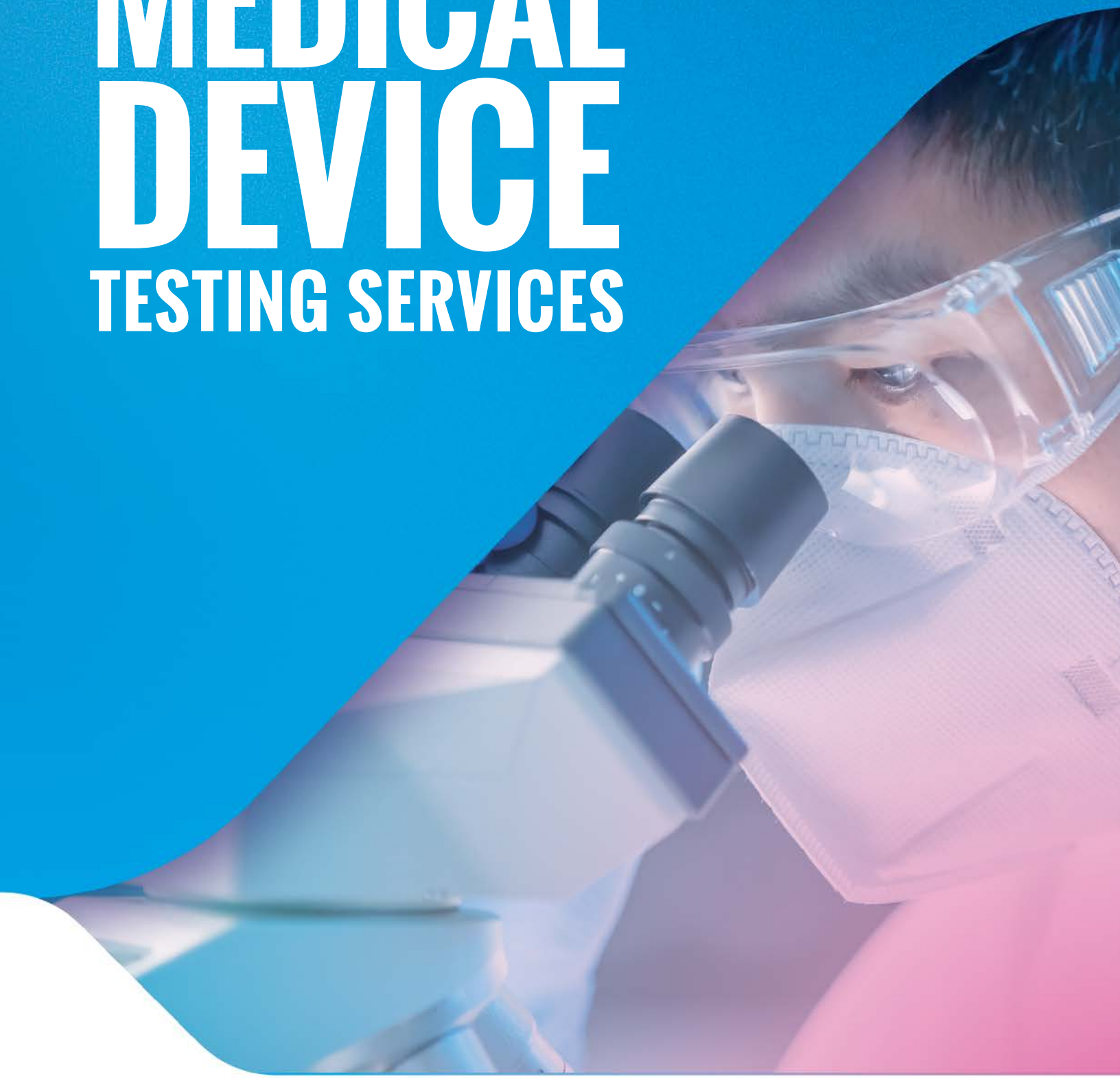
药明康德
WuXi AppTec

MEDICAL DEVICE TESTING SERVICES



LABORATORY TESTING DIVISION

药明康德
WuXi AppTec

SERVICES FOR MEDICAL DEVICES

INTRODUCTION & OVERVIEW

To support your product's safety in today's complex global marketplace, you need an approach that is tailored to your unique product and distribution strategy. WuXi AppTec partners with medical device manufacturers, guiding you through the often complicated regulatory process to successfully execute your project.

We have supported hundreds of thousands of devices with the strategies and testing needed to gain market access, avoid costly delays and support changing requirements throughout a product's lifecycle.

Your success is our success. WuXi AppTec works as a seamless extension of your team to develop a comprehensive program that will meet the endpoints you need to support your product's safety, while avoiding requests for additional information and other potential regulatory setbacks. Whether you require minimal testing or a complex customized program, our team will design the optimal strategy for your product, leveraging vast experience testing a wide range of devices and knowledge gained from leading and serving on international standards committees.

We are continuously refining our offerings to align with the needs of the global market. Currently, we are expanding our capabilities and opportunities for customers around the world with the addition of a new state-of-the-art facility analytical chemistry lab in Munich, Germany, providing extractable and leachable testing services.

Follow our blog, for the latest information.

PARTNERING FOR GLOBAL MEDICAL DEVICE SUCCESS

As your partner, our goal is to foster a collaborative engagement in which we work as an extension of your own internal team. We are able to leverage our diverse scientific, technical and regulatory expertise to help you achieve your goals.

We are an integrated platform with the flexibility to design customized solutions for each customer and project, and the ability to easily scale to commercialization. From materials characterization to custom efficacy studies, reprocessing validations to lot release, WuXi AppTec's medical device team has you covered.

– Counsel clients based on upcoming regulatory changes
– Actively participate in scientific discovery
– Support our clients through interaction with regulatory bodies
– Guide study design to achieve optimal outcomes
– Understand intent & focus of global regulatory groups
– Apply a broad base of regulatory experience across medical devices, biologics & combination products

WORKING WITH WuXi AppTec

CONFIDENTIALITY

WuXi AppTec's entire staff is sensitive to our clients' need for confidentiality regarding products, testing and laboratory reports. All information is held in strictest confidence and is released only when authorized by the client. Confidentiality agreements can be provided. Please contact your Business Development Manager for more information.

CLIENT AUDITS

We welcome the opportunity to show our scientific expertise and laboratory capabilities to our clients. Contact your Business Development Manager or the Quality Assurance Manager at the appropriate facility to arrange an audit of any of our facilities.

QUALITY SYSTEMS

Our quality is the very cornerstone of everything we do. Our team is committed to quality testing and continuous improvement.

WuXi AppTec complies with International Organization for Standardization (ISO) quality system and lab guidelines, and Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP).

CONTACT US FOR SERVICES OR TO REACH YOUR BUSINESS DEVELOPMENT MANAGER

ST. PAUL FACILITY

BIOCOMPATIBILITY TESTING
2540 Executive Drive
St. Paul, MN 55120

CHEMICAL CHARACTERIZATION CENTER OF EXCELLENCE
2520 Executive Drive
St. Paul, MN 55120

ATLANTA FACILITY

MICROBIOLOGY TESTING
1265 Kennestone Circle
Marietta, GA 30066

SUZHOU FACILITY

1318 Wuzhong Avenue, Wuzhong District,
Suzhou, Jiangsu, 215104, China

EMAIL
info@wuxiapptec.com

VISIT OUR WEBSITE
medicaldevice.wuxiapptec.com

PHONE
888-794-0077

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WuXi AppTec

PRECLINICAL SAFETY CONSULTING

OVERVIEW

WuXi AppTec is here to help you navigate global regulations by working with you to design optimal preclinical testing strategies for successful submission, respond to regulatory inquiries and support your commercial products. We have developed a database of reviewer questions, which further enhances our ability to identify new trends and quickly pass this learning on to our customers.

Our team will support you with a strategy that meets your individual needs and establishes the best path forward, avoiding potential roadblocks that can result in costly delays. We stand behind our testing, and fully support our customers by addressing any regulatory inquiries that may arise. Additionally, we can identify gaps in testing or compliance, and help you to develop a remedy to bring your testing up to date or resolve complicated regulatory concerns.

PROVEN EXPERTISE

Our active participation on global standards committees allows us to track and predict how regulators are interpreting new trends and regulatory changes. Using our consultation services provides you with direct access to the individuals at the forefront of medical device regulations, with subject matter expertise spanning custom *in vivo* models, reprocessing, package testing, osteoinduction, biocompatibility, histopathology, extractables / leachables, toxicological risk assessments and more.

Our team of consulting experts includes:

– Leaders and active participants on international standards committees, including multiple ISO 10993 committees, ASTM, AAMI and USP
– PhD and post-doctorate level experts, Masters-level scientists
– DVM (Doctorate of Veterinary Medicine)
– DABT (Diplomate of the American Board of Toxicology)

IN THIS SECTION

REGULATORY CONSULTING SERVICES

Biocompatibility Test Failure

We can help determine the cause of a test failure and provide a plan to address the results with written justification and/or alternative testing approaches.

Biological Evaluation Test Strategy Plan

This report, prepared by a toxicologist, will recommend and summarize an ISO 10993 biocompatibility testing strategy, including device details, standards followed, biological endpoints, chemical characterization and other elements, with the intention of increasing your likelihood of regulatory success.

Biological Evaluation Test Summary

This report, prepared by a toxicologist, will summarize the ISO 10993 biocompatibility testing performed, including device details, standards followed, biological endpoints, chemical characterization, etc., and provides an overview of results and device safety under intended clinical use.

Biological Evaluation with Toxicological Risk Assessment

This report includes the Toxicological Risk Assessment and ISO 10993 biocompatibility test results and summary.

Gap Analysis

A comprehensive review of pre-existing data to identify gaps when compared to current ISO 10993 standards. This report will assess impact and design a plan to address those gaps.

Initial Consultation

We have a team of experts dedicated to helping our customers execute appropriate studies to meet their needs. An initial consultation will identify project goals and help us understand your product.

REGULATORY CONSULTING SERVICES continued

Pre-Submission / Q-Submission Meeting

FDA Pre-Submission (Pre-Sub) / Q-Submission meetings are an effective way to gain important feedback and expectations for your product and submission strategy. To ensure your meeting is as effective as possible, our team of experts can assist with meeting preparation and are available to participate alongside you in those meetings, either as subject matter experts or to support scientific justifications, strategy or study designs.

Regulatory Inquiry Support

Regulatory and technical support are available to address inquiries from various regulatory agencies (e.g., A.I.'s, remediation, etc.)

Toxicological Risk Assessment

The toxicological risk assessment evaluates the safety of chemicals identified through chemical characterization and is based on relevant toxicological literature and the processes outlined in ISO 10993-17 to support biological safety.

Furthermore, we stand behind the testing we do, and we will support any inquiries related to our studies.

We strive for continuous improvement and staying at the forefront of scientific learning and discovery. Please contact your Business Development Manager for additional services. This catalog provides a comprehensive view of the tests we offer, but it is by no means exhaustive. We look forward to working with you in support of your medical device product portfolio.

