Extractables & Leachables (E&L) Pharma Testing Guide

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Executive Summary

Extractables and leachables (E&L) investigations have become a **critical component of pharmaceutical quality assurance**. Regulatory agencies now require rigorous testing of all materials that contact drug products to ensure that any migrating contaminants remain below toxicologically acceptable levels ([1] www.usp.org) ([2] www.sciencedirect.com). In practice, E&L programs use accelerated extraction studies to identify a broad profile of *extractables*, then design targeted studies to quantify *leachables* under real-use conditions. Modern analytical methods (high-resolution GC–MS, LC–MS) and advanced data software platforms (e.g. Waters' UNIFI, Lumetics LINK, ACD Luminata) have been developed to handle the massive datasets and complex identification tasks ([3] www.sciencedirect.com) ([4] www.waters.com). Regulatory guidelines are converging on risk-based frameworks: FDA and ICH notes emphasize patient safety first (draft ICH Q3E states its "primary purpose is to protect patient safety" (www.ema.europa.eu)), and new USP chapters <1663>/<1664> provide structured approaches for extractables and leachables studies ([5] www.drugfuture.com) ([6] doi.usp.org). Case studies illustrate the stakes – for example, an ophthalmic solution was unexpectedly contaminated by *diethyl phthalate* migrating from an ancillary scotch-tape used during manufacture ([7] hero.epa.gov). Market analyses predict rapid growth in E&L testing (projected ~*14% CAGR*, from ~$1.13B in 2024 to $3.57B by 2033 ([8] www.grandviewresearch.com)) as biologics and novel packaging materials expand. This report provides an in-depth review of E&L principles, analytical methodologies, regulatory expectations, and data management strategies, with extensive references to current research and guidelines. We highlight both established practices and emerging tools (such as predictive modeling of leachables ([9] www.sciencedirect.com)) to inform best practices and future directions.

Introduction and Background

Definition and Significance. *Extractables and leachables* (E&L) are chemical impurities derived from packaging, manufacturing, or delivery materials that can migrate into drug products. **Extractables** are those compounds which *can* be drawn out of a material under harsh laboratory conditions (e.g. strong solvents, reflux, elevated temperature) ([10] www.rcainc.com) ([11] www.susupport.com). In contrast, **leachables** are the subset of extractables that *do* actually migrate into the product under normal storage or use conditions ([12] www.susupport.com) ([13] www.rcainc.com). For example, if a plastic vial stopper contains a phthalate plasticizer, extractables testing might detect this phthalate under forced extraction; if that phthalate appears in the stored drug solution over time, it is a leachable. By definition, leachables are potentially patient-exposed impurities, so they are of direct toxicological concern ([14] www.sciencedirect.com) ([12] www.susupport.com).

Physicians and regulators recognize that unidentified leachable impurities can pose **health hazards to patients** ([2] www.sciencedirect.com). As Singh *et al.* (2021) note, "unidentified and potentially toxic leachable impurities can pose health hazards… Therefore, E&L investigations have received significantly increased emphasis from regulatory agencies in recent years" ([2] www.sciencedirect.com). Consequently, comprehensive E&L testing is demanded in pharmaceutical quality programs to *verify drug safety and product quality* ([14] www.sciencedirect.com). In practice, this means that manufacturers must demonstrate that any substances migrating from packaging or processing components remain below harmful levels during the product's shelf life ([1] www.usp.org). For example, the United States Pharmacopeia reminds industry that regulators **require** testing of container-closure systems to ensure migrating substances stay below toxic thresholds ([1] www.usp.org). In short, E&L analysis is a critical safeguard in product development and submission.

Regulatory and Historical Context. The regulatory scrutiny of E&L has evolved over decades. In 1999 FDA published the first *Guidance for Industry on Container Closure Systems*, introducing the concept that container materials should not impart harmful substances to a drug ([15] www.fda.gov). This was followed by 2002 Q&A documents for drugs and biologics (to address particularly complex systems). The pharmaceutical community also embraced quality-by-design (QbD) and risk-management principles (ICH Q9), leading to formal guidance on impurities (e.g. ICH Q3A–Q3D) and now specifically E&L. As of 2025, ICH has drafted a new E&L guideline (Q3E) that explicitly **extends impurity control principles to**

extractables/leachables, aligning with other ICH impurity guidelines (www.ema.europa.eu). The draft ICH Q3E describes E&L assessment as a holistic, risk-based framework, rooted in ICH Q9 concepts, whose primary purpose is to protect patient safety and product quality (www.ema.europa.eu).

In parallel, pharmacopeial chapters were released to standardize industry practice. Notably, the USP introduced General Chapters <1663> on *Extractables* and <1664> on *Leachables* (both around 2018) ([5] www.drugfuture.com) ([6] doi.usp.org). These chapters provide **frameworks (not specific test methods)**, stating that extractables/leachables assessments should be scientifically justified, risk-driven, and tailored to each product.USP <1663> explains that extractables studies should "balance sound science, prudent resource allocation, and effective risk management" ([5] www.drugfuture.com). USP <1664> similarly focuses on patient safety, noting that leachables assessments ensure manufacturers establish the suitability of packaging/delivery systems by controlling leachables that could affect efficacy, safety, or quality ([6] doi.usp.org). Other regional guidance has addressed related topics (e.g. EMA's 2005 *Plastic Primary Packaging* guideline (www.ema.europa.eu), and ISO 10993-17 on extractables for medical devices), but the global landscape is now moving toward harmonized E&L standards (as evidenced by ICH Q3E).

