The True Cost of Inadequate Extractables & Leachables Testing

White Paper

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Executive Summary

Extractables and Leachables (E&L) studies are critical analyses conducted when developing a pharmaceutical product. These studies assess the potential for chemical compounds to migrate from containers, closures, and other packaging into the drug product. Therefore, E&L assessments are vital to ensure patient safety and consistent product quality. E&L studies are often underappreciated in the drug development process. While a generic, one size fits all approach may provide a superficial understanding of potential chemical interactions, it frequently falls short in identifying all E&Ls. In this white paper, we cover the risks and true cost of inadequate E&L testing.

What are Extractables & Leachables?

Although often used interchangeably, “extractables” and “leachables” reflect two distinct concepts. Extractables refer to the substances that can be extracted from containers, closures, or other packaging by means of solvents or through stressed conditions (temperature, pH, exposure time). Extractable studies are meant to identify all compounds that could potentially leach into a product, enabling foresight into potential issues with the chosen containers, closures, or other packaging. This is done by measuring the accumulation levels of detected substances over the shelf-life of a product. Leachables testing, however, mimics expected storage conditions and assesses if chemical compounds might be released from the containers, closures or other packaging have in fact leached into the drug product.

Extractables are substances that can be extracted from containers, closures, or other packaging by means of solvents or through stressed conditions.

Leachables are chemical compounds that leach into the drug product from the containers, closures, or other packaging because of direct contact with the formulation.

Ultimately, data collected from E&L studies will enable pharmaceutical manufacturers to select appropriate packaging components (e.g., container-closure system, single-use systems) and ensure that the drug remains safe and potent for the duration of its shelf life. As a result, comprehensive detection of substances is essential to reduce the risk of contamination and safety problems.

The Most Common Refusal Reasons According to the FDA

The U.S. Food and Drug Administration (FDA) does a thorough examination of the data submitted as part of the application for drug approval and marketing authorization. The agency issues a Complete Response Letter (CRL) in situations where the application cannot be approved in its current state. The letter outlines key issues that need to be addressed before the drug can be approved.

Providing a rare inside look, the FDA analyzed 103 refusal-to-file letters spanning from 2008 to 2017 finding 644 refusal reasons. Although only 15% of sponsors disclosed these letters publicly, with a mere 5% revealing the outlined reason of the letters, the most common refusal reasons related to chemistry, manufacturing, and controls with 125 reasons. Almost 50% of these cases stated applicants had deficient or required new CMC processes.

While the specifics of CRL often remain elusive, we were able to identify 8 CRLs issued in the last 10 years which highlight concerns related to E&L studies. These documented regulatory rejections stemmed from inadequate E&L study design and characterization, a lack of validation or documentation, ultimately causing preventable delays.

644

refusal reasons in 103 refusal-to-file letters spanning from 2008 to 2017

125

CMC-related refusals

50%

of CMC-related refusals stated applicants had deficient or required new CMC processes

The Aftermath of a CRL

Receiving a CRL inevitably leads to a delay in a product's market launch, thus carrying significant financial implications. Consequences include the risk of a significant decline in company shares and the possibility of incurring substantial financial losses. The average period between the receipt of the CRL and the subsequent market authorization was around 17 months. As per findings from the University of Texas[1], “delays in drug approvals cost their creators an average of $1 million a day”, corresponding to a potential loss of over $500 million.

Reduce the Risk of Receiving a CRL

Investing in comprehensive E&L studies significantly reduces the risk of receiving a CRL. By tailoring the study to the specific materials, formulations, and particular conditions, a deeper understanding of potential risks and interactions is achieved. Conducting robust E&L studies fosters confidence in regulators, it demonstrates a genuine commitment to avoiding potential toxicological risks. Through diligent research you ensure product safety and regulatory compliance by assessing and proactively managing and mitigating risks. Presenting solid evidence to regulators ultimately increases your odds of expediting the approval process, permitting timely commercial distribution. In contrast, incomplete or inadequate E&L studies will raise concerns about product safety, thereby increasing the likelihood of receiving a CRL from authorities.