CHEMISTRY TESTING

In accordance with the latest guidance from ISO 10993, materials characterizations should be considered for every device. Extractable / leachable studies are conducted to get a full characterization of all chemicals, which is then used to create an accurate assessment of risk. WuXi AppTec Medical Device Testing is the leader in complete identification—to us, unknowns are unacceptable. Let our team design a chemistry program tailored to meet your analytical needs.

Full characterization of all chemicals is required for an accurate assessment of risk, and it is our goal to identify all of the potential chemicals that could come out of your product. Utilizing multiple analytical methods, our team of chemistry experts works tirelessly to understand your materials, process and product to detect a full range of organic, semi-volatile and volatile chemicals, providing you with the data you need to make informed decisions and meet current regulatory requirements.

EQUIPMENT

ICPMS	HPLC-UV-MS	SEM-EDS
ICP-OES	GC-MS-QTOF	Particle Count
AA	HS-GC-MS	Spectrophotometer
UPLC-UV-QTOF-MS	Direct Inject GCMS	
UPLC-UV-QQQ-MS	IC	
HPLC-DAD	Microscope FTIR	

IN THIS SECTION

ISO 10993 Part 18 and Part 17
- Materials Characterization (Extractables / Leachables)
- Toxicological Risk Assessment of Extractables / Leachables Chemistry Results

Analytical Chemistry

Wet Chemistry

Physical Chemistry

ISO 10993 PART 18 AND PART 17

Materials Characterization (Extractables / Leachables)

Designing an extractables / leachables study for your device requires an understanding of the materials and manufacturing process. Even commonly used materials can have different extractables / leachables results based on impurities and processing.

We approach studies in a consultative manner with our team of chemists and toxicologists meeting with our customers to develop an appropriate test plan. Then we conduct an extractables / leachables study that meets current regulatory expectations.

Analytical equipment commonly used for extractables and leachables studies includes:

– Inductively Coupled Plasma – Mass Spectrometry to identify elements and metals

– Gas Chromatography – Mass Spectrometry and Headspace Gas Chromatography – Mass Spectrometry to identify volatile and semi-volatile compounds

– Liquid Chromatography – Mass Spectrometry to identify semi-volatile compounds

Multiple analytical techniques aid in uncovering the extracted chemicals associated with your product. Regulatory bodies look for this as part of the assessment of risk associated with your product.

Identification of the chemicals is required, and unknowns are unacceptable and must be treated as worst-case chemicals (carcinogen / mutagen / genotoxic agent). WuXi AppTec is known as the industry leader in identification. Our chemistry program was built knowing that chemistry data alone does not support product safety. It takes a toxicological risk assessment of the data to support safety.

Toxicological Risk Assessment of Extractables / Leachables Chemistry Results

WuXi AppTec Medical Device Testing's toxicological risk assessments are written to provide a thorough vetting of the chemicals from an extractables / leachables report. Following ISO 10993-17, our toxicologists assess each chemical to establish a margin of safety and identify whether further testing or analysis is required in order to mitigate risk.

ANALYTICAL CHEMISTRY

400756.1

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), 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 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.

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

ANALYTICAL CHEMISTRY continued

400440.1

Trace Metals – Elemental Analysis

This method is used to determine the presence of trace metals by atomic absorption spectroscopy.

Trace Metals – Inductively Coupled Plasma (ICP) Scan

If the trace metal is unknown, it is recommended that an elemental scan be performed using ICP spectroscopy. This technology allows the simultaneous determination of 20–30 elements in a single sample. Allows simultaneous determination of over 60 elements.

400510.1

UV/VIS Spectrophotometry

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.

Particulate Matter Light Obscuration Method – Medical Device Extraction

This method is used to extract a medical device in water followed by analysis of subvisible particulates using a light obscuration particle counting method.

WET CHEMISTRY

For information on this test, contact your Business Development Manager.

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.

400360.2

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 continued

400160.1

Glutaraldehyde Residues

Glutaraldehyde is used as a liquid chemical sterilant in the medical device industry and in hospital environments. 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.

For information on this test, contact your Business Development Manager.

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.

400260.1

pH

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.

WET CHEMISTRY continued

400280.1

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 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.

400280.2

Physicochemical Tests, USP Test Panel – Elastomeric Closures for Injections <381>

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 and 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.

Ammonium
A colorimetric analysis is performed on the extract to determine ammonium content.

Volatile Sulfides
A qualitative colorimetric evaluation, using lead acetate test paper, to determine the presence of any volatile sulfides in the extract.

WET CHEMISTRY continued

400290.1

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).

400360.3

Purified Water, USP

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

400360.1

Total Organic Carbon (TOC)

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.

400253.1

Total Dissolved Solids (TDS)

TDS is a measure of the combined content of all inorganic and organic substances contained in a liquid, typically minerals and salts. The TDS is measured using a conductivity electrode.

400500.1

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.

WET CHEMISTRY continued

USP Chemistry Tests

Testing is based on each individual USP monograph.

Available tests include the following:

400446.1 Sodium Chloride Titration

300140.1 Hydrogen Peroxide Determination

400540.1

Water for Injection, USP

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

PHYSICAL CHEMISTRY

20661.1

Moisture – Residual by Gravimetric Analysis

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.

20661.2

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 and chemicals.

400434.1

Calcium – Residual

This method is used to determine the residual calcium of demineralized bone and other tissue-based products. It features an acid digestion followed by atomic absorption spectroscopy.

400320.1

Refractive Index

The refractive index of various liquids is measured using a Reichert AR200 digital refractometer.

400340.1

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.

PHYSICAL CHEMISTRY continued

400350.1

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.

400530.1

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.

We strive for continuous improvement and staying at the forefront of scientific learning and discovery. Please contact your Business Development Manager for additional services. This catalog provides a comprehensive view of the tests we offer, but it is by no means exhaustive. We look forward to working with you in support of your medical device product portfolio.

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BIOCOMPATIBILITY

OVERVIEW

Within the general safety testing framework, it remains the responsibility of the device manufacturer to select and justify the specific tests most appropriate for product safety and compliance with regulatory requirements.

It is recommended that testing be performed to comply with GLP regulations. With years of experience in biocompatibility testing, WuXi AppTec Medical Device Testing provides exceptional expertise to assist medical device manufacturers in designing thorough, well-constructed testing programs that meet global compliance standards.

REFERENCE INFORMATION

Device Categories

Framework for Development of Biocompatibility Evaluations

Guide to Sample Requirements for Biocompatibility Testing

IN THIS SECTION

DEVICE CATEGORIES

Device Categories by Nature of Contact

Medical devices fall into one of four categories based on the nature of patient contact:

Non-Contact Devices

Devices that do not directly or indirectly contact the patient are not required to undergo biocompatibility testing.

Surface Devices

— **Contacting Intact Skin**
(e.g., electrodes, external prostheses, fixation tapes, compression bandages)

— **Contacting Mucous Membranes**
(e.g., contact lenses, urinary catheters, colonoscopes, endotracheal tubes)

— **Contacting Breached or Compromised Surfaces**
(e.g., wound dressings, occlusive patches, healing devices)

External Communicating Devices

— **Contacting Blood Path Indirectly**
(e.g., solution administration sets, I.V. extension sets, blood transfusion sets)

— **Contacting Tissue, Bone or Dentin**
(e.g., laparoscopes, arthroscopes, draining systems, dental cements, skin staples)

— **Contacting Circulating Blood**
(e.g., intravenous and delivery catheters, temporary pacemaker electrodes, dialyzers, dialysis tubing, hemadsorbents, immunoabsorbents)

Implant Devices

— **Contacting Tissue and/or Bone**
(e.g., orthopedic pins and plates, pacemakers, breast implants, replacement tendons, ligation clips, drug supply devices)

— **Contacting Blood**
(e.g., pacemaker electrodes, heart valves, vascular grafts, ventricular assist devices, internal drug delivery devices, stents)

Device Categories by Duration of Contact

Devices generally are placed in one of three categories based on expected duration of contact with patient:

A	LIMITED [≤ 24 hours]
B	PROLONGED [> 24 hours and ≤ 30 days]
C	PERMANENT [> 30 days]

FRAMEWORK FOR DEVELOPMENT OF BIOCOMPATIBILITY EVALUATIONS

Based on Guidance issued by the US FDA September 4, 2020

Use of International Standard ISO 10993-1, "Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing within a Risk Management Process"

Note: The following is a framework for the development of a biocompatibility evaluation and is not a checklist for testing. For particular medical devices, different biological endpoints may require evaluation, including either additional or fewer endpoints than indicated. See section 6 of ISO 10993-1 2018 for additional information regarding how to use physical and chemical information, in addition to the table below, to further determine what testing is required.

MEDICAL DEVICE CATEGORIES			BIOLOGICAL ENDPOINT													
NATURE OF BODY CONTACT		CONTACT DURATION A – Limited [≤ 24 h] B – Prolonged [> 24 h to 30 d] C – Permanent [> 30 d]	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	[3]Reproductive/Developmental Toxicity	[4]Degradation
CATEGORY	CONTACT															
SURFACE DEVICE	Intact Skin	A	●	●	●										
		B	●	●	●										
		C	●	●	●										
	Mucosal Membrane	A	●	●	●										
		B	●	●	●	◊	◊	◊		◊					
		C	●	●	●	◊	◊	●	●	◊		◊			
	Breached or Compromised Surface	A	●	●	●	◊	◊								
		B	●	●	●	◊	◊	◊		◊					
		C	●	●	●	◊	◊	●	●	◊		◊	◊		
EXTERNAL COMMUNICATING DEVICE	Blood Path, Indirect	A	●	●	●	●	◊				●				
		B	●	●	●	●	◊	◊			●				
		C	●	●	◊	●	◊	●	●	◊	●	◊	◊		
	Tissue[1] / Bone / Dentin	A	●	●	●	◊	◊								
		B	●	●	●	●	◊	●	●	●					
		C	●	●	●	●	◊	●	●	●		◊	◊		
	Circulating Blood	A	●	●	●	●	◊		◊[2]		●				
		B	●	●	●	●	◊	●	●	●	●				
		C	●	●	●	●	◊	●	●	●	●	◊	◊		
IMPLANT DEVICES	Tissue[1] / Bone	A	●	●	●	◊	◊								
		B	●	●	●	●	◊	●	●	●					
		C	●	●	●	●	◊	●	●	●		◊	◊		
	Blood	A	●	●	●	●	◊		◊	●	●				
		B	●	●	●	●	◊	●	●	●	●				
		C	●	●	●	●	◊	●	●	●	●	◊	◊		

● = ISO 10993-1:2018 recommended endpoints for consideration*
◊ = Additional FDA recommended endpoints for consideration*

Note: All ● and ◊ should be addressed in the biological safety evaluation, either through the use of existing data, additional endpoint-specific testing, or a rationale for why the endpoint does not require additional assessment.

