Extractable and leachable (E&L) testing determines whether unwanted and potentially harmful compounds are pulled out of a product’s packaging, delivery system, or manufacturing surface under certain conditions (extractables) or passively migrate into a product over time (leachables). As part of the US FDA guidelines, all drug products in development must be submitted to the FDA for approval, which includes a review of E&L testing.

For years, the FDA focused its attention with respect to E&L testing on drug products that are considered a high risk to consumers, such as inhalation aerosols and sprays. In recent years, the agency has become increasingly strict about which types of drug product submissions require E&L testing, and the focus has shifted to include low-risk products such as oral tablets and capsules. This can also include manufacturing components that may have only transient contact with the product during manufacturing, such as tubing, hoses, gaskets, and stainless steel holding tanks, and may even include post-manufacturing exposures.

This increased vigilance is partly due to improving drug safety standards, but also to some high-profile contamination cases. In 2011, Ortho-McNeil-Janssen Pharmaceuticals recalled 40,000 bottles of tablets after consumers reported that the product gave off an “uncharacteristic odor.” The company found that its suppliers were using wooden pallets contaminated with 2,4,6-tribromoanisole (TBA), a byproduct of a chemical preservative often used to treat wood. In spite of the drug product’s packaging, the TBA had seeped through the cartons, product boxes, and bottles into the tablets themselves.

This kind of post-manufacturing storage process is one that had previously been ignored, along with most other non-packaging-related materials in the manufacturing chain. Ten years ago, it would have been surprising to hear that the FDA had asked about E&L studies on stainless steel holding tanks. Today it is commonplace.

Navigating this ever-changing E&L landscape can be difficult for pharma companies, especially when the FDA can find issue with E&L testing methods without precedent. It can cost a great deal of time and money to submit a product for FDA review, only to learn that the agency now requires E&L testing for a new part of the process.

Although the risk that a manufacturing component will contaminate a drug product is low, it is still important to take precautions. Now that the FDA is paying attention to low-risk aspects of product manufacturing, companies must learn how to perform testing and institute controls on warehousing and manufacturing components to avoid findings that may extend a product’s time to market.

Often, companies become aware of a change in FDA expectations when they receive a new finding indicating that they did not test an area that the FDA now expects. To respond to the finding, the company must perform the missing tests, often in a compressed time frame. Many companies turn to CROs to ensure that the work is completed quickly and correctly, even if the costs are significant.

To offer the highest standard of E&L testing, pharmaceutical CROs must offer capabilities that most pharmaceutical companies do not possess and must have polymer experts on staff to interpret results and identify unknowns. They must have toxicologists to perform safety assessments and metals analysis laboratories to perform E&L testing on stainless steel tanks, transfer lines, and pipes. Further, the CRO must be able to perform USP 232/233 testing to check for elemental impurities in its clients’ drug products and should have extensive knowledge of the additives likely to be found in commercially available plastics. These types of expertise are fundamental to quickly identifying contaminants in E&L studies.

The FDA’s quality standards for E&L testing will continue to evolve, requiring CROs to hire employees with a diverse range of expertise. CROs experienced at working with manufacturing materials in a variety of contexts bring an essential perspective to E&L testing for drug development. T&C

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