Container Closure Integrity (CCI)
- Helium Leak Detection
- Vacuum Decay
- Dye Ingress
- Microbial Ingress
- Bubble Test
- Package Integrity for Bags and Pouches
- Residual Seal Force

Compendial
- USP <381> & EP 3.2.9 Combined Protocol, Physicochemical & Functionality Tests
- USP <87> Biological Reactivity Tests, In Vitro
- USP <88> Biological Reactivity Tests, In Vivo
- USP <660> Containers, Glass
- USP <661> Containers, Plastics
- USP <671> Containers, Performance Testing
- USP <788> Particulate Matter in Injections
- USP <1> Volume in Containers (Syringe & Cartridge)
- EP 3.2.1 Glass Containers for Pharmaceutical Use
- EP 3.2.9 Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powder and for Freeze-Dried Powders
- JP 7.01 Test for Glass Containers for Injections
- JP 7.02 Test Methods for Plastic Containers
- JP 7.03 Test for Rubber Closure for Aqueous Infusions

Functionality
- Instron Force Testing

Process Validation/Qualification
- Karl Fisher Moisture
- Silicone Analysis
- Container Closure Integrity (CCI)
- Physical and Functional Analysis

Extractables and Leachables
- Consultation, Protocol Design and Generation
- Extraction Studies
- E_L™ (Extractables to Leachables) Risk Assessment
- Development, Validation and Testing of Extractable QC Methods for Packaging, Device and Administration Systems
- Leachables Method Development and Validation in Drug Product
- Leachables Testing in Drug Product Over Shelf Life
- Simulation Studies
- Migration Studies – labels, inks, adhesives
- Investigation of Unknowns
- Toxicological Evaluation Support
- Stability Storage (ICH conditions, programmable chambers for client specific requirements)

Problem Resolution
- Foreign Particulate Matter and Particle Identification
- Glass Delamination
- Tungsten Analysis
- Defect and Dimensional Analysis
- Material Characterization
- Silicone Oil Analysis
- Particle Counting
- Cleaning Validation, Method Development and Validation, Residual Limits
Testing for Syringe Systems (Glass or Plastic)

Container Closure Integrity (CCI)
- Helium Leak Detection
- Vacuum Decay
- Dye Ingress
- Microbial Ingress
- Residual Seal Force

Compendial
- USP <381> & EP 3.2.9 Combined Protocol, Physicochemical & Functionality Tests
- USP <87> Biological Reactivity Tests, In Vitro
- USP <88> Biological Reactivity Tests, In Vivo
- USP <660> Containers, Glass
- USP <661> Containers, Plastics
- USP <671> Containers, Performance Testing
- USP <788> Particulate Matter in Injections
- USP <1> Volume in Containers (Syringe & Cartridge)
- EP 3.2.1 Glass Containers for Pharmaceutical Use
- EP 3.2.9 Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powder and for Freeze-Dried Powders
- EP 3.2.1 Glass Containers for Pharmaceutical Use
- JP 7.01 Test for Glass Containers for Injections
- JP 7.02 Test Methods for Plastic Containers
- JP 7.03 Test for Rubber Closure for Aqueous Infusions
- ISO 7886 Sterile Hypodermic Syringes for Single Use
- ISO 8537 Sterile Single-Use Syringes, With or Without Needle, for Insulin

Functionality
- Breakloose and Extrusion
- Tip Cap Removal Force
- Needle Shield Removal Force
- Rod Pull Out Force
- Delivered Volume Studies

Process Validation/Qualification
- Karl Fisher Moisture
- Silicone Analysis
- Container Closure Integrity (CCI)
- Physical and Functional Testing

Extractables and Leachables
- Consultation, Protocol Design and Generation
- Extraction Studies
- E₂L™ (Extractables to Leachables) Risk Assessment
- Development, Validation and Testing of Extractable QC Methods
- Leachables Method Development and Validation in Drug Product
- Leachables Testing in Drug Product Over Shelf Life
- Simulation Studies
- Migration Studies – labels, inks, adhesives
- Investigation of Unknowns (LC/MS/MS, GC/MS)
- Toxicological Evaluation Support
- Stability Storage (ICH conditions, programmable chambers for client specific requirements)

Problem Resolution
- Foreign Particulate Matter and Particle Identification
- Glass Delamination
- Tungsten Analysis
- Defect and Dimensional Analysis
- Material Characterization
- Silicone Oil Analysis
- Particle Counting
- Cleaning Validation, Method Development and Validation, Residual Limits

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Container Closure Integrity (CCI)
- Helium Leak Detection
- Frequency Modulation Spectroscopy
- Vacuum Decay
- Dye Ingress
- Microbial Ingress
- Residual Seal Force

Compendial
- USP <381> & EP 3.2.9 Combined Protocol, Physicochemical & Functionality Tests
- USP <87> Biological Reactivity Tests, In Vitro
- USP <88> Biological Reactivity Tests, In Vivo
- USP <660> Containers, Glass
- USP <661> Containers, Plastic
- USP <671> Containers, Performance Testing
- USP <788> Particulate Matter in Injections
- EP 3.2.1 Glass Containers for Pharmaceutical Use
- EP 3.2.9 Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powder and for Freeze-Dried Powders
- EP 3.2.1 Glass Containers for Pharmaceutical Use
- JP 7.01 Test for Glass Containers for Injections
- JP 7.02 Test Methods for Plastic Containers
- JP 7.03 Test for Rubber Closure for Aqueous Infusions

Functionality
- EP 3.2.9 Functional Test Series, Penetrability, Self-Sealing, Fragmentation
- Coring Studies

Process Validation/Qualification
- Karl Fisher Moisture
- Silicone Analysis
- Container Closure Integrity (CCI)
- Physical and Functional Analysis

