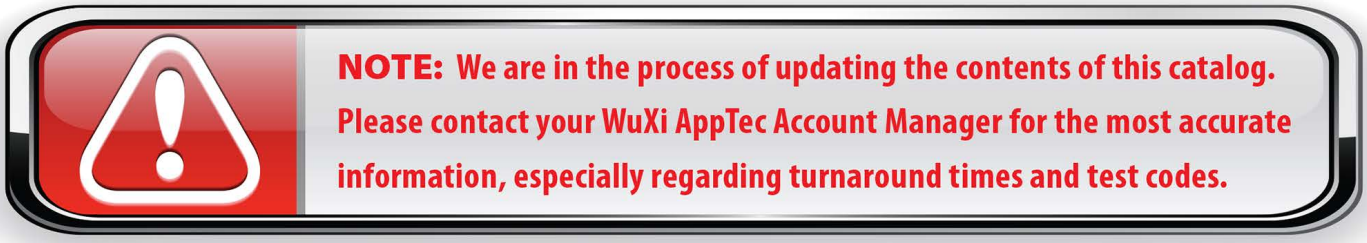

Chemistry Testing

ANSI/AAMI/ISO standards and FDA guidelines now emphasize the importance of material characterization as a key part of safety assessments. Analytical assessment should start early in the development process to begin the chemical characterization of the materials, processing aids and any potential leachable chemicals. These evaluations should continue through the lot release phase to ensure that products continue to meet specifications. Thorough understanding of all of these components is crucial to managing the risk to patients.

Analytical chemistry services coupled with risk assessments can be used to evaluate potential hazards that could be associated with the device itself or as a result of the manufacturing process. These multi-discipline analyses are also important components of lot release and risk management programs.

The chemical/physical tests listed in this section are commonly used during material selection, preclinical safety assessments, as well as for validation of manufacturing processes, quality control and release testing. Additionally, WuXi AppTec custom designs chemistry programs tailored to meet your analytical needs.

In this Section

ANALYTICAL CHEMISTRY PROGRAMS OVERVIEW

Characterization of medical devices and their parent materials has become a focus of both the FDA and ISO member countries as part of a complete safety evaluation. Chemical evaluations of medical devices and the component materials can take many forms, as current regulatory documents do not give clear guidance. Some studies can be performed with straightforward analyses. In other cases, analytical programs designed specifically around the product are required. WuXi AppTec's scientists can guide you through the process to design effective programs to give you the data you need to support safety claims. Our process is typically comprised of five components.

Consultation

WuXi AppTec's scientific staff assists clients in assessing the chemistry assays needed to meet desired endpoints and address regulatory questions. These evaluations can result in the development of multiple approaches ranging from a single assay to multiple analytical test methods.

Protocol Development

To meet testing needs, both standard protocols and custom protocols are available. Standard protocols are readily available for routine, previously qualified assays. For studies that require highly specific endpoints, a custom protocol is developed and written to meet the manufacturer's particular test needs.

Analytical Programs

Chemistry programs can involve multiple endpoints to identify and quantify components that are part of the finished device. Target analysis studies can be used to evaluate specific chemical components of materials, whereas materials characterizations studies can be designed to develop profiles of the materials. Exactable and leachable studies are designed to identify and quantitate chemical entities that can be removed from the device during use. Additionally, analytical programs can be used to identify undesired process contaminants. Equipment, including ICP, HPLC, UPLC, GC/MS, ion chromatography and particulate analysis can be used to semi-quantitatively or quantitatively evaluate devices and their component materials.

Support for Lot Release

In conjunction with finalizing the manufacturing process, WuXi AppTec can develop analytical lot release assays for release testing of raw materials, in-process materials and final products. WuXi AppTec's Lot Release Programs include Analytical, Sterilization and Bioactivity assays and can be scheduled to meet the timelines necessary to support manufacturing pressures.

Support for Risk Assessment

Once analytical work has been completed, WuXi AppTec toxicologists are available to perform risk assessments of the data to help you understand the safety profile of your product. Our toxicologists interface directly with chemists to develop toxicology risk profiles. These profiles can be used to drive additional analytical testing to further examine questionable entities, drive biocompatibility program choices or be combined with biocompatibility data for a thorough risk assessment.

Contact a WuXi AppTec Account Manager to learn more about our Analytical Chemistry services or to discuss your product-specific testing needs.

ANALYTICAL CHEMISTRY

For sample requirements and additional information about these tests, contact your WuXi AppTec Account Manager.