[1] Tissue includes tissue fluids and subcutaneous spaces

[2] For all devices used in extracorporeal circuits

[3] Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, devices with relevant target populations (e.g., pregnant women), and/or devices where there is the probability for local presence of device materials in the reproductive organs

[4] Degradation information should be provided for any devices, device components, or materials remaining in contact with tissue that are intended to degrade

GUIDE TO SAMPLE REQUIREMENTS FOR BIOCOMPATIBILITY TESTING

This chart is designed as a convenient quick guide for some of our most commonly ordered tests (and does not list all available tests).

Note: If a test article is or may be absorbent, additional test article will be required to complete an absorbency pretest.

Sample requirements represent the total number of extracts / replicates needed. For example, Partial Thromboplastin Time requires three replicates at 6 cm^2 each. The sample sizes reflect the minimum amount of sample, depending on the test being performed. For liquid samples, please inquire.

TESTS PERFORMED USING EXTRACTION RATIOS	< 0.5 mm thickness Ratio: 6 cm^2 / 1 mL	≥ 0.5 mm thickness Ratio: 3 cm^2/ 1 mL	Irregularly Shaped Ratio: 0.2 g / 1 mL	Membranes /Textiles Ratio: 0.1 g / 1 mL
CYTOTOXICITY				
MEM Elution Using L-929 Mouse Fibroblast Cells - ISO/USP	1 x 30 cm^2	1 x 15 cm^2	1 x 1 g	1 x 0.5 g
MEM Endpoint Dilution Using L-929 Mouse Fibroblast Cells— ISO	1 x 48 cm^2	1 x 24 cm^2	1 x 1 g	1 x 0.8 g
MTT Cytotoxicity Using L-929 Mouse Fibroblast Cells— ISO	1 x 36 cm^2	1 x 18 cm^2	1 x 1.2 g	1 x 0.6 g
Neutral Red Uptake (NRU) — ISO	1 x 60 cm^2	1 x 30 cm^2	1 x 2 g	1 x 1 g
Colony Formation Cytotoxicity Using V79 Cells — ISO	1 x 150 cm^2	1 x 75 cm^2	1 x 5 g	1 x 2.5 g
SENSITIZATION				
Maximization Sensitization (Guinea Pig) — ISO	6 x 60 cm^2	6 x 30 cm^2	6 x 2 g	6 x 1 g
IRRITATION				
In Vitro Skin Irritation — ISO	2 x 6 cm^2	2 x 3 cm^2	2 x 0.2 g	2 x 0.1
Intracutaneous Irritation — ISO / USP	2 x 36 cm^2	2 x 18 cm^2	2 x 2 g	2 x 1g
Vaginal Mucosal Irritation — ISO	10 x 60 cm^2	10 x 30 cm^2	10 x 2 g	10 x 1 g
ACUTE SYSTEMIC TOXICITY				
Acute Systemic Toxicity— ISO / USP	2 x 60 cm^2	2 x 30 cm^2	2 x 2.0 g	1 x 1.5 g
PYROGENICITY				
Materials Mediated Rabbit Pyrogen — ISO	1 x 900 cm^2	1 x 450 cm^2	1 x 30 g	1 X 15 g
SUBACUTE / SUBCHRONIC TOXICITY *NOTE: SEE SUBACUTE/SUBCHRONIC SECTION FOR ADDITIONAL DETAILS*				
Subchronic Intravenous Toxicity (Mice) — 14 Dose	14 x 48 cm^2	14 x 24 cm^2	14 x 1.6 g	2 x 0.8 g
Subacute Intraperitoneal Toxicity (Mice) — 14 Dose	14 x 30 cm^2	14 x 15 cm^2	14 x 1 g	14 x 0.5 g
Subchronic Intravenous Toxicity (Rats) — 14 Dose	14 x 270 cm^2	14 x 135 cm^2	14 x 9 g	14 x 4.5 g
Subacute Intraperitoneal Toxicity (Rats) — 14 Dose	14 x 90 cm^2	14 x 45 cm^2	14 x 3 g	14 x 1.5 g
Subacute Intraperitoneal Toxicity (Rats) — 28 Dose	14 x 90 cm^2	14 x 45 cm^2	14 x 3 g	14 x 1.5 g
Subchronic Intravenous Toxicity (Rats) — 28 Dose	28 x 270 cm^2	28 x 135 cm^2	28 x 9 g	28 x 4.5 g
Subchronic Toxicity – Dual Routes of Administration (Rats) – 14 day IV/5 day IP	14 x 300 cm^2 and 5 x 150 cm^2	14 x 150 cm^2 and 5 x 75 cm^2	14 x 10 g and 5 x 5 g	14 x 5 g and 5 x 2.5 g

TESTS PERFORMED USING EXTRACTION RATIOS (CONTINUED)	EXTRACT TYPE	< 0.5 mm thickness Ratio: 6 cm^2 / 1 mL	≥ 0.5 mm thickness Ratio: 3 cm^2/ 1 mL	Irregularly Shaped Ratio: 0.2 g / 1 mL	Membranes /Textiles Ratio: 0.1 g / 1 mL
GENOTOXICITY					
Bacterial Mutagenicity (Ames) *NOTE: quantity required would change from 2 to 3 if a DMSO/PEG compatibility pretest is required.*		2 x 30 cm^2	2 x 15 cm^2	2 x 1 g	2 x 0.5 g
***In Vivo* Mouse Micronucleus**		2 x 120 cm^2	2 x 60 cm^2	2 x 4 g	2 x 2 g
***In Vitro* Mouse Lymphoma (MLA) with Extended Treatment** *NOTE: For two extract MLA studies, sufficient test article for one polar and one non-polar extract will be required. Quantity required for non-polar extracts would also change from 1 to 2 if a DMSO/PEG compatibility pretest is required.*	Polar Extract- Normal Saline	1 x 72 cm^2	1 x 36 cm^2	1 x 2.4 g	1 x 1.2 g
	Polar Extract- Culture Media (without Serum)	1 x 570 cm^2	1 x 285 cm^2	1 x 19 g	1 x 9.5 g
	Non-Polar Extracts (DMSO or PEG)	1 x 12 cm^2	1 x 6 cm^2	1 x 0.4 g	1 x 0.2 g

GUIDE TO SAMPLE REQUIREMENTS FOR BIOCOMPATIBILITY TESTING continued

IMPLANTATION TESTS (NOTE: Turnaround times are in addition to implant duration.)	
Intramuscular / Subcutaneous Implantation (3 Rabbits) — ISO	Sufficient material to produce 18 implants, approx. 10 mm x 3 mm each
Intramuscular / Subcutaneous Implantation (5 Rabbits) — ISO	Sufficient material to produce 28 implants, approx. 10 mm x 3 mm each
Intramuscular Implantation — USP	Sufficient material to produce 13 implants, approx. 10 mm x 3 mm each
Intramuscular Implantation Toxicity Test – ISO (Currently only available in 13 week Rabbit)	Will require discussion with Study Director to determine sample requirements.

HEMOCOMPATIBILITY / BLOOD COMPATIBILITY TESTS			
	< 0.5 mm thickness Ratio: 6 cm^2/1mL	**≥ 0.5 mm thickness Ratio : 3 cm^2/ 1 mL**	**Irregularly Shaped Ratio: 0.2 g / 1 mL**
Complement Activation C3a and SC5b-9	6 cm^2	3 cm^2	0.2 g
Hemolysis: ASTM — Direct Contact	3 x 42 cm^2	3 x 21 cm^2	3 x 1.4 g
Hemolysis: ASTM — Extract	3 x 60 cm^2	3 x 30 cm^2	3 x 2 g
In Vitro Hemocompatibility	3 x 12 cm^2		
Partial Thromboplastin Time	3 x 6 cm^2		
Platelet and Leukocyte Count	3 x 12 cm^2		
Thromboresistance (*In Vivo*)	1 test sample and 1 comparison sample per animal		

**Concurrent testing of sponsor-supplied comparison product is recommended. (Required for thromboresistance studies.) Sample size of the comparison product should be the same as that of the test article.*

TESTS PERFORMED USING THE PATCH METHOD (SKIN CONTACTING)	
Agarose Overlay Using L-929 Cells – ISO / USP	Sufficient material to produce 3 patches, 1 cm x 1 cm each — Recommended 1 material per test, Maximum 2 materials per test
Primary Skin Irritation - ISO	Sufficient material to produce 7 patches, 2.5 cm x 2.5 cm each — Recommended 1 material per test, Maximum of 4 materials
Repeated Patch Dermal Sensitization Test - Buehler	Sufficient material to produce 116 patches, 2.5 cm x 2.5cm each – Recommended 1 material per test, maximum of 4 materials + 1 additional test article

CYTOTOXICITY TESTING

Cytotoxicity testing involves exposing test article to cell cultures via extracts or direct contact. Cell cultures are extremely sensitive to minute quantities of chemicals and readily display characteristic signs of toxicity in the presence of potentially harmful extractables/leachables. Cytotoxicity *In Vitro* testing is also required in testing the biocompatibility of medical devices. Typical testing programs will utilize the ISO test method to meet international regulatory requirements.

Cytotoxicity testing is frequently used for screening tests to characterize materials or to evaluate new materials against established ones.

AGAROSE OVERLAY

SAMPLE REQUIREMENTS

1 mL liquid (sterile)
Sufficient material to produce 3 patches,
1 cm x 1 cm each

140150.1 (GLP)
140150.2

ISO Agarose Overlay Using L-929 Mouse Fibroblast Cells

L-929 mouse fibroblast cells are overlayed with a permeable agar film. A solid sample or liquid saturated disc is then placed in triplicate containers on the agar surface. Cells are examined at 24 hours for signs of toxicity.

140100.1 (GLP)
140100.2

USP Agarose Overlay Using L-929 Mouse Fibroblast Cells

L-929 mouse fibroblast cells are overlayed with a permeable agar film. A solid sample or liquid saturated disc is then placed in duplicate containers on the agar surface. Cells are examined at 24 hours for signs of toxicity.

DIRECT CONTACT

SAMPLE REQUIREMENTS

1 mL liquid (sterile)
Sufficient material to produce 3 patches,
1 cm x 1 cm each

140250.1 (GLP)
140250.2

ISO Direct Contact Cytotoxicity Using L-929 Mouse Fibroblast Cells

A test article is placed in direct contact with L-929 mouse fibroblast cells. Cells are examined at 24 hours for signs of toxicity.

CYTOTOXICITY TESTING continued

MEM ELUTION

SAMPLE REQUIREMENTS

BY THICKNESS		BY WEIGHT	BY WEIGHT (Low Density Materials)	LIQUIDS
< 0.5 mm thick	≥ 0.5 mm thick	1 g	0.5 g	5 mL
30 cm^2	15 cm^2			

140300.1 (GLP)
140300.2

USP MEM Elution Using L-929 Mouse Fibroblast Cells

Solid materials are extracted in cell culture medium and the extracts are then placed in duplicate containers of L-929 mouse fibroblast cells. Cells are examined at 24 and 48 hours for signs of toxicity.

ISO MEM Elution Using L-929 Mouse Fibroblast Cells

Solid materials are extracted in cell culture medium and the extracts are then placed in triplicate containers of L-929 mouse fibroblast cells.