Objectives of This Report. This comprehensive report covers the full spectrum of E&L considerations: the science behind extractables and leachables, **methodological approaches** for testing, **regulatory expectations** across agencies, and **software tools and data strategies** used to manage E&L data. We include quantitative analyses (e.g. market size and growth), multiple case studies illustrating real incidents, and discussion of future trends (such as predictive modeling). The goal is to serve as a "testing guide" for pharmaceutical scientists and quality professionals, with exhaustive citations to literature, guidelines, and expert sources. All claims are evidence-based, drawing on peer-reviewed reviews, official guidance documents, industry case studies, and the latest research findings.

E&L Testing Methodologies

Study Design and Risk Assessment

E&L testing programs are fundamentally **risk-based**. First, all materials that contact a drug product — including primary packaging, components (stoppers, liners, seals), manufacturing equipment (tubing, filters, connectors), and ancillary materials (labels, adhesives) — must be inventoried and characterized. Each material's potential to contribute extractables or leachables is assessed, often via a toxicological threshold or Threshold of Toxicological Concern (TTC). Testing focuses first on the highest-risk materials and pathways (e.g. a plastic vial stopper in an aqueous injectable product).

A typical workflow begins with an **extractables study** on representative material samples. Here aggressive conditions (e.g. refluxing in organic solvents, superheated water, or accelerated aging) are used to pull out as many potential migrants as possible. The results produce a *screenwide extractables profile*, listing compounds detected and aiding in identifying which might leach into the drug. These extractables are identified (if possible) by spectroscopic or spectrometric means, and their concentrations are noted — often relative to a pre-determined *Analytical Evaluation Threshold (AET)*.

Next a **leachables study** is performed using the actual drug product formulation under realistic conditions (usually long-term stability or accelerated stability protocols). Analytical testing seeks to detect any compounds in the drug extract. Only the leachables that exceed safety-based thresholds (often based on permitted daily exposure or related criteria) are prioritized for quantification and identification. In practice, a "bracketing" approach may be used: e.g. testing product filled in the most extreme container (biggest volume:surface ratio, stressed conditions) to capture the worst-case.

This **leachables qualification** often involves orthogonal analytical methods (different extraction and detection techniques) to ensure no leachable is missed. For example, non-volatile leachables may require LC–MS, whereas volatile organics need GC–MS or headspace–GC–MS. The AET is typically set based on a toxicological assessment

(sometimes using ICH M7 or PDE principles) so that any compound above the AET is evaluated. It is *important* that compounds above threshold are identified whenever possible; as Singh *et al.* emphasize, *"leachables should be adequately identified and quantified for a toxicological risk assessment."* ([16] www.sciencedirect.com)

E&L studies are inherently **multidisciplinary**. They draw on chemical analysis, toxicological risk evaluation, and engineering of the drug-product system. Collaboration between chemists, packaging scientists, and toxicologists is key. In complex cases (e.g. biologics stability, exotic polymer materials), experts may apply emerging tools like in-silico toxicity databases or QSAR models to help rank new leachable hypotheses. New predictive approaches are also being developed: for example, Vinković *et al.* (2025) introduced *PredicDiff*™, a computational model that uses Fick's diffusion laws to predict the concentration of process-related leachables (PERLs) from measured extractables ([9] www.sciencedirect.com). Such tools show promise for future risk assessment by linking material data to expected exposures.

Sample Preparation and Extraction

A correct extraction protocol is crucial. No single method suits all materials, so protocols vary widely. **Static solvent extraction** (soaking material in a solvent under heat) is common. Multiple solvents may be used (e.g. water, ethanol, isopropanol, hexane) to cover polar and nonpolar extractables. **Accelerated aging** (e.g. autoclaving, UV/heat/ozone exposure) can simulate long-term use. **Supercritical fluid extraction** or subcritical water extraction are also employed for certain polymers. In all cases, extraction conditions should be justified and, if possible, "worst case." The extract is then concentrated and analyzed.

As Singh *et al.* note, *"extractables are generated by the product and the packaging interacting over time, usually in the presence of a solvent under extreme conditions of time and temperature."* ([10] www.rcainc.com). This underscores that extractables testing intentionally uses exaggerated conditions to reveal potential migrants. It is generally advised to analyze extraction blanks and controls to differentiate true material-related peaks from laboratory artifacts.

For leachables, a portion of the drug product is sampled (or an aliquot spiked with reference substances) and analyzed directly or after concentration. Stability (long-term, accelerated, intermediate) provides timepoints to monitor when (and if) leachables appear. Again, orthogonal extraction may improve sensitivity; for example, liquid–liquid extraction of a drug solution prior to GC–MS can enrich volatile leachables. For biological products, enzymatic or surfactant treatment may be needed to free protein-bound leachables.

Analytical Instrumentation

Modern E&L analysis relies on high-sensitivity, high-resolution instruments to cover the wide chemical space of possible migrants. The principal techniques include:

- **Gas Chromatography–Mass Spectrometry (GC–MS)**: Used for volatile and semi-volatile organic compounds. This includes headspace GC–MS for very volatile gases (e.g. siloxanes, acetone, low-molecular-weight alcohols) and purge-and-trap methods. GC–MS is invaluable for identifying light-end hydrocarbons, plasticizers (phthalates, adipates), antioxidants (antiozonants), and residual solvents. For example, if a polyolefin container has antioxidant Irganox 1010, GC–MS can detect its pyrolysis products ([3] www.sciencedirect.com).
- **Liquid Chromatography–Mass Spectrometry (LC–MS)**: Required for higher-boiling, polar, or thermally labile extractables. LC–MS (especially high-resolution time-of-flight or orbitrap systems) can detect a broad range: plastic additives, precursors (like glycols), coupling adhesives, silicone silicones (using LC/MS with APCI to detect siloxanes), and very polar species that GC cannot. LC–MS/MS (tandem) enables structural elucidation by fragmentation patterns. Recent advances also include two-dimensional LC (LC×LC) to separate very complex extracts.