400170

Fourier Transform Infrared (FTIR) Scan

This test is a type of infrared spectroscopy in which the sample is subjected to all the wavelengths in the region of interest at all times, instead of only a small portion at a time. An infrared spectrum can be used to characterize or identify organic compounds (e.g., polymers, solvents, etc.), establish a reference spectrum for future comparison, and determine functional groups of minor polymer components (e.g., organic additives, preservatives).

The Varian® IR database is also available, which allows performance of an IR search of over a 1,000 compounds and functional groups. It is also possible for the laboratory to set up a client sample IR database for quality control and comparison.

400150

Gas Chromatography (GC)

In this analytical process, the components of a mixture are separated from one another by volatilizing the sample into a carrier gas stream, which is passed through an analyte-specific column. Different components move through the column bed at different rates and appear separately at the effluent end, where they are detected and measured by thermal conductivity changes, density differences, or ionization detectors.

GC is typically used for the analysis of minute quantities of complex mixtures from industrial chemicals, biological fluids and pharmaceutical preparations.

Test code is dependent on element

Trace Metals

Atomic absorption spectroscopy is used to determine the presence of trace metals in a variety of samples. Most samples cannot be analyzed directly unless they are water or aqueous extracts. Most solid samples, if applicable, must undergo sample preparation techniques in order to completely dissolve the sample or to dissolve the elements of interest. Ashing and acid digestion are examples of common sample preparation techniques. The sample matrix usually dictates which sample preparation technique is followed.

Following are the elements typically analyzed by atomic absorption:

Aluminum	Gold	Potassium
Antimony	Iron	Rubidium
Arsenic	Lead	Selenium
Barium	Lithium	Silver
Beryllium	Magnesium	Sodium
Bismuth	Manganese	Tin
Boron	Mercury	Titanium
Cadmium	Molybdenum	Tungsten
Calcium	Nickel	Vanadium
Chromium	Palladium	Zinc
Cobalt	Platinum	Zirconium
Copper		

If the trace metal is unknown, it is recommended that an elemental scan be performed using ICP (Inductively Coupled Plasma) spectroscopy. This technology allows the simultaneous determination of 20–30 elements in a single sample. Sample preparation techniques are the same as those for the Trace Metals test (by atomic absorption) described above.	**400490** **Trace Metals – ICP Scan**
If a beam of light (electromagnetic radiation) is sent into a sample, it is possible for the sample to absorb a portion of the light. The characterization of chemical compounds by means of their ultraviolet or visible absorption spectra is achieved using an absorption spectrophotometer. This type of spectrophotometry can be used to determine the presence of UV absorbers in medical-grade polymers or for evaluating chromophore groups in the visible range.	**400510** **UV/VIS Spectrophotometry**

Contact your Account Manager for the most accurate information regarding test codes and turnaround times.

ETHYLENE OXIDE (EO) TESTING

Medical devices that are sterilized by ethylene oxide (EO) must be shown to have adequately degassed EO residues before the devices may be used. Analyses are performed for EO and ethylene chlorohydrin (ECH) according to current ANSI/AAMI/ISO standards (10993-7). The allowable limits are for EO and ECH; no exposure limits are set for ethylene glycol (EG). The allowable limits are based on patient contact duration and are designated as limited (≤24 hours), prolonged (>24 hours and ≤30 days), or permanent (>30 days).

Samples must be sent fully packaged and on dry ice, and should be shipped to WuXi AppTec's Atlanta facility.

See also EO Sterilization Validation in the "Sterilization Validation" section.

SAMPLE REQUIREMENTS	One product unit per sampling interval. All samples must be sent fully packaged.
SHIPPING REQUIREMENTS	Overnight to WuXi AppTec's Atlanta facility. Pack on dry ice.
TURNAROUND TIME	Dependent on selected post-sterilization date of testing

195000 **EO Residual Panel (Water Extraction) – EO, ECH and EG**	Water extraction for all 3 residuals. (24 hr., 37°C or specify time/temperature)
194500 **EO Residual Panel (Headspace Extraction) – EO, ECH and EG**	Headspace exhaustive extraction. (1 hr., 100°C or specify time/temperature) 3 extractions ECH and EG determined by water extraction.
195100 **EO Water Analysis**	Water extraction. (24 hr., 37°C or specify time/temperature)
195250 **EO Water Analysis - Exhaustive**	Additional water extractions for exhaustive analysis. (24 hr., 37°C or specify time/temperature)