140320.1 (GLP)
140320.2

24-Hour Extraction and 72-Hour Read

Extracted in cell culture medium for 24 hours. Cells are examined at 24, 48 and 72 hours for signs of toxicity.

140322.1 (GLP)
140322.2

72-Hour Extraction and 72-Hour Read

Extracted in cell culture medium for 72 hours. Cells are examined at 24, 48 and 72 hours for signs of toxicity.

140526.1 (GLP)
140526.2

24-Hour Extraction and 48-Hour Read

Extracted in cell culture medium for 24 hours. Cells are examined at 24 and 48 hours for signs of toxicity.

140527.1 (GLP)
140527.2

72-Hour Extraction and 48-Hour Read

Extracted in cell culture medium for 72 hours. Cells are examined at 24 and 48 hours for signs of toxicity.

140325.1 (GLP)
140325.2

Liquid Test Article

Liquid test article is mixed with cell culture medium and cells are examined at 24, 48 and 72 hours for signs of toxicity.

CYTOTOXICITY TESTING continued

MEM ENDPOINT DILUTION

SAMPLE REQUIREMENTS

BY THICKNESS		BY WEIGHT	BY WEIGHT (Low Density Materials)	LIQUIDS
< 0.5 mm thick	≥ 0.5 mm thick	1.6 g	0.8 g	8 mL
48 cm^2	24 cm^2			

ISO MEM Endpoint Dilution Using L-929 Mouse Fibroblast Cells

If a material is suspected to have cytotoxic properties, performing the cytotoxicity test with dilutions can be useful. Eight 2-fold dilutions are made to determine the toxic endpoint. Performance of the test will result in an estimation of the relative "strength" of the cytotoxic substance in the material.

140350.1 (GLP)
140350.2

24-Hour Extraction and 72-Hour Reading

Extracted in cell culture medium for 24 hours. Cells are examined at 24, 48 and 72 hours for signs of toxicity.

140351.1 (GLP)
140351.2

72-Hour Extraction and 72-Hour Read

Extracted in cell culture medium for 72 hours. Cells are examined at 24, 48 and 72 hours for signs of toxicity.

140353.1 (GLP)
140353.2

24-Hour Extraction and 48-Hour Reading

Extracted in cell culture medium for 24 hours. Cells are examined at 24 and 48 hours for signs of toxicity.

140355.1 (GLP)
140355.2

For Liquids

Liquid test article is mixed with cell culture medium and the cells are examined at 24, 48 and 72 hours for signs of toxicity

CYTOTOXICITY TESTING continued

MTT Cytotoxicity Using L-929 Mouse Fibroblast Cells

This assay is used to measure the viability of cells after exposure to a test material extract by photometric measurement of their ability to metabolize MTT into formazan. Solid materials are extracted in cell culture medium. Multiple dilutions of the extract are prepared and added to triplicate wells. After incubation, the MTT reagent {3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide} is added to each well. After a second incubation, the amount of formazan formed is determined. Cytotoxicity is calculated based on the formazan levels.

SAMPLE REQUIREMENTS

BY THICKNESS		BY WEIGHT	BY WEIGHT (Low Density Materials)
< 0.5 mm thick	≥ 0.5 mm thick		
36 cm^2	18 cm^2	1.2 g	0.8 g

140550.1 (GLP) 140550.2	**24-Hour Extraction**	140550.3 (GLP) 140550.4	**72-Hour Extraction**

Neutral Red Uptake (NRU) Cytotoxicity

This assay is used to measure the viability of cells after exposure to a test material extract by photometric measurement of their ability to incorporate and bind neutral red (NR), a supravital dye.

SAMPLE REQUIREMENTS

BY THICKNESS		BY WEIGHT
< 0.5 mm thick	≥ 0.5 mm thick	2 g
60 cm^2	30 cm^2	Low density: 1 g

140465.1 (GLP) 140465.2	**24-Hour Extraction**	140465.3 (GLP) 140550.4	**72-Hour Extraction**

140475.1 (GLP)
140475.2

Colony Formation Cytotoxicity Using V79 Cells

The purpose of this procedure is to evaluate the cytotoxic response of a specified mammalian culture cell line when exposed to an extract of the test article. This assay utilizes the sensitivity of low cell density to evaluate the cytotoxicity of medical devices. Test articles and controls will be prepared and extracted for 24-25 hours at 37 ± 1° C. Appropriate dilutions of the extracts will be prepared using E-MEM +10% FBS. After removing spent medium, 2.0 ml of the extract will be added to the plates. The cells will be incubated at 37 ± 1°C for 7-9 days before fixation, staining and counting.

SAMPLE REQUIREMENTS

BY THICKNESS		BY WEIGHT	LIQUIDS
< 0.5 mm thick	≥ 0.5 mm thick	5 g	25 mL
150 cm^2	75 cm^2	Low density: 1 g	

SENSITIZATION TESTING

Sensitization tests estimate the potential for contact redness or other edema response through the testing of appropriate materials or extracts.

ISO Guinea Pig Maximization Sensitization Test

9008547.1
2 extracts
(GLP)

9008547.2
2 extracts

9008547.3
1 extract
(GLP)

9008547.4
1 extract

Guinea pigs are exposed to test article extract(s) twice within a 2-week period (Inductions I and II). The animals are re-exposed (challenged) 14 ± 1 days after Induction II by placing fresh solution or extract in contact with previously unexposed skin. At 24 and 48 hours after removal of the challenge wrap, the animals are observed for signs of a delayed allergic response when compared to a control group. If necessary, a re-challenge can be conducted within 7-14 days of the initial challenge.

SAMPLE REQUIREMENTS (Per Extract)

BY THICKNESS		BY WEIGHT	BY WEIGHT (Low Density Materials)
< 0.5 mm thick	≥ 0.5 mm thick	2 g	1 g
60 cm^2	30 cm^2		

NUMBER OF ANIMALS
11 test
6 controls

EXTRACT OPTIONS
Normal Saline
Sesame Oil

Sample preparation complies with ISO 10993-12.

Repeated Patch Dermal Sensitization Test (Buehler Method modified for medical devices)

900899.1
Solid Patch
(GLP)

900899.2
Solid Patch

900899.3
2 extracts
(GLP)

900899.4
2 extracts

Guinea pigs are occlusively patched with the test article 3 days each week for 3 weeks. The contact duration will be approximately 6 hours. A negative control will be similarly patched to six designated guinea pigs. Fourteen ± 1 days after the last induction patch, the animals are shaved on the opposite flank and patched with the respective test or control article for approximately 6 hours. After removal of the patches, the sites will be scored for erythema and edema and assessed for incidence and severity of a sensitization reaction.

NUMBER OF ANIMALS
11 test
6 controls

SAMPLE REQUIREMENTS
For patches:
Sufficient material to produce 116 patches, approx. 2.5 cm x 2.5 cm each
Additional test article for archival as per 21 CFR 58

50 mL of liquid for liquid testing

For extracts:
See ISO Guinea Pig Maximization Sensitization Test requirements (per extract)
Additional test article for archival as per 21 CFR 58

SENSITIZATION TESTING continued

900847.1
(GLP)
900847.2

ISO Guinea Pig Maximization Sensitization Test (Method for Liquid Test Article)

Guinea pigs are exposed to the liquid test article twice within a 2-week period (Inductions I and II). The animals are re-exposed (challenged) 14 ± 1 days after Induction II by placing test article in contact with previously unexposed skin. At 24 and 48 hours after removal of the challenge wrap, the animals are observed for signs of a delayed allergic response when compared to a control group. If necessary, a re-challenge can be conducted within 7-14 days of the initial challenge.

SAMPLE REQUIREMENTS
30 mL

NUMBER OF ANIMALS
11 test
6 controls

900890.1
(GLP)
900890.2

Buehler Dermal Sensitization Test (Method for Chemical Compounds)

Guinea pigs will be shaved and occlusively patched with the Sponsor-supplied test article 1 day each week for 3 weeks. The contact duration will be approximately 6 hours. A negative control will be similarly patched to six designated guinea pigs. Fourteen days after the last induction patch, the animals will be shaved on the opposite flank and patched with the respective test or control article for approximately 6 hours. After removal of the patches, the sites will be scored for erythema and edema and assessed for incidence and severity of a sensitization reaction.

SAMPLE REQUIREMENTS
50 mL
Additional test article for archival as per 21 CFR 58

NUMBER OF ANIMALS
11 test
6 controls

IRRITATION TESTING (*IN VIVO*)

Irritation (reactivity) tests assess the localized reaction of tissues to device materials or extracts. The selection of a test method is based on intended patient contact type.

For breached tissue and blood contact, the intracutaneous test is usually selected. The dermal irritation test usually involves direct contact with the test material. The mucosal irritation test may involve either direct contact or use of extracts. Extract preparation uses solvents that will extract either hydrophilic (polar) or lipophilic (non-polar) compounds that may be present in the device materials..

9006000.1	2 extracts (GLP)
9006000.2	2 extracts
9006000.3	1 extract (GLP)
9006000.4	1 extract
9006000.5	4 extracts (GLP)
9006000.6	4 extracts
9006000.7	No extraction (GLP)
9006000.8	No extraction

USP Intracutaneous Irritation Test (2 rabbits)

Test material solution or an extract of a device is injected intracutaneously into rabbits to assess the possible irritancy of test article compounds. The animals are observed for dermal reactions over a 72-hour period. If the animals do not show significant signs of irritation above those animals observed in the concurrent test control groups, the test article passes the test.

SAMPLE REQUIREMENTS (Per Extract)

BY THICKNESS		BY WEIGHT	BY WEIGHT (Low Density Materials)	LIQUIDS
< 0.5 mm thick	≥ 0.5 mm thick	1 x 2 g	0.6 g	Inquire
36 cm²	18 cm²			

EXTRACT OPTIONS
Normal Saline
Sesame Oil
5% Ethanol in Saline
Polyethylene Glycol

Sample preparation complies with ISO 10993-12.

9107015.1	2 extracts (GLP)
9107015.2	2 extracts
9107015.3	1 extract (GLP)
9107015.4	1 extract
9107015.5	4 extracts (GLP)
9107015.6	4 extracts
9107015.7	No extraction (GLP)
9107015.8	No extraction

ISO Intracutaneous Irritation Test (3 rabbits)

Test material solution or an extract of a device is injected intracutaneously into rabbits to assess the possible irritancy of test article compounds. The animals are observed for dermal reactions over a 72-hour period. If the difference between the average scores for the test article and the control are less than or equal to 1.0, the test article passes the test.

SAMPLE REQUIREMENTS (Per Extract)

BY THICKNESS		BY WEIGHT	BY WEIGHT (Low Density Materials)	LIQUIDS
< 0.5 mm thick	≥ 0.5 mm thick	1 x 2 g	0.6 g	Inquire
36 cm²	18 cm²			

EXTRACT OPTIONS
Normal Saline
Sesame Oil
5% Ethanol in Saline
Polyethylene Glycol

Sample preparation complies with ISO 10993-12.

