QUALITATIVE AND QUANTITATIVE EXTRACTION STUDIES

The goal of an extraction study is to provide information on the chemistry of the CCS materials of construction. The major objectives for acquiring extractable data are to (*i*) screen potential CCS components under exaggerated conditions to learn the chemistry and identify possible "bad actors", (*ii*) select and qualify the components under worst-case conditions, (*iii*) gain knowledge to design and conduct a leachable study, and (*iv*) provide data for quality control and lifecycle management.

> Chemistry manufacturing and control information is expected for every material used in the manufacture of packaging components. The complete chemical composition and results of extractable/toxicological evaluations for pharmaceutical products that are likely to interact with packaging component and introduce extracted substances into patients should be submitted in the original application 2. Furthermore, the Common Technical Document format CTD section 3.2.S.6 indicates the suitability should be discussed with respect to choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction (5).

It is the regulatory expectation that extracted substances from CCS that have migrated into a pharmaceutical product (leachables) should be evaluated to identify, eliminate, and/or control the leachable substances. Identification of potential leachables is accomplished through comprehensive extractables studies. Migration of minor constituents from component materials into a solvent is dependent on the migrant's transport and thermodynamic properties in both the component and solvent. The potential for chemicals to migrate from the component(s) is ascertained through extraction studies and linking data to leachables, thereby helping to assure patient safety.

The presence or absence of leachables is substantiated using aggressive extraction conditions. Voluminous extractable data can be generated; however, all extractables detected are not necessarily leachables but all drug product leachables need to be traced back to extractables. Extractables may have a direct correlation to substances found in the pharmaceutical product that may have originated from the CCS formulation ingredients or indirect relationship resulting from an extractable degradation or interaction product. The extractable experimental design should be developed for broad application. The first phase of the study would screen to discover potential leachables using aggressive solvents of varying polarity and one with similar propensity to the pharmaceutical product. The CCS components would be exposed to exaggerated conditions and analyzed using multiple analytical techniques. The extractable data would then benchmark potential substances, which may contaminate the drug product and cause harm to a patient. Evidence of CCS performance and compatibility can also be derived from the extractable studies. Performance additives can be monitored and measured, when necessary, to indicate stability and proper function of the components. CQAs for protection, performance, compatibility, and safety developed for candidate CCS components will need to be managed holistically, and the understanding of the component chemistries is essential to show that a CCS is suitable for its intended purpose.