Extractables and Leachables
- Extraction Studies
- E2L™ (Extractables to Leachables) Risk Assessment
- Development, Validation and Testing of Extractable QC Methods
- Leachables Method Development and Validation in Drug Product
- Leachables Testing in Drug Product Over Shelf Life
- Simulation Studies
- Migration Studies – labels, inks, adhesives
- Investigation of Unknowns
- Toxicological Evaluation Support
- Protocol Design and Generation
- Stability Storage (ICH conditions, programmable chambers for client specific requirements)

Problem Resolution
- Foreign Particulate Matter and Particle Identification
- Glass Delamination
- Tungsten Analysis
- Defect and Dimensional Analysis
- Material Characterization
- Silicone Oil Analysis
- Particle Counting
- Cleaning Validation, Method Development and Validation, Residual Limits
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 drug product matrices 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 VeriSure™ verification is a product offering to support the pharmaceutical and biotech industry to effectively manage the complexity surrounding extractables evaluation. The VeriSure Technical Package provides a comprehensive list of baseline extractables of the formulation with supporting data that was acquired based on sampling multiple lots of elastomeric components of various configurations, processing and cure conditions obtained from representative manufacturing sites. Extractions with multiple solvents and analyses using multiple techniques to encompass non-volatile, semi-volatile, volatile, metal, ionic and specially targeted extractables comprise the data.

**Container/Closure Selection**
Extractables analysis is part of the qualification of a new container/closure system and is considered a standard by the pharmaceutical and biotech industries today and is expected by the global regulatory authorities. West has a thorough understanding of the materials and variables that can affect an extractables profile and is capable of developing and optimizing controlled extraction studies through extensive analytical capabilities, studies and interpretation. The body of VeriSure data and ability to assess risk through West’s E_L™ service allows customers to have confidence in their choice of a container/closure system.

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.

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Helium leak detection is a type of container closure integrity testing that provides quantitative results. This method is applicable to all container closure systems comprised of elastomer stoppers secured to containers with crimped aluminum seals as well as empty glass luer lock syringes. Helium leak detection as a means of container/closure system integrity testing can be used in lieu of sterility testing, per the FDA Guidance for Industry Container and Closure System Integrity Testing as a Component of the Stability Protocol for Sterile Products.

**Testing a Closed Container System**

West utilizes a Seal Integrity Monitoring System for helium leak detection. This instrument uses a mass spectrometer to determine the leak rate of a closed container system while under vacuum. This test method can be performed in two ways: either the container can be pre-filled with helium or be manually filled.

There are special fixtures for accommodating containers of varying sizes, with vacuum chambers accommodating containers up to 500 mL and specially designed attachments for securing various sizes of syringes. Additionally, containers can be analyzed at any range of temperature, from room temperature down to -80°C. All of these allow for a broader spectrum of sample submission.

In the event of a failing result on a container closure system, a sniffer probe can be utilized to locate the source of the leak. If the sniffer probe is not effective in determining the source of a failure, additional investigations can be done through microscopy.
Helium Leak (destructive)
West’s helium leak methodology is a highly sensitive quantitative test performed on vials/stoppers and prefillable syringe systems. The method is validated for a wide variety of containers across a broad range of temperatures. The value obtained is then compared to Dr. Kirsch’s helium leak rate (based on published research). Helium leak rates lower than the specified limit have been associated with acceptable microbial challenge results.

PTI Microleak/Vacuum Decay (non-destructive)
West’s methodology can be used to assess container closure integrity via vacuum decay on both vials and syringes. A container closure system is placed in a custom designed test fixture. The area surrounding the container is put under vacuum and monitored for pressure. An increase in pressure represents a leak in the container closure system being assessed.

Headspace Pressure Analyzer
Frequency modulation spectroscopy is a non-destructive technique that can be used to measure vacuum or moisture in a sealed vial. This testing requires clear vials with sufficient headspace for analysis. A multi-point calibration curve is acquired using standards made of exact vial dimensions to produce the most accurate results.

Dye Leak (destructive)
West has a variety of dye leak methods available. Test samples and positive controls are either submerged or partially submerged in methylene blue dye solution. Both positive and reduced pressure is applied to the chamber for set periods. Samples are rinsed and visually examined for the presence of blue dye. West also develops custom dye leak methods to address unique customer requirements.

Microbial Immersion
This testing is subcontracted to a third-party laboratory.
West's E₂L service from West Analytical Services is designed to assist customers bridge the gap between extractables data and leachables evaluation. It is a systematic approach utilizing West expertise and incorporates variables associated with properties of extracted compounds, exposure, detection, and concern for package/product interaction. This risk assessment tool can be applied to extractables data and focuses resources on a justifiable, risk-based extractables list.

The E₂L risk assessment report helps prioritize analytes for leachables method development. The assessment, based on measureable criteria, evaluates each extractable identified in the Extraction Study and ranks the risk in each of nine specified assessment categories based on three definitions:

- **Low Risk**: Extractables least likely to migrate (low potential impact to the patient)
- **Medium Risk**: Extractables more likely to migrate (possible impact to the patient)
- **High Risk**: Extractables most likely to migrate (probable impact to the patient)

The report includes full explanations of the categories and criteria used to assess the risk, a color-coded visual reference table that ranks the extractables, and a total risk priority for each extractable. So compounds of high concern quickly rise to the top for leachables consideration.

Extractables analysis is part of the qualification of a new container/closure system and is considered a standard by the pharmaceutical and biotech industries today and is expected by the global regulatory authorities. West has a thorough understanding of the materials and variables that can affect an extractables profile and is capable of developing and optimizing controlled extraction studies through extensive analytical capabilities, studies and interpretation. The ability to assess risk through the E₂L service allows customers to have confidence in their choice of a container/closure system.

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.