IRRITATION TESTING (*IN VIVO*) continued

9107900.1	2 extracts (GLP)
9107900.2	2 extracts
9107900.3	1 extract (GLP)
9107900.4	1 extract
9107900.5	No extraction (GLP)
9107900.6	No extraction

ISO Mucosal (Vaginal) Irritation Test (6 rabbits per extract)

Materials that come in direct or indirect contact with mucosal tissue can be assessed as to irritation potential by repeated administration of a test article solution or extract into rabbit vaginas. Acute irritation is evaluated by gross observation and histopathology of the vaginal mucosa and submucosa. Usually an application is performed on each of 5 days unless longer treatment is indicated due to the use of the device. Final evaluation is based on histopathological evaluation.

SAMPLE REQUIREMENTS (Per Extract)

BY THICKNESS		BY WEIGHT	BY WEIGHT (Low Density Materials)	LIQUIDS
< 0.5 mm thick	≥ 0.5 mm thick	5 x 2 g	5 x 1 g	Inquire
5 X 60 cm^2	5 X 30 cm^2			

EXTRACT OPTIONS
Normal Saline
Sesame Oil

Sample preparation complies with ISO 10993-12.

910699.1	(GLP)
910699.2	
910699.3	2 extracts (GLP)
910699.4	2 extracts
910699.5	1 extract (GLP)
910699.6	1 extract

ISO Primary Skin Irritation Test (3 rabbits)

This test is performed to assess the potential for topical irritation from acute exposure or use of the device material. The material is applied to intact skin of 3 rabbits and left in contact for 4 or 24 hours. (Extracts are used for irregularly shaped materials.) An assessment of irritation, erythema (redness) and edema (swelling) is made during the next 72 hours.

NOTE: Sponsor specifies contact duration on test request form.

SAMPLE REQUIREMENTS
Sufficient material to produce 7 patches, approx. 2.5 cm x 2.5 cm each
5 mL of liquid

SYSTEMIC TOXICITY TESTING

The purpose of this test is to screen solutions or test article extracts for potential toxic effects as the result of systemic injection dosing.

9007000.1	2 extracts (GLP)
9007000.2	2 extracts
9007000.3	1 extract (GLP)
9007000.4	1 extract
9007000.5	4 extracts (GLP)
9007000.6	4 extracts
9007000.7	No extraction (GLP)
9007000.8	No extraction

USP Acute Systemic Toxicity Test

Toxicity tests estimate the potential harmful systemic effects from a single exposure to polar or non-polar extracts of device materials.

Test article solution or extract is injected into mice (5 per solution / extract, 5 per control) to assess the possible toxicity of compounds in the test article. The animals are observed over a 72-hour period. If the animals exposed to the test article do not show signs of toxicity greater than the concurrent control groups, the test article passes the test.

SAMPLE REQUIREMENTS (Per Extract)

BY THICKNESS		BY WEIGHT	BY WEIGHT (Low Density Materials)	LIQUIDS
< 0.5 mm thick	≥ 0.5 mm thick	2.0 g	1.0 g	Inquire
60 cm²	30 cm²			

EXTRACT OPTIONS
Normal Saline
Sesame Oil
5% Ethanol in Saline
Polyethylene Glycol

Sample preparation complies with ISO 10993-12.

9017700.1	2 extracts (GLP)
9017700.2	2 extracts
9017700.3	1 extract (GLP)
9017700.4	1 extracts
9017700.5	4 extracts (GLP)
9017700.6	4 extracts
9017700.7	No extraction (GLP)
9017700.8	No extraction

ISO Acute Systemic Toxicity Test

Toxicity tests estimate the potential harmful systemic effects from a single exposure to polar or non-polar extracts of device materials.

Test article solution or extract is injected into mice (5 per solution / extract, 5 per control) to assess the possible toxicity of compounds in the test article. The animals are observed over a 72-hour period. If the animals exposed to the test article do not show signs of toxicity greater than the concurrent control groups, the test article passes the test.

SAMPLE REQUIREMENTS (Per Extract)

BY THICKNESS		BY WEIGHT	BY WEIGHT (Low Density Materials)	LIQUIDS
< 0.5 mm thick	≥ 0.5 mm thick	2.0 g	1.0 g	Inquire
60 cm²	30 cm²			

EXTRACT OPTIONS
Normal Saline
Sesame Oil
5% Ethanol in Saline
Polyethylene Glycol

For ISO, normal saline and/ or sesame oil extracts are recommended.

Sample preparation complies with ISO 10993-12.

PYROGENICITY TESTING *(IN VIVO)*

Pyrogenicity tests determine the potential of materials, extracts and/or a finished device to induce a fever response from sources other than endotoxin.

This section addresses the *in vivo* models for pyrogenicity. The most common type of pyrogen encountered is bacterial endotoxin. The detection method used is *in vitro* Bacterial Endotoxin/Limulus Amebocyte Lysate (LAL) test.

Information regarding LAL testing will be found in the Microbiology section.

900770.1 (GLP)

900770.2

900770.3 No extraction (GLP)

900770.4 No extraction

ISO Rabbit Pyrogen – Materials Mediated (3 rabbits)

To assess pyrogenicity, injections are made intravenously into rabbits. For extraction testing, an extract of the test article is prepared in a sterile saline solution. The animals are observed over a 3-hour period for an increase in body temperature. If the animals do not show significant increase in body temperature, the test article passes the test. If any single animal of the three has a temperature increase above the acceptable range, the test can be continued with 5 additional animals at the client's request (additional charges apply).

EXTRACT OPTION Normal Saline

BY THICKNESS		BY WEIGHT	BY WEIGHT (Low Density)	LIQUID
< 0.5 mm thick	≥ 0.5 mm thick	30 g	15 g	Inquire
900 cm²	450 cm²			

SUBACUTE / SUBCHRONIC TOXICITY TESTING

Subacute toxicity is assessed after single or multiple exposures to extracts of device materials. The exposure period is longer than typical acute toxicity tests, but not to exceed 10% of animal lifespan.

Subchronic toxicity is assessed after repeated intravenous injections of the device materials extract. These studies involve expanded evaluations and can include systemic changes, local irritation, body weight, blood values and tissue changes as part of the protocol. The length of time for the test and the parameters evaluated will depend on the end use of the device. WuXi AppTec will assist in the test program design.

Also Featuring: NEW! Dual Route (ISO 10993-11) available.

All of the following include Histopathology, Clinical Chemistry and Hematology.

800575.1 (GLP) — 14 day / 14 dose

ISO Subacute Intraperitoneal Toxicity Study — Mice

Multiple extracts of a device are prepared and injected into five male and five female mice over the test time period. Two similar control groups are also injected with control vehicle. The animals are observed during the test time period for signs of toxicity and are subjected to gross observations at study termination and histopathological evaluation. The test article passes if the test parameters (weight, survival, clinical observations, blood work (clinical chemistry and hematology), microscopic observations, and gross necropsy) are not significantly different from the concurrent control animal parameters.

800555.1 (GLP) — 14 day / 14 dose

800592.1 — 28 day / 14 dose

ISO Subacute Intraperitoneal Toxicity Study — Rats

Multiple extracts of a device are prepared and injected into five male and five female rats over the test time period. Two similar control groups are also injected with control vehicle. The animals are observed during the test time period for signs of toxicity and are subjected to gross observations at study termination and histopathological evaluation. The test article passes if the test parameters (weight, survival, clinical observations, blood work (clinical chemistry, coagulation, and hematology), microscopic observations and gross necropsy) are not significantly different from the concurrent control animal parameters.

800565.1 (GLP) — 14 day / 14 dose

ISO Subchronic Intravenous Toxicity Study — Mice

Multiple extracts of a device are prepared and injected into five male and five female mice over the test time period. Two similar control groups are also injected with control vehicle. The animals are observed during the test time period for signs of toxicity and are subjected to gross observations at study termination and histopathological evaluation. The test article passes if the test parameters (weight, survival, clinical observations, blood work (clinical chemistry and hematology), microscopic observations, and gross necropsy) are not significantly different from the concurrent control animal parameters.

SUBACUTE / SUBCHRONIC TOXICITY TESTING continued

800545.1
14 day / 14 dose
(GLP)

800593.1
28 day /28 dose

ISO Subchronic Intravenous Toxicity Study — Rats

Multiple extracts of a device are prepared and injected into five male and five female rats over the test time period. Two similar control groups are also injected with control vehicle. The animals are observed during the test time period for signs of toxicity and are subjected to gross observations at study termination and histopathological evaluation. The test article passes if the test parameters (weight, survival, clinical observations, blood work (clinical chemistry, coagulation and hematology), microscopic observations, and gross necropsy) are not significantly different from the concurrent control animal parameters.

EXTRACT OPTIONS
Sesame Oil (intraperitoneal injections)
Normal Saline (intravenous injections)

SAMPLE REQUIREMENTS (Per Extract)

TEST CODE	BY THICKNESS		BY WEIGHT	BY WEIGHT (Low Density)
	< 0.5 mm thick	≥ 0.5 mm thick		
800575.1	14 x 30 cm²	14 x 15 cm²	14 x 1 g	14 x 0.5 g
800555.1	14 x 90 cm²	14 x 45 cm²	14 x 3 g	14 x 1.5 g
800592.1	14 x 90 cm²	14 x 45 cm²	14 x 3 g	14 x 1.5 g
800565.1	14 x 48 cm²	14 x 24 cm²	14 x 1.6 g	14 x 0.8 g
800545.1	14 x 270 cm²	14 x 135 cm²	14 x 9 g	14 x 4.5 g
800593.1	14 x 270 cm²	28 x 135 cm²	28 x 9 g	28 x 4.5 g

Sample preparation complies with ISO 10993-12.

All of the following include Histopathology, Clinical Chemistry and Hematology.

800596.1
(GLP)
14 day IV / 5 day IP

ISO Subchronic Toxicity — Dual Routes of Administration — Rats

Multiple extracts of a device are prepared and injected into six male and six female rats over the test time period. The test animals are dosed with polar test sample extract intravenously over the duration of the study. The same test animals are dosed with the non-polar test sample extract intraperitoneally every third day over the duration of the study. The animals are observed during the test time period for signs of toxicity and are subjected to gross observations at study termination and histopathological evaluation. The test article passes if the test parameters (weight, survival, clinical observations, blood work (clinical chemistry, coagulation and hematology), microscopic observations and gross necropsy) are not significantly different from the concurrent control animal parameters.

SAMPLE REQUIREMENTS

BY THICKNESS		BY WEIGHT	BY WEIGHT (Low Density)
< 0.5 mm thick	≥ 0.5 mm thick		
14 x 300 cm²	14 x 150 cm²	14 x 10 g	14 x 5 g
5 x 150 cm²	5 x 75 cm²	5 x 5 g	5 x 2.5 g

IMPLANT TOXICITY TESTING

Implant toxicity tests assess the local tissue reaction and systemic toxic effects of material or finished product in contact with living tissue.

Intramuscular Implantation Toxicity Test

The purpose of these studies are to evaluate the potential for local tissue reaction and systemic toxic effects of a test article in direct contact with skeletal muscle for an extended duration. The material is implanted intramuscularly into both male and female rabbits. The negative control article is implanted into a separate set of male and female rabbits. The implants remain in the muscle for the sponsor-designated time period. After the in-life phase, blood is drawn for analysis. The muscle sections containing the implant sites and selected organs are collected and evaluated histopathologically.