Headspace extraction. (1 hr., 100°C or specify time/temperature) 3 extractions	**195210** **EO Headspace Analysis**
Water extraction. (24 hr., 37°C or specify time/temperature)	**194990** **ECH and EG Analysis**
Water extraction. (24 hr., 37°C or specify time/temperature)	**195500** **EO, ECH (Water Extraction)**
Headspace. (1 hr., 100°C or specify time/temperature) 3 extractions Water extraction. (24 hr., 37°C or specify time/temperature)	**195600** **EO (Headspace Extraction), ECH (Water Extraction)**
Water extraction. (24 hr., 37°C or specify time/temperature)	**195200** **ECH (Water Extraction)**

EXTRACTABLES / LEACHABLES PROGRAMS

Regulatory bodies are requiring chemistry data that fits ISO 10993-18: Chemical Characterization of Materials as part of the biological evaluation process for risk evaluation of medical devices. Coupled with the practices pointed out in ISO 10993-17: Establishment of Allowable Limits for Leachable Substances, sound evaluations of products can be made.

Extractable studies can be designed to first evaluate what compounds may be "pulled" from the device under rigorous conditions. These studies are typically followed by an abbreviated risk assessment to determine the correct targets to evaluation in the Leachable study. This study is designed with milder extractions conditions to determine what compounds may migrate out of the device under conditions similar to clinical use. The whole body of data should then be evaluated through a comprehensive risk assessment as part of the final biological evaluation. WuXi AppTec has developed a process to created targeted programs that meet your needs and scaled to fit your scope.

Chemical Profile of Extractables

Library Development:

- Multiple solvents, vigorous extraction conditions
- Detect and quantitate analytes presenting potential risk

Chemical Profile of Leachables

Target Analyte Plan

Targeted plan based on risk

Method Validation

Proof of analyte detection in relevant matrix

Leachable Studies

- Physiological solvents
- Mild extraction conditions
- Quantitative assessment of migrated analytes

Toxicology and Biologic Evaluation

Data analysis and interpretation
Biocompatibility / Safety Evaluation
Risk Assessment

Contact a WuXi AppTec Account Manager to learn more about our extractables / leachables testing programs.

For sample requirements and additional information about these tests, contact your WuXi AppTec Account Manager.

According to current USP specifications, "absorbent gauze" is cotton or a mixture of cotton and rayon (not more than 53% by weight) that is in the form of a plain woven cloth conforming to the standards set forth in the monograph. Testing includes general characteristics [thread count (warp and filling), length, width and weight] followed by several chemical and physical tests [water extract of gauze examined for dried and ignited residue, the presence of acid, alkali, dextrin and starch]. The gauze itself is analyzed directly for residue on ignition, fatty matter, alcohol-soluble dyes, cotton and rayon content.	**400100** **Absorbent Gauze, USP**
This test determines the temperature of a liquid at which its vapor pressure is equal to or very slightly greater than the atmospheric pressure of the environment. The boiling point is a parameter used to support identification and characterization of an unknown substance.	**400110** **Boiling Point**
Flashpoint is used to determine the temperature at which a liquid or volatile solid gives off vapor sufficient to form an ignitable mixture with the air just above the surface of the sample within the test vessel.	**400140** **Flashpoint**
The melting point of a chemical is the temperature at which a substance changes physical state from a solid to a liquid at normal atmospheric pressure. The melting point is an intrinsic property of a chemical and provides general information about the identity and purity of the chemical.	**400250** **Melting Point**
This is a gravimetric method for determination of water. The sample is placed in a convection oven set at 105°C and dried for 16-24 hours. Any weight loss is considered water and calculated as such. This method applies to samples in which water is the only volatile component.	**20661** **Moisture – Residual**
The refractive index of various liquids is measured using a Reichert AR200 digital refractometer.	**400320** **Refractive Index**

PHYSICAL TESTING

400340 **Residue on Ignition**	This test determines the total mineral content of a sample or extract when ignited to 800°C in a muffle furnace. The resulting residue will contain only those metallic salts that are not volatilized at that temperature.
400350 **Specific Gravity**	Specific gravity is the ratio of the density of a substance to the density of a reference substance. For solids and liquids, the specific gravity is the ratio of the density to that of water at 4°C. The data may be used to evaluate the manner and extent that chemicals will be transported in the environment and places they will be deposited.
400530 **Viscosity**	Viscosity is the internal resistance to flow exhibited by a liquid. A Brookfield viscometer is used to measure the viscosity of many Newtonian fluids.