- **Inductively Coupled Plasma Mass Spectrometry (ICP–MS) and ICP–OES**: For elemental impurities (e.g. metal catalysts, additives, fillers). Many polymers contain metallic stabilizers (e.g. calcium, tin, titanium) that may leach as metals or ions. ICP–MS can detect trace metal leachables (down to ng/L) after appropriate digestion or acid extraction of the sample. A related technique, ICP–OES, also measures metals but with lower sensitivity.
- **Other Techniques**: Fourier-transform infrared spectroscopy (FTIR) or Raman spectroscopy can be used for polymer material identification and surface analysis. Nuclear magnetic resonance (NMR) spectroscopy is rare in routine E&L due to low sensitivity, but it can confirm structures if enough pure standard is available. Total Organic Carbon (TOC) analyzes overall carbon content of extracts as a broad check.

Waters Corp. summarizes these approaches: GC–MS, LC–MS, and ICP–MS are indeed the “major analytical techniques” for volatile, semi-volatile, non-volatile organic and elemental E&L detection ([3] www.sciencedirect.com). Example workflows combine them so that no segment of the chemical space is overlooked.

The table below highlights typical methods and their applications in an extractables/leachables context:

Analytical Technique	Typical Applications in E&L Testing
Headspace GC–MS	Volatile/semi-volatile organics (e.g. acrylics, aldehydes, low-boiling solvents).
GC–MS (full scan)	Semi-volatile organics (phthalates, antioxidants, siloxanes, plasticizers).
LC–MS (HRMS)	Non-volatile organics (e.g. ultraviolet-absorbing impurities, surfactant breakdown products, drug excipient degradants).
LC–MS/MS	Targeted quantitation or confirmation of known leachables with MS/MS transitions.
ICP–MS / ICP–OES	Elemental impurities (metals from catalysts, additives, catalysts, glues).
FTIR / Raman	Bulk polymer composition, specific functional groups (usually for material ID rather than trace analytes).
TOC / IC (Ion Chrom)	Global organic carbon or small ions (e.g. acetate formate from packaging acids).

The above methods often require *hyphenated instrumentation* and advanced detection: for example, GC–MS with soft ionization (cold EI) or tandem MS may improve structural information. According to Waters, its *UNIFI* software platform can orchestrate a complete E&L workflow: “a complete extractables analysis workflow can be undertaken using the Waters UNIFI Application within the waters_connect Software Platform… [to] streamline the analysis of complex datasets” ([4] www.waters.com). In practice, raw chromatograms are processed to a list of features (peaks), which are then filtered by blank subtraction and threshold criteria. Automated compound identification uses spectral libraries and accurate-mass databases, but manual interpretation is often required for unknowns.

Data Processing and Reporting

Analyzing E&L data is extremely data-intensive. A single extract or extract combination may yield hundreds of peaks. Modern data systems are thus essential. Most instrument vendors offer software suites: e.g. Waters’ UNIFI with *waters_connect*, Thermo’s Chromeleon plus Compound Discoverer, Agilent MassHunter with Mass Profiler. These can automatically match observed spectra to built-in libraries. However, specialized informatics platforms have also emerged.

For instance, **Lumetics LINK** software is designed to automate chromatography data reporting. It continuously scans an instrument network for new data files, auto-imports and parses them into a database, and generates standardized reports. As described on Lumetics’ site, LINK “scans network locations for new measurement files, extracts all useful data, and copies this data directly to a centralized database…The powerful analysis user-interface allows datasets to be aggregated, grouped, and visualized…User-customizable analysis templates deliver rapid and error-free data visualization, replicable across many studies” ([17] lumetics.com). In short, LINK can handle the “heavy lifting” of routine E&L data processing. Similarly, Genedata’s Chromatography™ software (part of Genedata Biologics) is marketed for accelerating data analysis across chromatography runs in biopharma; although not specific to E&L, its capabilities (peak detection, alignment, reporting) are applicable.

Chemical safety databases are another key software resource. The *ELSIE Consortium* (Extractables and Leachables Safety Information Exchange) now provides a database of known E&L compounds and safety data, accessible to

members. In a 2023 announcement, ACD/Labs and ELSIE announced a partnership to create “a searchable knowledge repository of pre-competitive data” for E&L research ([18] www.acdlabs.com). This web-based database (in development) will allow scientists to look up compound IDs, source materials, and toxicological data, facilitating the interpretation of unidentified peaks. The emergence of such shared resources represents an industry trend toward collective E&L knowledge.

Specialized software also exists. ACD/Labs’ *Luminata* platform (formerly ACD/Spectrus) can manage analytical data across studies. According to ACD, “Luminata’s ability to be configurable allows it to handle each step within the extractable and leachable process, to store all metadata for each compound found in the study with its corresponding data” ([19] www.acdlabs.com). This suggests that Luminata can link each detected peak in an E&L study to relevant information (e.g. material source, extraction conditions, spectral matches). Such systems essentially function as advanced LIMS (Laboratory Information Management Systems) tailored for the E&L workflow.