The final analysis of the local tissue reaction of the test article will be based on the clinical, gross and histopathologic data. Depending on the nature of the device micro-structure, the specimens may be fixed to stabilize the tissue device interface and then oriented and cut-in for histology processing. Microscopic evaluation will include such things as: cell type, cell distribution, fibroplasia and calcification. Control implants typically consist of similar dimensional pieces of USP high density polyethylene RS (HDPE) implanted in separate animals. Sponsor supplied, clinically marketed predicate materials may be more appropriate controls used in conjunction with or in replacement of HDPE. Gross and histologic photomicrographs can be provided at the request of the sponsor.

The final analysis of the systemic toxicity of the test article will be based on the body weight data collected throughout the study, blood samples obtained at termination, gross necropsy findings, and the histopathology of the selected tissues.

If the test article is irregular in shape, mesh material, contains metal, or has vacant spaces, the test article may require plastic embedding. Standard paraffin embedding requires the test article to either be removed or easily cut with the microtome (razor blade). If the test article is forcibly removed while ingrown into the tissue to perform the paraffin embedding, the critical interface where the tissue meets the test article will be destroyed. The plastic embedding process allows the test article to remain in the tissue during the slide making process which preserves the tissue / test article interface.

TEST CODE	DESCRIPTION
903501.1	13-Week Intramuscular Implant Toxicity – One implant site per rabbit (GLP)
903502.1	13-Week Intramuscular Implant Toxicity – Two implants site per rabbit (GLP)
903503.1	13-Week Intramuscular Implant Toxicity – Three implants site per rabbit (GLP)
903504.1	13-Week Intramuscular Implant Toxicity – Four implants site per rabbit (GLP)

Note 1: These test codes are intended for testing of a single component only. Devices that require testing of multiple components may be assessed under multiple studies or under a customized study protocol.

Sample preparation complies with ISO 10993-12.

BIOCOMPATIBILITY

GENOTOXICOLOGY TESTING

Genotoxicology (mutagenicity) tests evaluate the ability of a material to cause mutation or gross chromosomal damage. Any materials intended for implantation or long-term exposure should be evaluated for mutagenic properties. Unpolymerized materials, additives, trace monomers or oligomers and biodegradative products can all be potential mutagens.

Extracts are prepared using solutions that will extract both hydrophilic (polar) and lipophilic (non-polar) compounds possibly present in device materials.

190860.1	5 *Salmonella* Strains (GLP)
190860.2	5 *Salmonella* Strains
190862.1	4 *Salmonella* Strains + 1 *E. coli* Strain (GLP)
190862.2	4 *Salmonella* Strains + *1 E. coli* Strain
190863.1	5 *Salmonella* Strains + 1 *E. coli* Strain (GLP)
190863.2	5 *Salmonella* Strains + 1 *E. coli* Strain

ISO Bacterial Mutagenicity Test (Ames Assay) – Two Extracts

These tests are performed according to ISO 10993-3 using OECD test method 471. Tester strains of bacteria are exposed to extracts of the test material in the presence and absence of an exogenous metabolic activation system. One dose level (undiluted extract) of the test article per extract and both positive and negative controls are used.

SAMPLE REQUIREMENTS (Per Extract)

BY THICKNESS		BY WEIGHT	LIQUIDS
< 0.5 mm thick	≥ 0.5 mm thick		
30 cm²	15 cm²	1 g Low Density: 0.5 g	5 mL

EXTRACT OPTIONS

Normal Saline (Polar Extract)

DMSO / Polyethylene Glycol (PEG) (Non-polar Extract)

NOTE: If a DMSO / PEG compatibility pretest is needed, additional test articles will be required

190760.1	5 *Salmonella* Strains (GLP)
190760.2	5 *Salmonella* Strains
190762.1	4 *Salmonella* Strains + 1 *E. coli* Strain (GLP)
190762.2	4 *Salmonella* Strains + 1 *E. coli* Strain
190763.1	5 *Salmonella* Strains + 1 *E. coli* Strain (GLP)
190763.2	5 *Salmonella* Strains + 1 *E. coli* Strain

ISO Bacterial Mutagenicity Test (Ames Assay) – One Extract

These tests are performed according to ISO 10993-3 using OECD test method 471. Tester strains of bacteria are exposed to extracts of the test material in the presence and absence of an exogenous metabolic activation system. One dose level (undiluted extract) of the test article per extract and both positive and negative controls are used.

SAMPLE REQUIREMENTS (Per Extract)

BY THICKNESS		BY WEIGHT	LIQUIDS
< 0.5 mm thick	≥ 0.5 mm thick		
30 cm²	15 cm²	1 g Low Density: 0.5 g	5 mL

EXTRACT OPTIONS

Normal Saline (Polar Extract)

DMSO / Polyethylene Glycol (PEG) (Non-polar Extract)

GENOTOXICOLOGY TESTING continued

190845.1 2 extracts (GLP)
190845.2 2 extracts

190845.3 1 extract (GLP)
190845.4 1 extract

ISO *In Vitro* Mouse Lymphoma Assay with Extended Treatment

Mouse lymphoma cells are used to determine whether a test material has the capacity to induce either point mutations or clastogenic (chromosomal breakage) events in a cultured mammalian cell line. The cell line is exposed to the test article extract for both a 4-hour period and an extended treatment for an approximate 24-hour period. Mutants can be selected and mutant frequencies derived by including a thymidine analog (trifluorothymidine, TFT) in the culture medium of cells after exposure to test material. The assay utilizing two extracts satisfies the ISO requirement for assessing *in vitro* DNA genotoxic effects.

SAMPLE REQUIREMENTS (Per Extract)

		BY THICKNESS		BY WEIGHT	LIQUIDS
	Extract Type	< 0.5 mm thick	≥ 0.5 mm thick		
Polar Extracts	Normal Saline	72 cm²	36 cm²	2.4 g	12mL
	Culture Media (without serum)	570 cm²	285 cm²	19 g	95mL
Non-Polar Extracts	DMSO	12 cm²	6 cm²	0.4 g	2mL
	PEG	12 cm²	6 cm²	0.4 g	2mL

190853.1 2 extracts (GLP)
190853.2 2 extracts

190852.1 1 extract (GLP)
190852.2 1 extract

ISO *In Vivo* Mouse Micronucleus Assay

This test is used for the detection of damage induced to the chromosomes or mitotic apparatus of erythroblasts by analysis of erythrocytes from bone marrow of treated mice. In this assay, male and female mice are injected with one dose level of the test article extract or positive or negative control. Cells are collected for analysis at 24 and 48 hours after dosing.

SAMPLE REQUIREMENTS (Per Extract)

BY THICKNESS		BY WEIGHT	LIQUIDS
< 0.5 mm thick	≥ 0.5 mm thick		
120 cm²	60 cm²	4 g Low Density: 2 g	20 mL

IMPLANTATION TESTING

Implantation tests assess the local effects of material or finished product in contact with living tissue. The implant site selection is based on the intended use of the device.

Intramuscular Implantation Test

The purpose of these studies is to evaluate the potential for local effects of a test article in direct contact with skeletal muscle for an extended duration. The material is implanted intramuscularly into rabbits along with a concurrent negative control article to assess the reaction of the surrounding tissue. The implants remain in the muscle for the sponsor-designated time period.

If animals exposed to the test article do not show significant signs of irritation above that observed in the concurrent control article, the test article passes the test for USP testing. Scoring of the sample and control reactions will be by gross observation.

For the ISO tests, after the in-life phase, tissue samples are collected and evaluated histopathologically.

The final analysis of the local effect of the test article will be based on the clinical, gross and histopathologic data. Depending on the nature of the device micro-structure, the specimens may be fixed to stabilize the tissue device interface and then oriented and cut-in for histology processing. Microscopic evaluation will include such things as: cell type, cell distribution, fibroplasia and calcification. Control implants typically consist of similar dimensional pieces of USP high-density polyethylene RS (HDPE) implanted contralaterally. Sponsor supplied, clinically marketed predicate materials may be more appropriate controls used in conjunction with or in replacement of HDPE. Gross and histologic photomicrographs can be provided at the request of the sponsor.

For ISO testing, if the test article is irregular in shape, mesh material, contains metal, or has vacant spaces, the test article may require plastic embedding. Standard paraffin embedding requires the test article to either be removed or easily cut with the microtome (razor blade). If the test article is forcibly removed while ingrown into the tissue to perform the paraffin embedding, the critical interface where the tissue meets the test article will be destroyed. The plastic embedding process allows the test article to remain in the tissue during the slide making process which preserves the tissue / test article interface.

STANDARD	IMPLANT DURATION
USP	1 wk
ISO (3 rabbits)	1 wk 2 wk 4 wk 6 wk 8 wk 9 wk 13 wk
ISO (4 rabbits)	26 wk 52 wk
ISO (5 rabbits)	13 wk 26 wk 52 wk 78 wk

For ISO, sample preparation complies with ISO 10993-12.

NOTE: If plastic embedding is required for histopathology, additional time will be required to complete the study.

IMPLANTATION TESTING continued

900100.1 (GLP)	1 wk implant	**USP Intramuscular Implantation Test (2 Rabbits)**
900100.2	1 wk implant	
902100.1	1 wk implant (GLP)	**ISO Intramuscular Implantation Test with Histopathology (3 Rabbits)**
902100.2	1 wk implant	
902200.1	2 wk implant (GLP)	
902200.2	2 wk implant	
902300.1	4 wk implant (GLP)	
902300.2	4 wk implant	
902310.1	6 wk implant (GLP)	
902310.2	6 wk implant	
902400.1	8 wk implant (GLP)	
902400.2	8 wk implant	
902430.1	9 wk implant (GLP)	
902430.2	9 wk implant	
902505.1	13 wk implant (GLP)	
902505.2	13 wk implant	
902511.1	26 wk implant (GLP)	**ISO Intramuscular Implantation Test with Histopathology (4 Rabbits)**
902511.2	26 wk implant	
902509.1	52 wk implant (GLP)	
902509.2	52 wk implant	
902605.1	13 wk implant (GLP)	**ISO Intramuscular Implantation Test with Histopathology, Clinical Chemistry and Hematology (5 Rabbits)**
902605.2	13 wk implant	
902596.1	26 wk implant (GLP)	
902596.2	26 wk implant	
902597.1	52 wk implant (GLP)	
902597.2	52 wk implant	
902598.1	78 wk implant (GLP)	
902598.2	78 wk implant	

IMPLANTATION TESTING continued

Subcutaneous Implantation Test

The purpose of these studies is to evaluate the potential for local effects of a test article in direct contact with subcutaneous tissue for an extended duration. The entire device or a portion / appropriate sample and an appropriate reference control will be implanted subcutaneously into rabbits to assess the reaction of the surrounding tissue. Implants remain for the sponsor-designated time period. If applicable, blood will be drawn for clinical chemistry and hematology at defined intervals; at minimum, blood will be collected pre-implant and at termination.