For sample requirements and additional information about these tests, contact your WuXi AppTec Account Manager.

400120

Chloride

The chloride ion, one of the major inorganic anions found in the environment, is an integral component, in the form of a "salt," of many isotonic and physiological solutions. The ubiquitous chloride ion is also a major inorganic contaminant of water and wastewater.

This test determines the chloride level colorimetrically, using mercuric thiocyanate.

400130

Conductivity

Conductivity is a physical test that measures the ability of an aqueous solution to carry an electric current. Conductivity is normally expressed in microSiemens per centimeter, μS/cm. The conductivity of a water sample results from the presence of positive and negative ions. Water molecules tend to dissociate into ions as a function of pH and temperature, resulting in a very predictable conductivity. Extraneous ions (chloride, sodium, carbonates, ammonia, etc.) also affect the conductivity and have significant impact on the water's chemical purity and suitability for use in pharmaceutical and other applications.

Water conductivity is a requirement for Purified Water and Water for Injection under current USP specifications.

In the USP monograph, the tests for conductivity are divided into three stages.

Stage I requires conductivity to be measured in an uncompensated temperature mode against a standard conductivity solution, with a calibrated conductivity meter. By using the following chart, the measured conductivity of the water sample is compared to the chart value corresponding to the next lowest temperature in which the conductivity was measured.

Temperature (°C)	Conductivity (μS/cm)	Temperature (°C)	Conductivity (μS/cm)
0	0.6	30	1.4
5	0.8	35	1.5
10	0.9	40	1.7
15	1.0	45	1.8
20	1.1	50	1.9
25	1.3	55	2.0

If the measured value is lower than the chart value, the sample passes the test for water conductivity. If not, Stage 2 is applied.

Stage 2 involves stirring the sample at 25 ± 0.1°C until the drift in conductivity (due to the uptake of atmospheric carbon dioxide) is less than 0.1 μS/cm over a 5-minute period. In order to pass this stage, the final conductivity must not be greater than 2.1 μS/cm. Stage 3 is applied if this specification is not met.

Stage 3 compares the conductivity with the pH of the water sample. If the conductivity of the sample at its actual pH is less than the allowed conductivity at the same pH listed in the following chart, then the sample passes the requirement for water conductivity.

pH	Conductivity (μS/cm)	pH	Conductivity (μS/cm)	pH	Conductivity (μS/cm)
5.0	4.7	5.7	2.5	6.4	2.3
5.1	4.1	5.8	2.4	6.5	2.2
5.2	3.6	5.9	2.4	6.6	2.1
5.3	3.3	6.0	2.4	6.7	2.6
5.4	3.0	6.1	2.4	6.8	3.1
5.5	2.8	6.2	2.5	6.9	3.8
5.6	2.6	6.3	2.4	7.0	4.6

WET CHEMISTRY

400160

Glutaraldehyde Residues

Glutaraldehyde is used as a liquid chemical sterilant in the medical device industry and in the hospital environment. The reagent 3-methyl-2-benzothiazolinone hydrazone hydrochloride in the presence of ferric chloride produces a blue color if glutaraldehyde is present. The intensity of the blue color is then determined colorimetrically from a standard plot.

400200 USP Method I
400210 USP Method II
400220 USP Method III

Heavy Metals

This USP semi-quantitative test determines whether the total level of metallic impurities that react with the sulfide ion, under test conditions, exceeds the heavy metals limit specified in the individual USP monograph. Results are reported as weight percent (wt%) lead, based on color-comparison.

Note: The laboratory will determine USP method based on the type of sample.

USP Method I
For substances that yield clear, colorless preparations under specified test conditions.

USP Method II
For substances that do not yield clear, colorless preparations under test conditions specified in Method I, or for those that interfere with sulfide precipitation, or for fixed and volatile oils.

USP Method III
A wet-digestion method that is used when Methods I and II cannot be utilized.

Should results exceed the heavy metals limit, it may be necessary to test for the elements that typically respond to this test (e.g., antimony, arsenic, bismuth, cadmium, copper, lead, mercury, molybdenum, silver and tin) by atomic absorption (AA) or inductively coupled plasma (ICP) spectroscopy.

400501

Moisture Determination – Karl Fischer

The Karl Fischer reaction uses a coulometric titration to determine the amount of water in a sample. It can determine concentrations of water from ppm to percent. It is often used to find the amount of water in substances such as powders, oils, chemicals, etc.

