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Focus on Detecting Extractables and Leachables in Drug Products to Improve Patient Safety and Avoid Costly Product Launch Delays

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Well-documented incidents of contaminants leaching from containers and packaging has brought heightened awareness of the health risks posed by extractables and leachables in the manufacture of pharmaceutical container systems and product packaging. In fact, the U.S. FDA and the EMEA are now placing increased scrutiny on potential extractables and leachables in drug product container and closure systems.

Any pharmaceutical packaging and container system — everything from glass and plastic bottles to foil pouches and the ink used in labels and packaging materials — has the potential to leach unwanted contaminants into a drug product. While orally inhaled and nasal drug products (OINDP) and parenteral and ophthalmic drug products (PODP) generally present a higher risk for extractable and leachable contamination, volatile/semi-volatile and non-volatile extractables and leachables can be released or migrate from any drug product container and closure system. As a result, the FDA requires manufacturers to identify and quantify contaminants in all drug products at release and on stability.

With this in mind, savvy pharmaceutical product management teams are elevating the importance of packaging and container system development. Product packaging and container systems can no longer be an afterthought in product development. Manufacturers must consider packaging as early as possible during the drug development process to avoid costly delays in delivery of the finished product. If a safety issue due to extractables and leachables is not identified until the late stages of product development, the manufacturer will likely experience delays in product development, regulatory reviews and market launch. These delays almost always carry a high cost to the manufacturer.

Meeting the Challenge

Analytical methods are needed to detect leachables in drug products. The first step toward developing analytical methods for leachables is to identify the extractables that could become leachables by doing extraction studies. Extraction studies are designed to simulate both intended-use and “worst-case-scenario” models to identify the extractables and leachables that could migrate into

the drug product. Analytical methods are then developed with the sensitivity to detect the leachables in the drug product at the threshold determined by the toxicity of the leachable. Analytical methods for leachables are validated in a way similar to methods intended to evaluate the stability of the drug product. Leachable analysis can then be used in the long-term stability studies or in migration studies designed to specifically evaluate leachables.

NSF Health Sciences offers extractables and leachables testing and analysis in support of pharmaceutical and bio-medical device manufacturers. But before understanding the value of these services, it’s important to fully understand the dangers that extractables and leachables present to manufacturers and patients.

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Understanding Leachables

Leachables are compounds that migrate into a drug product from the sample container closure (SCC) system under normal storage conditions. Both the primary SCC in direct contact with the drug product (metered dose inhaler, prefilled syringe, eye dropper, IV bag, HDPE bottle, LDPE ampoule, etc.) and the secondary SCC, which does not contact the drug product (printed label, cardboard box, foil pouch, environmental exposure, etc.), can be sources of leachables. These leachables present a potential risk to the patient both from the toxicity of the leachable and from the possible negative impact upon stability and efficacy of the drug product.

Although many types of materials can be used in a primary SCC system, the three most common are glass, polymers and elastomers. One may expect the manufacturer of any component of an SCC to be able to provide a complete list of the formulation and process used to manufacture the component, but this is not always be the case. The two main reasons for manufacturers not providing this information are:

1. The manufacturer may consider the information to be proprietary or the manufacturer may not have the information.
2. The manufacturers of polymer SCCs may use upstream suppliers that do not place strict controls over their processes.

For example, a resin manufacturer will set specifications for their product on its physical characteristics only and then sell the same resin to a manufacturer of a pharmaceutical SCC and a manufacturer of lawn furniture. In this example, the resin manufacturer may not have needed to keep accurate records on the amounts and type of antioxidants used as long as the resin met the manufacturer's specifications, but these antioxidants do have the potential to leach into a drug product.

Leachables can enter any type of drug product, including solid dosage forms. Generally, orally inhaled and nasal drug products (OINDP) and parenteral and ophthalmic drug products (PODP) are the most common drug products at high risk of leachables. But don't overlook lower risk container systems such as glass or HDPE bottles. Low risk is not the same as no risk, as has been evident in several high-profile recalls of solid dosage forms due to leachables. An assessment of the risk of leachables into a given drug product needs to be done when considering a testing strategy for leachables.

The toxicity of a leachable is dependent upon the route of entry into the body. For example, levels of a compound that can be safely ingested can have a toxic effect when the same level is inhaled. As a result, the potential route of administration of a leachable must be considered when assessing the risk of a leachable.

Leachables present unique analytical challenges. Since leachables are not related to the drug product, the analytical methods used to detect impurities in the drug product may not be able to detect the leachables. Even when leachables could be detected by drug product impurity methods, the leachables are often at levels which are orders of magnitude lower than drug degradation products or related substances, thus below the sensitivity of the testing method. Thus, separate analytical methods are usually needed for the analysis of leachables in the drug product.

