Extractables and Leachables Testing for Medical Applications

By Michael Ruberto, Ph.D. Material Needs Consulting, LLC

About Impact Analytical

Impact Analytical is a contract analytical testing laboratory that provides testing for four main sectors: specialty chemicals including polymers and silicon materials, medical devices, pharmaceuticals, and agricultural products. Impact Analytical provides release testing, R&D support, method development and validation, extractable/leachable studies, stability studies, actives quantitation, raw materials testing, problem solving, and competitive analysis. Impact Analytical is ISO 9001:2015 certified, DEA licensed, FDA registered, cGMP and GLP compliant.

Introduction

The materials used to fabricate container closure systems (CCS), medical devices, and processing equipment are often polymers, such as plastic or elastomers (rubber), as opposed to the traditional metal or glass. Polymers offer more versatility, since they are light-weight, flexible and much more durable than their traditional counterparts. Additives can be incorporated into polymers to give them clarity that rivals that of glass or to add color to the materials which could be used as a form of labeling or coding of various types of processing components. However, given all of the positive attributes that polymers possess, there are also some negatives to consider when working with them in medical applications. In the presence of heat, light, oxygen and various external influences, such as sterilization, polymers can degrade over time if not properly stabilized. This degradation can manifest itself as cracking, discoloration, or surface blooming/exudation and can severely impact the mechanical properties of the polymers. Stabilizers, which are a type of additive, are incorporated into the polymers to prevent this degradation. Yet this results in a more complex formulation than typical metal and glass, and makes materials such as plastic and rubber much more prone to leaching unwanted chemicals into the drug product formulation when they are used in applications such as manufacturing, drug delivery devices, or packaging. This does not in any way mean that these materials should not be used in these applications. In fact, their benefit greatly outweighs their risk. However, the risk must be managed.

Successfully Managing the E&L Risk

The extent to which chemicals will leach from various substrates is governed by the principles of thermodynamics and kinetics. Therefore, the conditions of contact or exposure to various types of drug formulations can greatly influence the rate of migration. As would be expected, solids generally are less prone to leachables than liquids. The pH, polarity, and ionic strength of liquid drug formulations can increase the rate of leaching if there is an interaction with the material used to make the packaging or processing equipment. For example, the polarity of the formulation might cause swelling of the material which would increase the migration rate of leachables. The rule of "like dissolves like" also applies, so aqueous buffers of higher ionic strength can be expected to cause a preferred leaching of inorganics from polymers, glass, or metals. Higher temperatures, more surface area, and longer contact time will also increase the kinetics and push the thermodynamics in favor of greater leachability.

Leachables are defined as chemical entities that migrate into the final drug product formulation from primary and secondary packaging as well as from processing equipment used in the manufacturing of the drugs. Depending on the toxicity of the chemicals, they can present a significant safety risk to the patient. Leachables can also interact with the active pharmaceutical ingredient in the drug formulation thereby reducing the efficacy of the drug. Therefore, the risk from leachables is twofold: patient safety and drug compatibility. A service to the pharmaceutical market that includes a combination of consulting and testing has developed to evaluate packaging materials, medical devices, and processing equipment for leachables.

The testing involves the conducting of "leachables studies" which monitors the migration of chemicals from these systems during normal usage or interaction with the drug. For example,

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a leachables study for a container closure system is performed on the drug in its final commercial packaging and is often run in parallel with stability studies. Another set of testing called controlled extractables studies is also performed in addition to the leachables studies to predict the worst-case possible chemicals that can potentially migrate into the drug product. The extractables can be considered as target compounds to analyze for in the leachables testing. This extractables study is performed under exaggerated conditions of time and/or temperature in the laboratory using common, neat solvents that bracket the solvating power of the drug. A third type of testing, known as routine extractables studies, is the quality control evaluation of new batches of packaging components and is conducted periodically based on the risk associated with the presence of leachables in the drug. Factors that are used to determine this risk include type of material, dosage form, route of entry into the body, and patient population.

These three types of studies: controlled extractables testing, leachables testing, and routine extractables testing are the responsibility of the pharmaceutical company that is marketing the final drug product. However, portions of the E&L testing can also be performed by the vendors that manufacture the packaging or processing components as well as contract manufacturing organizations that synthesize and distribute the drug or portions thereof, such as the active pharmaceutical ingredient or excipients. Designing a study plan can often be a challenge depending on the nature of the drug and complexity of the packaging system or manufacturing component. For example, a CCS that also delivers the drug to the patient, such as an inhaler or pre-filled syringe has many more components to evaluate for extractables and leachables than a simple vial with a closure. Years of expertise and familiarity with the materials, testing “best practices,” and global regulations are usually required.

The recognized “best practices” vary slightly by application:

- CCS and Packaging
  - Product Quality Research Institute (PQRI1,2)
  - United States Pharmacopeia <661.1>, <661.2>, <1663>, and <1664>
- Disposable Processing Equipment - BioProcess Systems Alliance (BPSA3)
- Medical Devices - ISO 10993 Parts 12, 17, and 18

A thorough E&L testing program is considered to be standard practice by the FDA’s Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH) for these medical applications. Therefore, knowledge of this sort is quite valuable and can lead to efficiently conducted E&L testing programs that result in well-characterized packaging, devices, and processing equipment. Sophisticated laboratory instrumentation is essential for quantitatively analyzing trace levels of these extractables and leachables in very complex drug matrices. The extracts are typically screened for volatile, semivolatile, non-volatile, and inorganic based extractables and leachables using techniques such as head space GC/MS, direct inject GC/MS, LC/MS, and ICP/MS. The benefits of partnering with the correct contract testing lab can shorten the time to market for a new pharmaceutical product as well as ensure a sustainable supply chain for the packaging and/or manufacturing components.

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Conclusion

A thorough understanding of the mechanical and physical properties of the polymers used to construct packaging, devices, and processing equipment as well as the chemistry of the additives used in their formulation is essential for successfully designing the appropriate extractables conditions that will accurately predict the “worst case” leachables for these medical applications. This materials-based approach will also facilitate the analysis of the extracts and the quantitative identification of all extractables and leachables. Following the industry recognized “best practices” for E&L testing as described above will also help to meet the expectations of regulatory bodies, such as the FDA, as well as help to control the supply chain for the components used to fabricate these CCS, devices, and manufacturing equipment. Partnering with a contract laboratory that has the materials and regulatory knowledge can substantially reduce the time to market for new drugs and devices.

References

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