert Perspective:
E&L in Radiopharmaceutical Systems

Radiopharmaceutical production systems frequently involve disposable synthesis cassettes, tubing sets, filters, and highly specialized fluid paths. These components increase the number of potential material contact surfaces and can therefore expand the extractables and leachables risk landscape compared with more conventional pharmaceutical setups.

In addition, radioactive product environments may impose specific practical constraints on sampling strategies, analytical workflows, and material assessment. Short product half-lives, shielding requirements, and specialized handling conditions can influence how E&L investigations are designed and executed.

At the same time, the underlying scientific and regulatory principles remain unchanged. Radiopharmaceutical systems must be evaluated using the same risk-based framework applied across pharmaceutical products: material characterization, extractables screening, targeted leachables assessment, and toxicological evaluation.

Laboratories with expertise in both pharmaceutical analytics and radiopharmaceutical environments are therefore particularly well positioned to assess these systems in a scientifically robust and operationally feasible manner.

Any questions?
Let´s talk.

CUP contract labs
Leading the way in Complex Pharmaceutical Analysis.

CUP Laboratorien Dr. Freitag GmbH
Carl-Eschebach-Straße 7
01454 Radeberg
Germany

Phone: +49 3528 2290920
E-Mail: office@cup-contract-labs.com
Web: www.cup-contract-labs.com