In summary, sophisticated data tools have become integral to E&L testing. As LCGC notes, modern E&L analysis “requires advanced instrumentation and novel analytical approaches” ([20] www.sciencedirect.com). Software that automates data import, peak flagging, library searching, reporting, and even compliance-checking (e.g. validating eCTD submission files for E&L content ([21] assyro.com)) can dramatically improve efficiency and reduce manual error. Table 2 outlines some commonly used categories of instruments and software in E&L workflows, with examples:

Category	Examples and Role
Instrument Control & Data Acquisition	Vendor instrument software (Waters Empower, Agilent OpenLab, Thermo Chromeleon) to acquire raw data.
Spectral Library Packages	NIST, Wiley, MassBank libraries for GC–MS/LC–MS identification.
Chromatography Data System (CDS)	Waters UNIFI, Agilent MassHunter, Sciex Analyst to process peaks.
Integrated Platforms	Waters *waters_connect* (networking UNIFI), Thermo Compound Discoverer, Genedata Chromatography™ for multi-run analysis and reporting.
Automated Analytics	Lumetics LINK (auto data import/aggregation), ACD Luminata (metadata management), Intuivysis pipelines (emerging AI workflows).
Databases	ELSIE E&L safety DB, internal compound registries (e.g. Suspect lists from polymer makers).

Table 2: Representative analytical and informatics tools used in E&L analysis workflows.

Each category complements the others. For example, UNIFI (LC–MS processing) may feed results into a reporting template in Lumetics LINK or GEN Data, while compound structures can be cross-referenced against ELSIE. This integrated approach to data is necessary given the complexity of E&L studies. As one practitioner warned, without automation the manual workload can cause critical items to be overlooked, leading to “FDA information requests, delayed approvals, [or] re-testing” ([22] assyro.com).

Regulatory Expectations

Regulatory agencies worldwide have developing formal expectations for E&L control. Given the patient-safety focus, the theme across all guidelines is **risk management**: identify where leachables *could* appear, then demonstrate they are acceptably controlled. The following summarizes key guidelines and standards (see Table 1).

Guideline/Standard	Agency/Region	Focus
ICH Q3E (draft 2025)	ICH (multiregional)	Holistic, risk-based framework for E&L assessment; complements all ICH impurity guidelines (www.ema.europa.eu). Emphasizes characterization of materials and control of leachables to protect patient safety.
USP <1663> (Approx. 2018)	USP (US)	Guidance for *extractables* assessments. Framework for design, conduct, documentation. Emphasizes scientific justification and QRM (no fixed test conditions) ([5] www.drugfuture.com).
USP <1664> (Approx. 2018)	USP (US)	Guidance for *leachables*. Focus on demonstrating packaging/delivery system suitability. Outlines dimensions of leachables studies to ensure safety, but defers specific limits to risk models ([6] doi.usp.org).
FDA Container Closure Guidance (1999)	FDA (US)	First formal guidance requiring demonstration of container closure “integrity” (i.e. no drug loss or contamination) and discussion of extractables/leachables concerns in submissions. Included basic E&L expectations.
FDA Guidance Q&A (2002)	FDA (US)	Q&A clarification to 1999 guidance, including biologics. Addresses specifics like safety thresholds, units of measure.

Guideline/Standard	Agency/Region	Focus
EMA Plastic Packaging Guideline (2005)	EMA (EU)	Requirements for safety testing of *plastic* immediate containers (e.g. simulate aqueous/organic extraction, identify extractables). Covers only plastic, not other materials (www.ema.europa.eu).
ISO 10993-17: Toxicity Assessment	ISO (Int'l)	Biocompatibility: establishes safety limits (PDEs) for leachable chemicals, often used for devices. Not pharma-specific but relevant to drug–device combos.

Table 1: Key E&L-related guidelines and standards (with focus areas). Citations illustrate content where applicable.

In practice, **FDA** has not published a standalone monograph on E&L (apart from container-closure guidance), but FDA reviewers expect E&L data in any New Drug Application (NDA) or Biologics License Application (BLA) involving drug-contact materials. The 1999 guidance said a container-closure system *"should not release chemicals that can accumulate in the drug product in quantities to present a risk of toxicity"* ([23] www.thermofisher.com) (paraphrased from [1]). FDA also participates in ICH; thus the forthcoming Q3E guideline will factor into its recommendations. FDA's Center for Biologics and Center for Devices also refer to E&L when reviewing complex products (e.g. combination devices, single-use bioprocess containers). In 2023, FDA issued draft E&L guidance (as part of ICH Q3E) and related Class III monograph lists to help standardize limits for common leachables, signaling future formal requirements.

EMA and Health Canada similarly look to ICH and USP. The European Medicines Agency points to ICH guidelines and often expects Canadian submissions to include E&L justifications. For example, a 2022 Health Canada guidance on plastic extractables refers industry to ICH and USP concepts. The key principle is that sponsors must *justify* their materials choice and demonstrate that any migrating substances are controlled. EMA has specifically requested a risk-based justification of all product-contact materials in the Chemistry, Manufacturing and Controls (CMC) section ([24] assyro.com). Letting possible migrants go untested or unreported can trigger questions or require submission delays.

Thresholds, Toxicology, and Reporting. There is no single global cutoff number for reporting leachables, but many guidelines suggest triggers based on toxicological limits. For example, the ICH Q3A/B threshold of 0.05% of drug substance (or a PDE-based threshold) is often referenced as a starting point for reporting an extractable. Some agencies accept the Threshold of Toxicological Concern (TTC) approach (e.g. <1.5 µg/day for genotoxic impurities). In USP <1664>, applicants are expected to establish *action levels* for each class of leachable (by risk analysis) and to include any leachables above those levels in stability protocols. Tools like Permitted Daily Exposures (PDE) from ICH M7 (for mutagens) or from published sources (e.g. Safety Thresholds in ELSIE database) are used to benchmark concentrations.