The final analysis of the local effect of the test article will be based on the clinical, gross and histopathologic data. Depending on the nature of the device microstructure, the specimens may be fixed to stabilize the tissue device interface and then oriented and cut-in for histology processing. Microscopic evaluation will include such things as: cell type, cell distribution, fibroplasia and calcification. Control implants typically consist of similar dimensional pieces of USP high-density polyethylene RS (HDPE) implanted contralaterally. Sponsor supplied, clinically marketed predicate materials may be more appropriate controls used in conjunction with or in replacement of HDPE. Gross and histologic photomicrographs can also be provided at the request of the sponsor.

STANDARD	IMPLANT DURATION	SAMPLE REQUIREMENT
ISO (3 rabbits)	1 wk 2 wk 4 wk 6 wk 8 wk 9 wk 13 wk	Sufficient material to produce 15 implants, approx. 10 mm x 3 mm
ISO (4 rabbits)	26 wk 52 wk	Sufficient material to produce 20 implants, approx. 10 mm x 3 mm
ISO (5 rabbits)	13 wk 26 wk	Sufficient material to produce 25 implants, approx. 10 mm x 3 mm

Sample preparation complies with ISO 10993-12.
NOTE: If plastic embedding is required for histopathology, additional time will be required to complete the study.

IMPLANTATION TESTING continued

901310.1 901310.2	1 wk implant (GLP) 1 wk implant	**ISO Subcutaneous Implantation Test with Histopathology (3 Rabbits)**
901320.1 901320.2	2 wk implant (GLP) 2 wk implant	
901340.1 901340.2	4 wk implant (GLP) 4 wk implant	
901350.1 901350.2	6 wk implant (GLP) 6 wk implant	
901380.1 901380.2	8 wk implant (GLP) 8 wk implant	
902440.1 902440.2	9 wk implant (GLP) 9 wk implant	
901430.1 901430.2	13 wk implant (GLP) 13 wk implant	
901445.1 901445.2	26 wk implant (GLP) 26 wk implant	**ISO Subcutaneous Implantation Test with Histopathology (4 Rabbits)**
901460.1 901460.2	52 wk implant (GLP) 52 wk implant	
901555.1 901555.2	13 wk implant (GLP) 13 wk implant	**ISO Subcutaneous Implantation Test with Histopathology, Clinical Chemistry and Hematology (5 Rabbits)**
901560.1 901560.2	26 wk implant (GLP) 26 wk implant	

HEMOCOMPATIBILITY TESTING

An important measure of hemocompatibility is the hemolysis test, which measures the ability of a material or material extract to cause red blood cells to rupture. Hemolysis testing should be performed on all materials directly contacting the bloodstream, or any materials used to form a conduit for fluids entering the circulatory system. Each method (direct and extract) prepares and tests the test articles in triplicate. It is recommended that each replicate is prepared using separate test articles.

150300.1 (GLP)

150300.2

ASTM Hemolysis Assay – Direct Contact Method

This test, intended for materials that directly contact the bloodstream or compromised tissues, is performed in triplicate and uses rabbit blood in direct contact with the test material. The degree of hemolysis is measured spectrophotometrically.

SAMPLE REQUIREMENTS

BY THICKNESS		BY WEIGHT
< 0.5 mm thick	> 0.5 mm thick	3 x 1.4 g
3 x 42 cm^2	3 x 21 cm^2	

150500.1 (GLP)

150500.2

ASTM Hemolysis Assay – Extract Method

This test, intended for materials through which fluids pass before entry into the body, is performed in triplicate and uses saline to extract leachable substances. The material is removed and rabbit blood is added to the extract. The degree of hemolysis is measured spectrophotometrically.

SAMPLE REQUIREMENTS

BY THICKNESS		BY WEIGHT
< 0.5 mm thick	> 0.5 mm thick	3 x 2 g
3 x 60 cm^2	3 x 30 cm^2	

150505.1 (GLP)

150505.2

ASTM Hemolysis Assay – Direct Contact and Extract Method (ASTM (F756) Method)

This test incorporates both the direct and extraction methods of contact. See test descriptions above.

SAMPLE REQUIREMENTS

BY THICKNESS		BY WEIGHT
< 0.5 mm thick	> 0.5 mm thick	6 x 2 g
6 x 60 cm^2	6 x 30 cm^2	

HEMOCOMPATIBILITY TESTING continued

The following tests offer evaluation of the interaction of biomaterials, polymers and medical devices with circulating blood. The assay designs meet compliance requirements for ISO 10993-4.

NOTE: Testing a sponsor-supplied comparison product is recommended when requesting these assays to aid in clarifying interpretation of test results. Additionally, there may be maximum volume limitations due to the nature of the test system used.

150620.1
SC5B-9 ASSAY (GLP)

150620.2
SC5B-9 ASSAY

150630.1
C3A AND SC5B-9 (GLP)

150630.2
C3A AND SC5B-9

Complement Activation Assay

The activation of complement resulting from the use of a medical device has been associated with many adverse clinical findings. An enzyme immunoassay is used to screen for complement component(s) in human serum that has been incubated with the test article. Elevated levels of complement components C3a and SC5b-9 indicate activation of the complement system. The complement activation study is run using only one replicate for testing.

SAMPLE REQUIREMENTS (Per Assay)

BY THICKNESS		BY WEIGHT
< 0.5 mm thick	≥ 0.5 mm thick	0.2 g Low density: 0.1 g
6 cm^2	3 cm^2	

150625.1
SC5B-9 (GLP)

150625.2
SC5B-9

150635.1
C3A & SC5B-9 (GLP)

150635.2
C3A & SC5B-9

Complement Activation Assay with Sponsor-Supplied Comparison Product

The activation of complement resulting from the use of a medical device has been associated with many adverse clinical findings. An enzyme immunoassay is used to screen for complement component(s) in human serum that has been incubated with the test article. Elevated levels of complement components C3a and SC5b-9 indicate activation of the complement system. The complement activation study is run using only one replicate of the test article and comparison article.

SAMPLE REQUIREMENTS (Per Assay)

BY THICKNESS		BY WEIGHT
< 0.5 mm thick	≥ 0.5 mm thick	0.2 g Low density: 0.1 g
6 cm^2	3 cm^2	

HEMOCOMPATIBILITY TESTING continued

155200.1 (GLP)
155200.2

Partial Thromboplastin Time (PTT)

The PTT assay is a general screening test for the detection of coagulation abnormalities in the intrinsic coagulation pathway. The test determines the time it takes citrated human plasma to form a clot when it is exposed first to the test material, then to calcium chloride and finally to partial thromboplastin. (Partial thromboplastin is a phospholipid suspension extracted from rabbit brain cephalin.) Test results report the "partial thromboplastin time," which is the time it takes the recalcified citrated plasma to clot once the partial thromboplastin has been added. Shortening of the PTT following contact with a material under standardized conditions indicates activation of the contact phase of blood coagulation. For PTT testing, the test articles are prepared and tested in triplicate. It is recommended that each replicate is prepared using separate test articles.

SAMPLE REQUIREMENTS
3 x 6 cm^2

155205.1 (GLP)
155205.2

Partial Thromboplastin Time (PTT) Including Sponsor-Supplied Comparison Product

The PTT assay is a general screening test for the detection of coagulation abnormalities in the intrinsic coagulation pathway. The test determines the time it takes citrated human plasma to form a clot when it is exposed first to the test material, then to calcium chloride and finally to partial thromboplastin. (Partial thromboplastin is a phospholipid suspension extracted from rabbit brain cephalin.) Test results report the "partial thromboplastin time," which is the time it takes the recalcified citrated plasma to clot once the partial thromboplastin has been added. Shortening of the PTT following contact with a material under standardized conditions indicates activation of the contact phase of blood coagulation. For PTT testing, the test and comparison articles are prepared and tested in triplicate. It is recommended that each replicate is prepared using separate articles.

SAMPLE REQUIREMENTS
3 x 6 cm^2

HEMOCOMPATIBILITY TESTING continued

155600.1 (GLP)
155600.2

Platelet and Leukocyte Counts (PLC or P&L)

The Platelet and Leukocyte count assay is a general screening test in which platelet and leukocyte counts are measured after exposure of a test article to minimally heparinized human blood. A reduction in platelet or leukocyte count in comparison to an unexposed whole blood control may indicate cellular activation, adhesion, aggregation, or lysis. For PLC testing, the test articles are prepared and tested in triplicate. It is recommended that each replicate is prepared using separate test articles.

SAMPLE REQUIREMENTS 3 x 12 cm²

155605.1 (GLP)
155605.2

Platelet and Leukocyte Counts Including Sponsor-Supplied Comparison Product

The Platelet and Leukocyte count assay is a general screening test in which platelet and leukocyte counts are measured after exposure of a test article to minimally heparinized human blood. A reduction in platelet or leukocyte count in comparison to an unexposed whole blood control may indicate cellular activation, adhesion, aggregation, or lysis. For PLC testing, the test and comparison articles are prepared and tested in triplicate. It is recommended that each replicate is prepared using separate articles.

SAMPLE REQUIREMENTS 3 x 12 cm²

155610.1 (GLP)
155610.2

In Vitro Hemocompatibility Assay

The *In Vitro* Hemocompatibility assay involves the Platelet and Leukocyte Count assay, described above, while also measuring additional hematology values: hemoglobin, red blood cell count, and hematocrit. The test articles are prepared and tested in triplicate. It is recommended that each replicate is prepared using separate test articles.

SAMPLE REQUIREMENTS 3 x 12 cm²

155615.1 (GLP)
155605.2

In Vitro Hemocompatibility Assay Including Sponsor-Supplied Comparison Product

The *In Vitro* Hemocompatibility assay involves the Platelet and Leukocyte Count assay, described above, while also measuring additional hematology values: hemoglobin, red blood cell count, and hematocrit. The test and comparison articles are prepared and tested in triplicate. It is recommended that each replicate is prepared using separate articles.

SAMPLE REQUIREMENTS 3 x 12 cm²

800520.1

2 dog, 4-hour contact (GLP)

Thromboresistance Evaluation *(In Vivo)*

Test article (*e.g.*, tubing or catheter) is implanted in the jugular veins on one side and a sponsor- supplied comparative control article on the contralateral side. The test article and implant sites are removed and examined for the presence of thrombi, and the vein is examined for patency (occlusion). These observations are augmented with photographs.

SAMPLE REQUIREMENTS 2 test articles + 2 comparisons
8-15 cm in length

Contact your Business Development Manager for assistance in designing a thromboresistance evaluation in species other than a dog or for contact duration longer than 4 hours.

IN VITRO SKIN IRRITATION TESTING

In Vitro Skin Irritation testing is a new recommendation introduced in the 2021 revision of ISO-10093-10. Using a three-dimensional reconstructed human epidermis (RhE) model, medical device extracts can be screened for potential to cause irritation without the need for animal testing. After application of the extract to the tissues, cell viability is quantitatively evaluated using a colorimetric MTT assay.