1) Dannenmaier, M. (2020, June 19). Old Drug Standards Delay New Drug Approvals. UT News. https://news.utexas.edu/2020/06/19/old-drug-standards-delay-new-drug-approvals/

Trusted Solutions

Keep Pace with the Ever-Tightening Regulatory Demands

In recent years, the biopharmaceutical manufacturing landscape has witnessed a notable shift towards the use of 'high-risk' materials, innovative packaging solutions, and advanced manufacturing practices such as single-use systems. This transformation has garnered increased attention from the FDA, prompting a heightened need for extensive E&L assessments. Through various discussions, it has also come to our knowledge that regulatory bodies occasionally request E&L studies to be initiated at earlier stages in the development process (e.g., Phase I/II). In such instances, the initiation of clinical trials is contingent upon the completion of these studies.

This evolving regulatory landscape underscores the critical importance of proactive and thorough E&L assessments to ensure compliance and facilitate the timely progression of biopharmaceutical product development. Therefore, with a primary focus on patient safety, the importance of E&L studies cannot be overstated, and regulatory requirements will likely only grow more rigorous in the future. To this end, a well-designed and comprehensive E&L study not only reflects commitment to safety and quality but will greatly minimize reduce the risk of receiving a CRL and impacting the company financially.

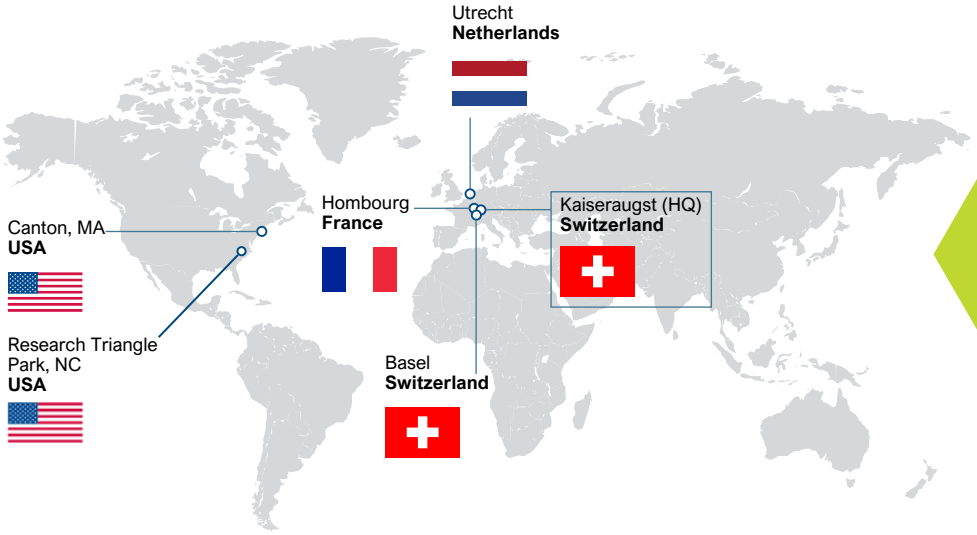
Ensure full regulatory compliance

When partnering with Solvias, anticipate receiving expert guidance, dedicated project managers, and a commitment to scientific rigor facilitating a seamless path to market. Our subject matter experts provide a consultative tailored approach to meet challenging low detection limit requirements. In fact, Solvias' experienced analysts have routinely performed hundreds of successful E&L studies over more than 20 years, with no regulatory observations or CRLs issued. With a proprietary database of over 6000 compounds, we illuminate the unknowns with a 99% success rate.

In summary, with Solvias' impeccable track record, we stand as your ideal partner and are uniquely positioned to expertly guide you through the intricate regulatory landscape of E&L studies and help execute comprehensive E&L assessments towards ensuring full regulatory compliance.

Why partner with us?

- CDMO/CRO
- Founded in 1999
- 800+ team members
- 175+ PhD-level scientists
- GMP, GLP, ISO9001 certified
- 22.5K sqm of lab capacity
- 700+ customers worldwide
- 6 centers of excellence



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