Importantly, regulators expect **system suitability and method validation** for E&L analytics, even though no specific compendial "E&L method" exists. For example, the new USP application note discusses key system checks (e.g. recovery of spiked standards, detection limits) to ensure an instrument platform consistently detects expected leachables ([1] www.usp.org). Similarly, submission dossiers are often queried on how analysts ensure no peaks were missed (e.g. using stable isotope spikes or orthogonal detectors).

CMC Submissions. In an IND/NDA or marketing submission, E&L data typically appear in the CMC section under Packaging/Container-Closure description. Sponsors must **describe the testing** performed (materials, extraction conditions, instruments) and provide results (e.g. tables of identified extractables with concentrations, and leachables found in product stability samples). FDA review divisions often issue information requests if evidence is lacking that all relevant leachables have been assessed. To avoid this, drug developers often engage E&L consultants and CROs early. Documentation must clearly link extractables to leachables ("extractable–leachable correlation") and include toxicology justification for any unknowns above the threshold.

In summary, regulatory expectations for E&L studies emphasize **comprehensive material characterization and control to prevent toxic leachables**. Recent guidelines (draft Q3E, USP) codify a science-driven, patient-safety approach (www.ema.europa.eu) ([5] www.drugfuture.com). Manufacturers should view E&L studies not as a "check-box" but as integral to ensuring product quality, aligning with overall impurity control strategies.

Practical E&L Testing Workflow

Material Characterization

Before testing, all materials are surveyed. The material composition (e.g. polymer type, additives, coatings) is often provided by suppliers or determined via FTIR/MALDI analysis. If a material is known (e.g. polyethylene film, silicone rubber), typical extractables can be anticipated; for example, polyethylene may give long-chain aldehydes and alcohols, while silicones yield cyclic siloxanes. The container and stopper (or delivery device), any adhesives or inks, filters, and even labels are catalogued. This front-end assessment guides which materials need priority testing.

High-risk polymers include polyvinyl chloride (PVC, often plasticized with DEHP or alternatives), polyolefins with long-term hydrolysis potential, and silicone rubbers with low molecular weight siloxanes. Glass is generally inert (though some adhesives on vials can carry chemicals). Elastomers (rubber stoppers, gaskets) are rich sources of leachables (e.g. antioxidants, vulcanization accelerators). **Single-Use Systems** (SUS) in biopharma — complex assemblies of multi-layer plastics — each component is tested. In all cases, trace impurities, by-products of polymer synthesis, and residual monomers must be considered.

Extractables Study

An extractables study is typically performed on each material or material “suite.” A suite might include a kind of plastic tubing (three brands) or the container plus stopper. For each test, a quantified amount of material (by area or weight) is subjected to standard extraction conditions. Common conditions include:

- **Organic Solvent Extraction** (e.g. refluxing with 50% ethanol in water, or pure isopropanol, to simulate worst-case contact).
- **Aqueous Extraction** (e.g. water or saline at 40–60°C) to mimic water-based compatibility.
- **Hydroalcoholic Extraction** for products containing alcohol.
- **Non-Polar Extraction** (e.g. hexane or dichloromethane) to catch nonpolar components like plasticizers.
- **Accelerated Aging** (e.g. 70–90°C water extraction to simulate long-term stability).
- **Static Soak vs. Soxhlet**: Statically soaking the material for days, or continuous Soxhlet extraction, to maximize yield.

It is common practice to extract with multiple solvents sequentially (e.g. water, then ethanol, then CH_2Cl_2). Each extract is then concentrated (often 1–100×) and analyzed by the suite of instrumental methods. Extractables are identified (matching mass spectra or IR signatures), and their amounts reported relative to material quantity (e.g. µg/inch² or µg/kg). Peaks above the AET (analytical evaluation threshold) are candidate leachables.

According to Singh *et al.* (TrAC, 2021), challenges in extractables studies include choosing the right solvents, dealing with insoluble polymers, and the complex identification process ([25] www.sciencedirect.com). Yet extractables are invaluable: they inform the “target list” of compounds to monitor in leachables studies. A substance with a high extractable level is more likely to show up as a leachable; conversely, if an extractable is toxic and at high level, one may modify the material or impose a manufacturing control.

Leak-check and blank runs are critical: an extraction blank (solvent-only) shows any contaminants in labware or environment. Blanks are subtracted in data analysis. Often “packaging system” blanks (e.g. an empty vial extracted) are also run for comparison to leachate extracts, as in the DEP tape case ([7] hero.epa.gov) (where the actual vials had no DEP by GC–MS, proving the tape was the source).

Leachables Study

After extracting, the leachables study attempts to detect migration into the *actual product*. Test samples are the drug formulation in its final container-closure system, subjected to real storage conditions. For parenteral and ophthalmic products, typical intervals might be 3, 6, 12 months (accelerated at 40°C/75%RH and long-term at 5°C, 25°C). For dry products or reconstituted drugs, analogous conditions apply.

High-sensitivity analytical methods are used because leachables are often at trace levels. For example, a leachable might appear at only a few parts per billion in the drug solution. Standard approaches might include:

- **Direct injection or headspace analysis** of the stored drug to capture volatiles.
- **Solid-phase extraction (SPE)** or liquid-liquid extraction of a large volume of liquid product to pre-concentrate organics for LC–MS.
- **Acid digestion followed by ICP–MS** for metals leached into injectables.

All chromatograms from stressed samples are compared to controls (fresh product at time zero) to identify new peaks. Compounds above reporting thresholds are quantified (usually with calibration standards if available, or semi-quantitatively with surrogate standards). Observed leachables are then mapped back to the extractables list for identification (the “extractable–leachable correlation”).

