Recent updates to guidances help standardize extractables and leachables testing

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Risk assessment for extractables and leachables (E&L) contained in polymeric manufacturing components is an important step to evaluate patient safety. In medium to high risk applications, testing for extractables by using solvents that simulate the worst case is the first step to determine what the potential leachables are. If patient safety cannot be demonstrated under these conditions, then evaluating leachables, substances that migrate under typical conditions, may be required. Leachables studies are critical for the pharmaceutical and medical device industries where packaging safety and toxicology studies are required for product registration. Risk assessment is becoming more standardized, and this trend is being driven by the evolving industry guidances on E&L for single-use manufacturing, an approach that has become quite common in the pharmaceutical industry.

The challenge posed by single-use systems

Single-use manufacturing systems are for the most part made from plastic materials and can be used to replace many of the fixed stainless steel components that previously predominated process equipment. The transition has facilitated a more flexible way of manufacturing pharmaceuticals and led to the current hot topic of continuous manufacturing. It allows rapid switching between different products in the same manufacturing suite, simply by exchanging one module for another once a run is complete.

However, single-use systems come with their own challenges, notably extractables and leachables. A safety assessment must be performed to ensure that leachables coming from the polymeric materials and contacting the drug product do not negatively impact patient safety. Leachable substances also have the potential to impede a drug's efficacy or cause production issues. For example, a breakdown product of the secondary antioxidant Irgafos 168, found in polyethylene-film based bags, has been discovered to inhibit cell growth.

E&L testing: The regulatory expectations

Although formal guidelines for E&L assessments have not yet been enacted for single-use systems, there is nonetheless a regulatory expectation that researchers will test for these potentially harmful contaminants. Agencies such as the FDA's Center for Biologics Evaluation and Research recommend a risk-based approach to evaluation. As discussed, the purpose of evaluating extractables & leachables is to demonstrate patient safety with respect to the identity and quantity of potential leachables in the final drug product and their potential toxicity to patients. The purpose is not to test every material that comes in contact with the product during the manufacturing process, but to evaluate the risk and perform extractables testing based on the risk assessment. The risk assessments published both by BioPhorum and in the USP <1665> draft *Characterization of Plastic Materials, Components, and Systems Used in the Manufacturing of Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products*, evaluates criteria including temperature and duration of contact, chemical nature of the process stream, materials of construction, and distance to the final drug product/clearance steps.

The guidances are converging

Over the last few years, the implementation of specific extractable protocols for single-use manufacturing systems have been based on two main efforts: the BioPhorum protocol and the USP <665> draft for fluid-contact plastic components used in pharmaceutical processing, which should be finalized by the end of 2021. Both of these guidances have recently been updated to more closely align their test conditions and extraction solvents—a standardized approach helps suppliers to simplify risk assessment. Our Emprove® Program has already been updated to provide comprehensive extractables data for filters and single-use components following the most recent guidelines.

The BioPhorum protocol updated in April 2020 has reduced the number of extraction solvents to water for injection, 50% Ethanol, 0.1 M phosphoric acid, and 0.5 N sodium hydroxide. This overlaps with the USP <665> draft, which was updated in September 2020, except for the USP's recommendation for a less caustic 0.1 M phosphate buffer solution at pH 10.

Reference materials for E&L testing

Reference standards may be used for a variety of purposes, for example to calculate a relative retention time, ascertain system suitability, determine accuracy and identify impurities. It is preferable to use reference materials that are certified to quantify a specific extractable compound by a response factor or a calibration curve.

Given the number and chemical diversity of extractables, it is unreasonable to expect that authentic reference compounds will be available to confirm each and every identification. It is therefore necessary that levels of identification confidence be established and appropriately utilized. Data typically available from GC/MS and LC/MS analyses are used to identify individual extractables. Certified reference materials can streamline this identification process, especially for priority substances of toxicological concern. These materials are commercially available as individual compounds or as mixtures of a larger number of common extractables.

Browse our certified reference materials

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