Potential leachables need to be identified before an analytical method for leachables can be developed. This is done by performing an extraction study on the SCC under exaggerated conditions with the goal of identifying the observed extractables.

Understanding Extractables

Extractables are the compounds that can be extracted from the SCC that might become leachables. The conditions of an extraction study are selected based upon the drug product and are designed to mimic a worst-case-scenario for the intended drug product. Care must be taken in the selection process so that conditions are aggressive enough to ensure that the extractables include all leachables while not being too aggressive and generating an impractically large number of extractables that are not leachables. The extraction study should not lead to a complete deformulation of the material.

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There are two types of extraction studies: Controlled Extractions and Simulated Use Extractions. These two extractions can be done in series or in parallel. In some cases, just one of the extraction studies may be sufficient.

A Controlled Extraction study (also called materials characterization study) involves extracting the SCC in two or three solvents of varying polarities. The solvents are selected based upon the drug product with one of the solvents representing a worst-case scenario. The extraction conditions used are aggressive, typically reflux or Soxhlett extraction. The combination of the worst-case-scenario solvent with the aggressive extraction conditions is intended to yield a high number of extractables. The end result of this approach is that all potential leachables (except those that react or have a unique affinity for the drug product) will be identified.

A Simulated Use Extraction study (also called a simulation study) involves extracting the SCC in two solvents of varying polarities. The solvents are selected based upon the drug product with goal of representing a slightly more aggressive environment than that of the drug product. The extraction conditions are usually static storage of the SCC in the solvent at a temperature above the intended storage condition of the packaged final drug product. The end result of this approach is that the observed extractables are likely to be leachables.

A simulated use extraction is designed to be less aggressive than a controlled extraction study, thus fewer extractables are expected to be identified in a simulated use extraction compared to a controlled extraction. The simulated use study is more likely to identify only the extractables that will become leachables compared to the controlled extraction study which will potentially identify many extractables that will not become leachables. However, a simulated use study is more likely to "miss" a potential leachable than a controlled extraction study. Both studies reveal useful information on the potential leachables from a given material, but the project team must be aware of the strengths and weaknesses of each study. In some cases, for example if the controlled extraction study results in a low number of extractables, the project team may decide only one type of extraction study is necessary.

Regardless of type of extraction study performed, once completed, the sample extracts are analyzed by at least GC-MS, LC-MS and ICP-MS technologies. The goal of these analyses is to identify as many extractables as possible and to semi-quantitatively determine the level of each extractable. Based on the material, additional analysis may be required for specific extractables known to be highly toxic. Since the methods are designed to detect unknowns, these methods cannot be validated. Results from these analyses are reported as the amount of the extractable (usually in µg) per weight (usually in g) or surface area (usually in cm2) of the SCC component.

At the completion of the extraction studies, a list of extractables is generated. The challenge at this point is to select which extractables are the most likely leachables, which are the highest toxicological risk, and what levels are acceptable in the drug product. The most likely leachables are those that were observed in the most polar extraction solvents that modeled the intended drug product. This will apply to extractables from both controlled and simulated use studies. Extractables observed in intermediate non-polar solvents can also be selected as target leachables if the intermediate non-polar solvent is deemed to represent a realistic model for the drug product. Extractables observed only in worst-case-scenario solvents are only selected as target leachables when the extractable is highly toxic.

Next Steps

After completion of the extraction studies, the next steps are:

1. Developing analytical methods with sufficient sensitivity to detect all of the target leachables.
2. Validating the analytical methods.
3. Analyzing for leachables in the drug product from samples stored in the SCC under the intended storage conditions over the intended shelf life.
4. Observed leachables should be submitted for toxicological review.

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Completion of these studies early in the product development process helps manufacturers identify potential problems with extractables and leachables. This gives the product management team sufficient time to develop a solution and bring the product to market (possibly in a different form or container system) while still meeting market launch date targets, patient needs and regulatory approvals.

NSF Pharmalytica partners with pharmaceutical and bio-medical device manufacturers to provide key extractable and leachable testing and strategic consulting services, including:

- Method development and validation
- Controlled extractions under GMP and PQRI guidance
- Identification of major extractables by GC/MS, LC/MS, ICP/MS and FTIR
- Determination of Analytical Evaluation Threshold (AET)
- Monitoring of leachables on drug product stability

For more information about NSF Health Sciences, please call 1 (860) 940-6550 or email hstesting@nsf.org.

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