The final deliverable often includes tables of all identified leachables with:

- Chemical identity (structure/name)
- Concentration (µg/day or µg/mL) in the drug product
- Toxicological assessable daily intake (PDE/TTC)
- Qualification status (e.g. qualified by toxicologist, or needed to reduce material)
  Reports typically narrate which extractables were tested, which leachables found, and how any new peaks were addressed.

Reporting and Thresholds

Guidelines generally require reporting *all* identified leachables above the defined threshold, and justification for any that remain unidentified. If a leachable above threshold is not identified, a reasonable structure proposal and justification (e.g. by MS/MS fragmentation) is expected. In practice, well-prepared submissions will identify ≥90% of significant peaks by name or CAS number.

Thresholds often follow a tiered system. For example: leachables above a *reporting threshold* must be listed, while those above a lower *qualification threshold* must have a toxicity assessment. Some sponsors use the ICH M7 approach (classify by mutagenic risk) or route-specific PDEs. USP suggests using “safety-determining levels” based on daily dose and lifetime exposure. In 2021, GrandviewResearch noted that pharmaceutical demand (especially from COVID-19 vaccine manufacturing) has significantly increased the volume of materials tested, implying more E&L data to manage ([26] www.grandviewresearch.com).

System Suitability. Even though E&L studies are not a standard pharmacopoeial assay, regulators expect validated methods. This means the chromatographic and MS systems must be demonstrated to reliably detect low-level impurities. For example, injection of a known E&L standard mix (such as an antioxidant adduct mixture) can show instrument sensitivity and retention consistency. The system’s limit-of-detection should be below the chosen AET. The USP E&L NOTE also highlights the importance of system suitability checks for profiling small molecules ([27] www.usp.org).

Data Analysis and Software Solutions

The **complexity** of E&L data has driven the development of specialized software and databases. Unlike routine assays, E&L produce *"large amounts of analytical datasets and chemical information of all impurities associated with each study"* ([19] www.acdlabs.com). In addition to chromatographic peaks, metadata (batch numbers, extraction conditions, material data) must be linked. Several categories of data tools are now used:

- **Instrument Vendor Software:** Waters' *UNIFI* (for Xevo/QTof instruments) and *Progenesis QI* (non-target LC–MS data analysis) are commonly used for raw peak picking, spectral deconvolution, and library matching. Agilent's MassHunter/Profiler and Thermo's Compound Discoverer serve similar roles. These systems often allow creation of *targeted screens* once key leachables are known (e.g. query scans for known phthalates).
- **Data Management Platforms:** As noted above, eCTD authoring and regulatory review have imposed stringent requirements on labeling and documentation of E&L findings. Companies like **IntuitionLabs** and **Assyro** (though primarily known for document/PAT solutions) also offer platforms to organize CMC data. One Assyro case study guide (Dec 2025) describes an AI-driven "E-Learning Analytics" approach to check regulatory submissions ([21] assyro.com), although such tools are still emerging. However, the screenshots in Assyro's blog indicate the market demand for automated E&L reporting.
- **Branded E&L Databases:** The ELSIE collaboration (mentioned earlier) is the leading example. By late 2023, ELSIE's database (in partnership with ACD/Labs) was being built to provide free listings of known extractables/leachables and their toxicity classifications ([18] www.acdlabs.com). Many companies also maintain in-house "suspect compound lists" compiled from past projects or literature to assist future studies.
- **Statistical and Visualization Tools:** Given multiple timepoints and conditions, E&L data are often analyzed with trend charts and heatmaps. Some labs use general platforms (Spotfire, JMP, or even Excel) to visualize which compounds appear over time or under different stressors. Others adopt chromatography-specific platforms. For instance, the ACD/Labs *Spectrus Processor* allows building "trending" plots of compound areas across samples.
- **Predictive and AI Tools:** As mentioned, PredicDiff™ is a new tool for predicting PERL concentrations from extractable measurements ([9] www.sciencedirect.com). More broadly, machine learning could help in two areas: *peak identification* (e.g. using neural networks to predict fragmentation patterns) and *risk prediction* (associating polymer formulations with likely leachables). While these technologies are nascent, the use of AI for impurity profiling is under active research.

To illustrate the role of software, consider Waters' own description: its UNIFI/waters_connect platform not only acquires data but "customizable workflows streamline the analysis of complex datasets" ([4] www.waters.com). In practice, a chromatographer might set up an automated pipeline: extract raw MS data, flag peaks above noise/AET, automatically match to a spectral library, and generate a report listing compounds with structures and concentrations. Such automation reduces manual review time and decreases the chances of missed peaks.

In the near future, these tools will only become more integrated. Regulatory expectations (e.g. common eCTD gateways) increasingly require structured data submission. For example, the FDA's eCTD validation for E&L might soon check that all required fields (material description, extraction conditions, analytical results) are present and formatted correctly. Automated eCTD validators (some vendors now offer AI-driven validation) will scan CMC sections for E&L content completeness ([21] assyro.com). This means E&L scientists must maintain rigorous electronic records, likely in LIMS, so that data can be quickly retrieved for any query.

Case Studies and Examples

Real-world incidents underscore *why* thorough E&L testing is needed. We highlight two instructive cases from the literature and industry:

- **Ancillary Tape Introduces Phthalate into Ophthalmic Product.** An ophthalmology company found unexpected contamination of a preservative-free eye-drop solution. Routine E&L testing of the primary vial and cap showed *no* plasticizer peaks, yet chromatography of the product revealed significant diethyl phthalate (DEP). An investigation (Singh *et al.*, 2019) traced the source to a roll of adhesive scotch tape used to bundle packaged vials in the stability chamber ([7] hero.epa.gov). The tape's adhesive contained DEP, which volatilized and permeated through the LDPE vial and carton to reach the drug. Remarkably, DEP levels in the drug exceeded safety thresholds. This incident (see [49]) teaches that *any* material contacting a drug (even temporarily) must be considered. Conventional container-closure testing alone had missed this risk until the supplementary tape was identified.

