Q&A

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Extractables and leachables (E&L) studies play a pivotal role in ensuring the safety and regulatory approval of drug products. Yet, recent FDA data show how often companies stumble: 202 Complete Response Letters (CRLs) issued earlier this year showed that nearly one in five cited E&L-related deficiencies. To better understand why this happens and what developers can do to avoid these pitfalls, we sat down with Christopher Latendresse, Ph.D., Director of Analytical Services at the Solvias E&L Center of Excellence in Canton, Massachusetts, who shared his expertise and practical guidance for drug developers.

Q What are the key factors that influence the presence of E&L in a drug product?

E&L levels are shaped by three main elements: the materials in contact with the formulation, the drug product itself, and the conditions that they go through throughout their lifecycle. For example, many of the elastomers and plastics used in rubber stoppers, syringe plungers, IV bags, tubing, and single-use systems contain additives that can migrate into a formulation. Drugs with extreme pH, high organic (e.g. ethanol or surfactant) content, or complex biologic and cell- or gene-therapy compositions tend to have higher leaching propensity and therefore pull compounds from contact materials more readily. Process and storage conditions further influence E&L. Heat, long storage times, shipping stress, and sterilization methods can all accelerate the breakdown of polymers and increase extractables. These effects are even more pronounced in formats with a high surface-area-to-volume ratio, such as syringes and autoinjectors.

Q Do E&L risks differ across small molecules, biologics, and cell & gene therapies?

Yes, because each class of product interacts differently with the materials in its container or manufacturing system. For small molecules, the primary concern is typically chemical aggressiveness. Many small-molecule formulations contain organic solvents, surfactants, or extreme pH conditions that can extract a wide range of compounds from plastics, elastomers, and adhesives. Because these formulations tend to be relatively stable and well-characterized, E&L studies often focus on predictable interaction pathways and well-defined toxicological thresholds. With biologics, the risk shifts toward sensitivity rather than aggressiveness. Proteins, peptides, and other large molecules are highly susceptible to even trace levels of leachables, which can trigger aggregation, unfolding, loss of potency, or unexpected immunogenicity. Additionally, biologics often rely on single-use systems during manufacturing, which introduces many polymeric materials that need thorough extractables evaluation. For cell and gene therapies (CGT), E&L risk is even more complex. CGT products are extremely sensitive, and even very low levels of leachables can impact cell viability, vector integrity, transduction efficiency, or overall therapeutic performance. Because CGT workflows rely heavily on multilayer bags, single-use assemblies, and novel packaging formats, understanding the extractables profile of each component becomes mission-critical.

Q What technologies are the best for E&L studies?

Chromatographic systems with high-resolution accurate-mass (HRAM) spectrometers are exceptionally well suited for E&L studies. They can detect and quantify impurities at trace levels while providing the detailed structural

information needed to match those impurities against known compounds in databases. In addition to publicly available resources, Solvias has built an extensive proprietary E&L-specific database with more than 6,000 compounds, enabling us to identify more than 99% of the unknown compounds detected. In practical terms, that means almost every peak observed in a chromatogram can be confidently matched to a specific chemical entity. From a regulatory standpoint, this level of identification accuracy is a major advantage. Submissions require clear, defensible knowledge of what E&L are present and their toxicological relevance. When nearly all unknown peaks can be structurally identified, it eliminates ambiguity, strengthens the safety assessment, and significantly reduces follow-up questions from regulators.

Q Where do you see the most common E&L pitfalls among developers?

Our recent analysis of 202 FDA Complete Response Letters issued earlier this year revealed that E&L issues remain a major stumbling block for developers: 18% of CRLs cited E&L deficiencies, and most fell into just a few recurring pitfalls. The biggest problem is unknown compounds above regulatory thresholds. About 60% of E&L-related CRLs were triggered because developers could not identify compounds that exceeded Safety Concern Thresholds. Proper identification often requires high-resolution accurate mass spectrometry and large, specialized databases — capabilities many teams or generalist labs lack. The second major pitfall is inadequate toxicological risk assessment. Even when compounds were identified, developers frequently misapplied thresholds or provided incomplete toxicology justifications. Two additional trends stood out: many sponsors start E&L testing too late, discovering issues only in late-stage development when fixes are costly and delay approval; and others rely on generic, one-size-fits-all testing strategies that don't reflect the specific risks of their formulation, route of administration, or materials. Regulators increasingly expect tailored, product-specific E&L strategies, not templates.

Q What makes an E&L package submission-ready?

A successful regulatory-compliant E&L package should typically contain: **(1)** a study protocol inclusive of design justification (aligned with applicable regulatory guidance, e.g. USP <1663>, <1664>, PQRI, FDA/EMA guidance); **(2)** analytical methods validated or qualified as appropriate for suitability of use, inclusive of detection and quantitation approach; **(3)** detailed list of E&L compounds, including identification and concentrations; **(4)** toxicological risk assessment of E&L compounds based on appropriate thresholds (AET, SCT, PDE evaluations); **(5)** program summarization: leachable-to-extractable correlation for quality control and outcome of toxicological risk assessment for patient safety.

Q Any recent regulatory changes affecting E&L strategies?

Several regulatory documents govern E&L studies, most notably USP <1663> and USP <1664>. While these chapters have not been updated in recent years, the United States Pharmacopeia has introduced a series of newer standards that more clearly define expectations for plastic and elastomeric packaging materials. USP <665> is one of the most significant developments. Scheduled to become effective on May 1, 2026, this chapter outlines how polymeric and single-use manufacturing components — such as bags, tubing, connectors, and filters — must be characterized through risk assessment and extractables studies. This is especially impactful for biologics and cell & gene therapies, where reliance on single-use systems is the norm and E&L risks are tightly linked to patient safety.

Q At what point in development should drug developers begin thinking about E&L?

Integrate E&L studies into container-closure and formulation decisions at the earliest stages as phase and risk appropriate. Typically, this could be once container-closure and formulation modification are unlikely, but initial studies may be leveraged to select container closure from multiple options. Early detection enables corrections before issues become costly or turn into regulatory liabilities that delay your path to market.

Q One key tip for teams planning their first E&L study?

Partner with an experienced analytical lab. Many of the companies that come to us do so after receiving a CRL that could have been avoided. At Solvias, we've built more than 20 years of E&L expertise with no CRLs issued on any E&L packages we've supported. That track record comes from combining advanced technology with a risk-based, regulatory-aligned approach, and from working as true partners with our clients, embedding E&L planning into their development strategy rather than treating it as a late-stage obligation. The bottom line: well-designed E&L studies are a competitive advantage that supports safety, compliance, and ultimately speed to market.