Extractables Testing

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Development of a complete extractables profile is a necessary step in the process of determining which, if any, components of the container closure system should be targeted for the development and validation of specific analytical methods for the detection of those compounds in the Client's drug product matrix. Extraction is performed in three solvents representing a broad range of polarities. This practice allows for the detection and identification of the greatest number of extractable species regardless of the chemical nature of the Client's actual drug product matrix. The most common solvents chosen are water, isopropanol and hexane. Specific aqueous buffers may be substituted for water in the event that the drug product for which a packaging system is intended has a pH level below 5 or greater than 9.

In order to detect and identify the greatest number of extractable components, West uses a series of orthogonal techniques, typically LCMS, GCMS (both direct injection of extracts and headspace analysis), ICP for metals and IC for anions. These techniques were developed for and are intended for use with pure solvent extracts. They are not optimized for, and in some cases may be unsuitable for use with, drug products or drug product matrices. For that reason, West recommends limiting the initial extraction experiment to pure solvent extracts, with drug products or placebo products considered for subsequent stages of the investigation. The use of pure solvents also avoids the interferences that almost inevitably are introduced by the use of drug products or drug product placebos.

Estimated Quantities of Extracted Components

Rough estimates of the concentration of each species detected are provided for each extract. For individual elastomeric closure components such as stoppers, needle shields and syringe plungers, these concentrations are expressed in terms of micrograms per gram of material. For large contact-surface components such as bottles or intravenous fluid bags, or other articles for which mass may be a secondary consideration to surface area, concentrations may be expressed in terms of micrograms per square centimeter of surface. It must be stressed that the concentrations are estimated quantities of extracted components, not a measure of the amount of component contained in the polymer.

While inorganic ions can be identified reliably by spectral comparison to known standards which also allow for reasonably accurate estimates of concentration in solution, it is not feasible to analyze a standard for every organic compound that may be detected in an extract. For practical reasons, therefore, a single external standard compound is chosen as a surrogate for estimating the concentration of each extractable organic compound in solution. This estimate may not correlate to the actual propensity for a given compound to migrate from the packaging system into any given drug product; however, an estimate of the quantity of material extracted may assist the Client in determining the overall risk posed by that material.

A "First Pass" Evaluation

The extractables study is intended to be a "first pass" evaluation of the extractable species from packaging components whose purpose is simply to identify those components that may be extractable under any conditions, not just the specific conditions related to a given drug product. The techniques that are employed are general qualitative screening methods that are not validated for any given extractable or solvent matrix. In many cases an extractable compound or group of compounds may not be identifiable based on the available data. In these instances the compounds will be listed as "unknown." The Client may opt to pursue additional analysis to explore the identity of these unknown compounds using additional analytical resources available at West.

West Analytical Services
www.WestAnalyticalServices.com

In the United States
800-345-9800
Option 5

Outside of the United States
+1 610-594-2900
Option 5

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