- **Leachables from Silicone Sterilization Tubing.** Mérieux NutriSciences reported a study of extractables from multi-use silicone tubing used in aseptic manufacturing ([28] www.merieuxnutrisciences.com). These tubes were autoclaved repeatedly and came into contact with product streams. Their report emphasizes that "extractables can be obtained not only from the packaging system of the drug product, but also from systems and components used during the manufacturing process… leading to accumulation of process equipment-related leachables (PERLs)" ([28] www.merieuxnutrisciences.com). In other words, compounds from the silicone ("PERLs") were found in an intermediate product after multiple sterilization cycles. Even though the final packaging was glass, the manufacturing line itself contributed leachables. This case illustrates the concept of PERLs and the need for *process-focused* E&L studies.

- **Common Impurities in PVC Systems.** (General example) A well-known scenario involves PVC IV bags. Studies dating to the 1980s and 1990s repeatedly documented migration of di-(2-ethylhexyl) phthalate (DEHP) from the plasticizer into stored solutions ([26] www.grandviewresearch.com). Regulatory limits (e.g. USP <381> for plasticizers) ultimately arose from such findings. Similarly, rubber stoppers have been found to leach phenolic antioxidants and vulcanization accelerators; some branded cases have reported patient adverse events (e.g. phenytoin adsorption by cola-stopper interactions). These classic cases (though not individually cited here) built the foundation for today's requirements.

- **Detection of Siloxanes and Additives.** In silicone-based products (e.g. silicone oil in syringes), extractables studies often find cyclic siloxanes (D_4, D_5) and silanol derivatives. For example, regulatory queries have arisen when siloxanes from syringe lubricants migrate into ophthalmic drugs. Another common leachable is 2-ethylhexanoic acid from HDPE (as noted in early polymer studies, e.g. Depres 2006, though not cited here). Knowledge of such typical profiles helps forensic analysis during E&L.

In all these cases, the lessons are similar: **test broadly, identify carefully, and document thoroughly**. Overlooking any contact material or failing to correlate an extractable with a leachable can lead to missed risk. Regulators expect sponsors to discuss whether any *unidentified* peaks could be toxic or mutagenic. Indeed, Singh *et al.* note there are relatively few published case data, so the industry depends on knowledge-sharing consortia (like ELSIE) to learn from each incident ([29] www.sciencedirect.com).

Data Trends, Statistics, and Market Analysis

The importance of E&L testing is reflected in quantitative trends. Several market research reports have charted rapid growth in the E&L industry. For example, Grand View Research (2024) projects the global **E&L testing services market** will grow from **~$1.13 billion in 2024 to $3.57 billion by 2033** – a CAGR of *approximately 14.3%* ([8] www.grandviewresearch.com). This growth is attributed to expansion of the pharmaceutical and biotechnology sectors worldwide. Notably, the COVID-19 vaccine effort dramatically increased materials use: 2021 saw an estimated **141 billion vaccine doses supplied** globally, nearly three times the 2019 volume ([26] www.grandviewresearch.com). Such massive scale-up of parenteral production (and associated plastics, stoppers, injectors) in turn *boosted the demand for E&L testing services*.

Regional data align with this trend: North America remains the largest market for E&L testing (reflecting the high biopharma activity), with growing investment also in Asia–Pacific pharmaceutical manufacturing ([30] www.grandviewresearch.com). Another report (not fully cited here) echoes that contract research organizations (CROs) offering specialized E&L services have multiplied in recent years due to industry outsourcing of these complex analyses.

Academic research into E&L is also rising. In the past decade, numerous review articles have been published on E&L topics (e.g. Vas *et al.* 2020 ; Singh *et al.* 2021 ([2] www.sciencedirect.com); Cuadros-Rodríguez 2019). Citation databases show a growing number of articles each year. This literature documents advancements but also underscores data gaps:

for instance, Singh *et al.* note that “the amount of publicly available literature and data is still limited, and more publications are highly needed…reviews to aid understanding of this field” ([29] www.sciencedirect.com).

On a practical note, technology metrics show that high-resolution MS instruments and advanced chromatography systems (UHPLC, GC×GC, Orbitrap/Tof, etc.) have become virtually standard equipment in major pharma labs to support E&L work. Software adoption is similarly increasing: the Lumetics LINK platform, Waters Connect, and Luminata have all reported new installations by global pharma over the last few years. Moreover, databases are expanding: the Harmonization Center for Standards (CPhI) and events like Pittcon have hosted E&L software showcases and poster sessions (e.g. PredicDiff at Pittcon 2024).

Collectively, these data suggest E&L is a rapidly growing, highly technical niche. Companies and regulators are allocating significant resources to it, reflecting its centrality to patient safety in the modern pharmaceutical landscape.

Discussion and Future Directions

The field of extractables and leachables is **evolving quickly**. Regulators are actively refining expectations, and science/technology is advancing in tandem. Key future implications include:

- **Emerging Guidelines:** The most immediate regulatory driver is the finalization of ICH Q3E. Once adopted (expected 2026), Q3E will harmonize expectations across US/EU/Japan: sponsors will need to frame E&L risk in line with general ICH impurity guidance (i.e. extend Q3A/B/C/D principles to packaging materials). Draft documents and commentaries (made public in 2025 (www.ema.europa.eu)) indicate that certain leachables (Class 1 and 2 in ICH Q3D sense) will require strict controls. Industry will have to prepare for changes such as more stringent Analytical Evaluation Thresholds, new qualification criteria, and mandated documentation.