38110

Osmolality Determination

Osmotic pressure is fundamentally related to all biological processes that involve diffusion of solutes or transfer of fluids through membranes. Osmolality, a measure of the osmotic pressure exerted by a real solution across a semi-permeable membrane, is reported in osmoles of solute per kilogram of solvent (osmol/kg). In chemistry, the osmole (osmol) is a non-SI unit of measurement that defines the number of moles of a chemical compound that contribute to a solution's osmotic pressure.

The osmolality is determined using an Osmometer, based on freezing point depression, where the sample is placed in a cooling chamber, supercooled and crystallized. The sample temperature then rises due to the heat of fusion being released during the freezing process. The temperature at the plateau of the freezing point is then converted to units of osmolality.

The pH value represents the acidity or alkalinity of an aqueous solution or suspension. The electrometric method, using a pH meter and suitable electrode, is used.	**400260** **pH**

This series of tests is designed to provide information about the physical and chemical characteristics of elastomeric (rubber) closures. Prepared test samples (of a specific surface area) are extracted with purified water in an autoclave at 121°C. **[Sample requirements = 100 cm^2.]** The extract is then subjected to the following tests: **TURBIDITY (OPALESCENCE)** The turbidity and opalescence of the extract is no more than that of the reference suspension. **DETERMINATION OF COLOR** The extract is not more intensely colored than the Color Standard. **ACIDITY OR ALKALINITY** The difference in the titrant from the blank and extract is less than specified amounts. **ABSORBANCE** A measure of the absorbance of the filtrate between 220-360 nm meets the requirements of the specific type of closures. **REDUCING SUBSTANCES** The difference between the titration volumes of the extract and blank meets the requirements of the specific type of closures. **HEAVY METALS** Heavy metals content is determined by color comparison after reacting with sulfide ion. The difference between the sample and the blank is the heavy metals content, as lead. **EXTRACTABLE ZINC** The extract is analyzed by Atomic Absorption spectroscopy for zinc. **AMMONIUM** A colorimetric analysis is performed on the extract to determine the ammonium content. **VOLATILE SULFIDES** A qualitative colorimetric evaluation, using lead acetate test paper, to determine the presence of any volatile sulfides in the extract.	**400275** **Physicochemical Tests, USP Test Panel – Elastomeric Closures for Injections <381>**

WET CHEMISTRY

400280

Physicochemical Tests – Plastics

These tests, designed to determine the physical and chemical properties of plastics and their extracts, are based on the aqueous extraction of the polymer. Prepared test samples are extracted in purified water for 24 hours at 70°C. **[Sample requirements = 600 cm^2.]** The extract is then subjected to the following tests:

NON-VOLATILE RESIDUE
A 50-mL aliquot of the extract is evaporated to dryness and the residue weight is determined. The difference between the amounts obtained from the sample and blank may not exceed 15 mg.

RESIDUE ON IGNITION
The residue from non-volatile residue test is ashed, with addition of sulfuric acid. The difference in amounts of ignited residue for the sample and blank may not exceed 5 mg.

HEAVY METALS
The heavy metals content is determined by color comparison with a 1 ppm lead standard. The color is measured after pH adjustment and the reaction with the sulfide ion. The final sample color should not be darker than the 1 ppm lead standard.

BUFFERING CAPACITY
A 20-mL aliquot of the extract and the blank are titrated potentiometrically to a pH of 7.0 with either 0.010 N acid or base. If the same titrant is used for both sample and blank, the difference in the amount of titrant may not exceed 10 ml. If different titrants are used, then the combined volume of the titrants may not be greater than 10 ml.

400290

Protein Assay

The modified version of the classic Lowry protein assay is used to determine the amount of saline-extractable protein associated with products made from natural rubber (e.g., latex gloves).

400300

Purified Water, USP

USP requirements for purified water include water conductivity and total organic carbon.

400360

Total Organic Carbon (TOC)

Total organic carbon (TOC) is a measure of the organic compounds (reported as carbon) present in water. It is an excellent method for measuring water purity because it is non-specific, highly sensitive, and theoretically capable of quantitating any carbon-containing compound. TOC analysis can be used to quantify nearly all of the commonly encountered organic contaminants (feedwater impurities, biofilm, etc.) expected from any water purification and distribution system.

400256

Total Solids

Total solids is the term applied to the material residue left in a vessel after evaporation of the sample and its subsequent drying in an oven at a specified temperature, usually between 103°C and 105°C. The test is often used as a quality control check for water, material extracts and many industrial solutions.

400540

Water for Injection, USP

USP requirements for water for injection include water conductivity and total organic carbon.