I. Introduction

Development of a comprehensive extractables profile is a necessary step in evaluating suitability of packaging materials for their intended use. The process begins with determining which components of the container closure system should be targeted for the development and validation of specific analytical methods for the detection of those compounds, known as "leachables," in the drug product matrix. General guidance for conducting extraction studies on packaging components can be found in the US Food and Drug Administration (FDA) guidance documents i and Product Quality Research Institute (PQRI) Thresholds and Best Practice Recommendations.ii

Taking into consideration the above industry guidance and the emerging Parenteral and Ophthalmic Drug Products (PODP) recommendationsiii; West Analytical Services has adopted the following general approach. The intent of the study design is to understand the chemistry of the components in relation to intended use and potential for drug product/container closure interaction.

Many types of materials are involved in the production and containment of drug products. These include elastomeric closures, prefllable syringe components, cartridges and bioprocessing equipment, as well as items such as labels, inks, adhesives, dropper bulbs and overwraps. All of these items may affect the quality of the drug product (and potentially patient safety) over time. In order to predict which chemical species may migrate from the components of a container closure system into a drug product, it is important to characterize those components and to develop a thorough understanding of the extractable species that are present therein. Extraction is performed in a minimum of 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 a 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.

II. Analytical Methodology

In order to detect and identify the greatest number of extractables, West uses a series of orthogonal techniques, such as liquid chromatography/mass spectrometry (LC/MS), gas chromatography/mass spectrometry (GC/MS, both direct injection of extracts and headspace analysis), inductively-coupled plasma (ICP) for metals and ion chromatography (IC) for anions. The methodologies for these techniques were developed for characterization studies only and are intended for use with pure solvent extracts; they are not optimized for use with drug products or drug product matrices. For this 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.

Estimates of the concentration of each species detected are provided for each extract. For individual packaging components these concentrations are typically expressed in terms of micrograms per gram of material. 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 likelihood 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 in determining the overall risk posed by that material.
West has adapted the PQRI model for determining the threshold of significance of an extractable to include as reportable any individual chemical species detected at an estimated concentration of:

- One microgram per gram of component for articles which are, or are potentially, in direct and prolonged contact with the drug product, such as vial stoppers, syringe plungers and primary containers.
- Ten micrograms per gram of component for articles that are not likely to be in direct and prolonged contact with the drug product, such as needle shields, secondary seals and secondary containers.
- Any detectable amount of volatile species. For volatiles, any experimentally-derived concentration will represent a concentration in air only and does not correlate to the actual concentration available for migration from a test article; furthermore, volatile components do not require direct drug contact in order to be detected as leachables.

West considers only those species that are shown to originate or are likely to arise from the test article to be reportable in an extraction study. Infrequently, compounds may be detected that originate from sources other than the polymer itself. These include compounds introduced in sample handling by a client or by West, during packaging or shipping, or any of a variety of other sources. In order to minimize the impact of such compounds on the development of an extractables profile, West's standard practice is to perform all extractions in duplicate. Species that are present in extraction blanks or in only one of two replicate extracts are considered most likely to arise from sources other than the test article and are not listed as extractables. West does not routinely re-analyze samples in which an analyte appears inconsistently among replicates unless specifically requested by the client.

III. Data Interpretation and Next Steps

The extractables study is intended to be a "first pass" evaluation of the extractable species from packaging components. The techniques that are employed are general qualitative screening methods that are not validated for any given extractable or solvent matrix, although their development has taken into account a wide variety of formulation components. 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." A client may opt to pursue additional analyses to explore the identity of these unknown compounds using additional analytical resources available at West; such exploration, however, is beyond the scope of the standard extraction study and will require an additional quotation and protocol.

Once the extractables profile has been established, the next step is to determine which of the extractable compounds should be targeted for development and validation of analytical methods. Ideally, methods would be developed for every extractable compound; however, in some cases it may be more practical to exclude certain species based on the level of risk they present. In order to assist a client in this pursuit, West Analytical Services has developed the West E2L® Evaluation of Extractable Species. This system assesses each extractable component on the basis of nine measurable criteria, five of which are specific to the container closure system and four of which are specific to the drug product. The results are presented as a color-coded visual reference. The risk of each extractable compound is ranked as follows:

- Low Risk: Extractable is least likely to migrate from the packaging system to the drug product (low potential impact to the patient).
- Medium Risk: Extractable is more likely to migrate from the packaging system to the drug product (possible impact to the patient).
- High Risk: Extractable is most likely to migrate from the packaging system to the drug product (probable impact to the patient).
The E2L report serves as a tool for advancing the project in an efficient manner from extractables into leachables testing by presenting the list of extractable compounds in a prioritized form based on overall risk. It is not intended to be a replacement for leachables testing in the drug product; it is for informational purposes only and is intended to serve as a guideline to assist the client in determining which, if any, of the extractable species are to be targeted for further method development and validation in the client's drug product matrix. West cannot recommend any individual extractable compound for inclusion or exclusion from further testing.

IV. Summary

Packaging information is critical for drug application filings within the U.S. Food and Drug Administration (FDA), the EU Medicines and Healthcare products and Regulatory Agency (MHRA), and most other regulatory agencies. The development of a comprehensive extractables profile in a wide range of solvents, not just those that are similar to the intended drug product, is crucial to developing an understanding of those chemical species that may migrate into a drug product over time. It is from this profile that the decision can be made regarding which packaging-related compounds should be targeted for development and validation of specific analytical methods. West Analytical Services offers a full range of service from extractables testing to method development and validation.

West's products are sold on the basis that it is the customer's responsibility to evaluate and test the West product to determine its compatibility with other materials and fitness for any end use.

This technical bulletin dated 20 September 2013, supersedes any other previously released versions of this bulletin.