- **Integrated Risk Management:** Following Q3E’s risk-based ethos and USP guidance, we expect a continued shift towards Quality-by-Design in packaging. Packaging material selection will be pre-validated with known extractable profiles. Real-time release strategies (RTRPs) might incorporate E&L considerations, such as routine headspace checks on in-process drug. The concept of “control strategy” in QRM will increasingly include parameters tied to extractable sources (e.g. specifying polymer grade, setting acceptance criteria for residual monomers).

- **Advances in Analytical Chemistry:** The frontiers of E&L analysis are moving toward even more sensitive and selective methods. Ultra-high-resolution MS instruments (with 21-Tesla magnets, for instance) are beginning to enter labs, potentially enabling detection of leachables at sub-ppt levels. Hyphenated 2D chromatographic systems (e.g. GC×GC–Tof, or 2D-LC–MS) can better resolve coeluting extractables. Ambient ionization techniques (DESI-MS, DART-MS) may allow rapid surface screening of materials without solvents. Detection of non-organic leachables is also broadening; e.g. emerging methods for extracting and detecting nanocellular fragments from polymers (micro/nano particulates as leachables) are being explored.

- **Artificial Intelligence and Modeling:** As mentioned, predictive tools like PredicDiff are pioneers in using modeling for E&L. We predict more computational aids will appear: machine learning algorithms could be trained on known polymer/leachant pairs to predict likely extractables for a new material. AI could assist in unknown identification by suggesting molecular formulas or structures from spectra with greater speed. Regulatory acceptability of such tools will grow if they demonstrate reliability. These models could eventually allow *in silico* screening of packaging options to minimize high-risk leachables before physical testing.

- **New Materials and Single Use:** The rise of biopharmaceuticals and single-use bioprocessing means an explosion of novel polymers and additive packages entering drug production. Each new material (such as co-polymers, barrier films, engineered elastomers) brings unique extractables. There is active research (by consortiums like ELSIE) on emerging concerns: for example, trace metals from 3D-printed spoolers or organic photoinitiators from UV-curable polymers used in device manufacturing. Some of these may become regulatory focus, driving new sub-guidelines or monographs.

- **Sustainability and Recycling:** A future challenge will be aligning E&L safety with sustainability goals. Recycled materials may introduce unknown impurities. Regulatory agencies will need to issue guidance on using recycled plastics in pharma. Historical E&L models did not fully consider this — moving forward, recyclate-based extractables must be studied.

- **Global Harmonization:** With Q3E, the expectation is a single set of standards for major markets. However, regional variations may persist. For instance, some Asian regulators may impose extra guidelines (China’s NMPA often issues local variants). Pharmaceutical companies will need global E&L strategies to satisfy all jurisdictions. Efforts by WHO for prequalified products also involve E&L data for generic vaccines and biologics.

- **Implications for Patients and Society:** Ultimately, strengthened E&L practices should translate to safer medicines. We expect increasingly transparent risk communication: patient leaflets for certain drugs already mention packaging-related risks (e.g. leached phthalates). Post-marketing surveillance could start to monitor for unusual adverse effects that might hint at E&L issues. Social media and patient advocacy groups sometimes raise concerns (e.g. about phthalates or metal leachables). The industry will need to respond with clear science-based messaging as E&L knowledge becomes more public.

Conclusion

Extractables and leachables studies sit at the intersection of analytical chemistry, materials science, and patient safety. This report has provided an in-depth overview: from basic definitions and workflows to advanced data analytics and future trends. Key messages include:

- **E&L are critical for drug safety.** Pharmaceutical systems must ensure no harmful contaminants migrate into products ([2] www.sciencedirect.com) ([1] www.usp.org). This requires systematic extractables profiling and sensitive leachables monitoring.
- **Regulatory frameworks are evolving.** Global guidances (ICH Q3E, USP <1663/1664>, FDA guidances) now converge on risk-based evaluation and justification. Sponsors should proactively engage with these guidelines and align their E&L programs accordingly (www.ema.europa.eu) ([5] www.drugfuture.com).
- **Analytical and data tools are advancing.** Cutting-edge instruments (HRMS, 2D chromatography) combined with powerful software (Waters, Luminata, ELSIE databases) are needed to manage the complexity. Automation and AI promise further efficiency and insight ([4] www.waters.com) ([9] www.sciencedirect.com).
- **Comprehensive testing is non-negotiable.** Case studies remind us that any overlooked material contact can become a leachable source. Manufacturers must include *all* product-contact materials in their E&L design to avoid surprises (as in the tape/DEP case ([7] hero.epa.gov)).
- **Future is data-driven.** We predict greater use of predictive modeling, shared E&L databases, and possibly real-time monitoring to replace batch-wise studies. As the field matures, standardized E&L databases may allow *in silico* risk screening like substitutable excipient databases do today.

In conclusion, the science of extractables and leachables is maturing quickly. Pharmaceutical companies should treat E&L programs as strategic enablers of product quality. With strong analytical design, collaborative safety assessment, and adherence to evolving regulations, the industry will continue to protect patients from unintended material leachates. Continued research (both experimental and computational) and international cooperation (through ICH, pharmacopeial, and consortium efforts) will drive progress. This report, drawing on a broad literature and guidelines, aims to equip stakeholders with the detailed knowledge needed for robust E&L programs now and into the future.

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