9107019.1
Single Test Article (GLP)

9107019.3
Additional Test Articles submitted simultaneously (GLP)

ISO *In Vitro* Skin Irritation Test

This assay complies with the recommendations in ISO 10993-10 and provides a quantitative method to screen materials for irritation potential using reconstructed human epidermis (RhE). Extraction conditions may be selected from 37 °C / 72 hours, 50 °C / 72 hours, or 70 °C / 24 hours as directed by ISO 10993-12. Cell viability is measured after exposure of RhE tissues to extracts to evaluate irritation.

Sample preparation complies with ISO 10993-12.

SAMPLE REQUIREMENTS

BY THICKNESS		BY WEIGHT
< 0.5 mm thick	≥ 0.5 mm thick	0.2 g
6 cm^2	3 cm^2	

USP PLASTICS TESTING

USP Class Testing determines the biological response of animals to elastomerics, plastics and other polymeric material. Six Plastic Classes based on responses to a series of *in vivo* tests relating to the intended end-use of the plastic articles.

All of these tests include issuance of a Certificate of Compliance upon completion.

555636.1 (GLP)	**USP Class VI** – Acute Systemic (NS, AS, PEG, SO), Intracutaneous Irritation (NS, AS, PEG, SO), 7-Day IM Implant
555606.1	**USP Class VI** – Acute Systemic (NS, AS, PEG, SO), Intracutaneous Irritation (NS, AS, PEG, SO), 7-Day IM Implant

NS = Normal Saline AS = Alcohol Saline PEG = Polyethylene Glycol SO = Sesame Oil

We strive for continuous improvement and staying at the forefront of scientific learning and discovery. Please contact your Business Development Manager for additional services. This catalog provides a comprehensive view of the tests we offer, but it is by no means exhaustive. We look forward to working with you in support of your medical device product portfolio.

IN VIVO SMALL ANIMAL MODELS

We recognize that standard study designs or animal models might not fit your novel technology, address your unique endpoints, or provide data to support additional marketing claims. Our technical experts will work with you to customize a study design or select an animal model that meets your specific needs, while maintaining the required level of regulatory compliance.

In addition, when consulting on a test strategy, our regulatory experts may recommend or address a regulatory agency inquiry through an *in vivo* study with a small animal model that adequately addresses product safety or efficacy, leveraging industry standards as well as horizontal guidance documents.

We work with you to quickly adapt to your needs, offering flexibility in our studies to make changes that best suit the goals and outcomes of the study in support of your product or device.

PRECLINICAL ANIMAL MODEL DEVELOPMENT

Preclinical *In Vivo* Surgical / Injection Studies

- Route(s): ID, IM, IP, IV, PO, SC
- Infection Models (bacterial dose optimization and microbial efficacy studies)
- Resorption
- Tissue Defect and Repair
  - Dermal, muscular (e.g., hernia), osseous (e.g., tibia), soft tissue (e.g., Achilles tendon, dura)
- Toxicity
  - Subchronic, Chronic
- Biodistribution
- Tumorgenicity
- Wound Healing
- Pharmacokinetics
- Drug Elution / Analytical Chemistry
  - Systemic and local endpoints combination products study

ON-SITE SERVICES

- Board Certified
  - Toxicologists
  - Veterinary Pathologists
- In-house IACUC, AAALAC accreditation
- BSL-1, ABSL-1, BSL-2 and ABSL-2
- Cell production

GUIDELINE EXPERTISE AND CONSULTATION

- GMP, GLP and non-GLP
- ISO 10993
  - Local Effects / Tissue Response
  - Irritation / Sensitization
  - Systemic Toxicity

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药明康德
WuXi AppTec

PRODUCT AND ENVIRONMENT VALIDATIONS

Validations of Your Product

REPROCESSING VALIDATIONS

The FDA expects manufacturers to validate all instructions for reusable devices, including cleaning, disinfection, sterilization parameters and dry times, if applicable. WuXi AppTec offers a comprehensive program for evaluation of cleaning and sterilization processes for reusable medical devices.

STERILIZATION VALIDATIONS

All sterilization processes require validation of the efficacy and reproducibility of the process. WuXi AppTec offers a full range of services in this area – from stand-alone testing to complete validation management.

Validations of Your Manufacturing Environment

ENVIRONMENTAL MONITORING

An environmental monitoring program assesses the microbial levels of critical areas and evaluates the effectiveness of various manufacturing controls including cleaning procedures, HEPA filtration, disinfection, gowning and aseptic handling procedures.

SURFACE DISINFECTANT EFFICACY

Controlled manufacturing environments and cleanrooms must meet a high degree of scrutiny regarding their cleanliness and surface disinfection. We offer testing that supports feasibility studies and validation of the disinfectant(s) used within your facilities.

IN THIS SECTION

PRODUCT AND ENVIRONMENT VALIDATIONS

WuXi AppTec Medical Device Testing's technical and regulatory experts leverage their scientific knowledge of microbiology for product and manufacturing environment validations. The processes we validate are cleaning, disinfection and sterilizing of single-use, reusable and third-party reprocessed devices. Sterilization validations include moist heat (steam) and both radiation and ethylene oxide (EO). We also support ongoing product testing through dose audits of sterilized product. The manufacturing environment validation we offer includes environmental monitoring of water, surface, air and personal protective equipment (PPE), as well as surface disinfectant efficacy studies. For these studies, we will also support your continued testing for your validated manufacturing environment.

REPROCESSING VALIDATION

The responsibility falls to device manufacturers to develop and validate their cleaning, disinfection and/or sterilization instructions to ensure they are adequate and comprehensive. Regulatory bodies expect device manufacturers to validate their instructions to demonstrate a reliable and repeatable process using worst-case scenarios. Our team will work with you to develop a test plan that meets these stringent guidelines and recent standards. We construct a protocol and experimental design that challenges the device to meet the latest regulatory expectations. Our test plans and final reports support regulatory submissions, remediation projects, product adoptions, design changes, line extensions and process transfers. The types of reprocessing validations provided are:

- Manual Cleaning
- Automated Cleaning
- Low-Level Disinfection
- Intermediate-Level Disinfection
- High-Level Disinfection
- Steam Sterilization (Gravity)
- Steam Sterilization (Pre-Vacuum)

DEVICE CYCLING

Design and process validations may require additional preparation of the devices prior to testing. Devices may need to be cycled through the reprocessing procedure or other customized sequence to create a worst-case scenario for functional testing, durability, reliability, or biocompatibility. The sequences can involve various steps of cleaning, disinfection, and sterilization to complete a simulated worst-case cycle on the product. We work with our clients to customize an experimental design that meets their testing needs and develop a comprehensive protocol to document that testing plan. Whether cycling devices one time or hundreds of times, we comprehensively ensure the testing sequence and execution is in line with the client's needs and documentation is gathered for each cycle to provide evidence of proper execution.

STERILIZATION VALIDATION

Radiation Sterilization Validation

For validation of radiation (gamma, electron beam or x-ray) sterilization, critical steps are outlined in ISO and AAMI standards. As part of the performance qualification, a dose-setting or dose substantiation study must be performed to demonstrate the adequacy of the minimum dose to achieve the desired sterility assurance level (SAL). Several methods are available for validation of the minimum SAL dose, and the choice of method is dependent on a number of variables. Our study design for complete radiation validation studies is for a specific product and process, and all aspects of the studies follow the requirements of ISO and AAMI standards.

GUIDE TO SAMPLE REQUIREMENTS	
TEST NAME	**SAMPLES REQUIRED**
ANSI / AAMI / ISO 11137 METHOD 1 VALIDATION NOTE: Single batch validations are also available.	
Bioburden Panel	10 products from three batches
Bioburden Recovery Efficiency Test	3-5 products from any batch
Sterility Method Suitability Test (B / F) – One Medium	3 products from any batch
Product Test of Sterility	100* samples from one batch
VDMAX VALIDATION NOTE: Single batch validations are also available.	
Bioburden Panel	10 products from a single batch
Product Test of Sterility	10 samples from a single batch
ANSI / AAMI / ISO 11137 METHOD 2 VALIDATION	
The requirements of Method 2 are not outlined here because of the complexity of the sampling scheme. Contact the laboratory for more information.	

***A reduced number of samples may apply, based on specific criteria. Contact the Atlanta facility.**

Per ANSI / AAMI / ISO 11137, to confirm the ongoing validity of the sterilization dose, regularly scheduled dose audits must be performed and documented. Dose audits are also used to show that any changes in process or facilities/control have not affected the validation dose.

STERILIZATION VALIDATION continued

WuXi AppTec's Dose Audit Services

With more than 25 years of experience and extensive knowledge of the regulatory requirements, WuXi AppTec offers unmatched expertise and the convenience of three levels of dose audit services. Your choice of service level would depend on how much of your company's time, manpower and expertise you want to commit to your ongoing dose audit program.

Options for level of service

1. At the most basic level, WuXi AppTec provides only the testing services while you schedule and manage all aspects of the sterilization services and develop all the documentation to present an organized and compliant study.

2. Or, in addition to the testing, we can also handle all the sterilization services for you, and you would be responsible only for producing the final documentation showing compliance.

3. Or we can take care of everything. You simply give us your product samples and at the end we give you a complete summary report manual showing dose audit compliance.

And the dose audit reports provide criteria that could lead to a reduction in the frequency of your dose audits and/or the number of samples needed.

We also ensure transferring a dose audit program to WuXi AppTec is simple and straightforward for you. Contact your Business Development Manager for more information.

METHOD 1 AND METHOD 2 DOSE AUDIT	
Bioburden Panel	10 products from three batches
Product Test of Sterility	100* samples from one batch
VDMAX DOSE AUDIT	
Bioburden Panel	10 products from one batch
Product Test of Sterility	10 samples from one batch

*A reduced number of samples may apply, based on specific criteria. Contact the Atlanta facility.

STERILIZATION VALIDATION continued

Ethylene Oxide (EO) Sterilization Validation

For validation of ethylene oxide (EO) sterilization, critical steps are outlined in ISO and AAMI standards. As part of the performance qualification, a microbial challenge must be performed to demonstrate the adequacy of the process to achieve the desired sterility assurance level (SAL). One of the most utilized methods is the half-cycle (overkill) method, which uses a biological indicator (BI) challenge, typically 10^6 spores of *Bacillus atrophaeus*. Our study design for complete EO validation studies is for a specific product and process, and all aspects of the studies follow the requirements of ISO and AAMI standards.

GUIDE TO SAMPLE REQUIREMENTS	
TEST NAME	SAMPLES REQUIRED
SUB-LETHAL CYCLE STUDIES	
Bioburden Panel	10 products
Bioburden Recovery Efficiency Test	3-5 products from any batch
Inoculated Biological Indicators	Dependent on load size
Sterility Method Suitability Test (B / F) – One Medium	6 products from any batch
Product Test of Sterility	Dependent on load size
TERMINAL STERILIZATION STUDIES	
Biological Indicators	Per client specifications
EO Residual Panel	Varies

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).

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.

ETHYLENE OXIDE (EO) TESTING

195000.2 **EO Residual Panel (Water Extraction) – EO, ECH and EG**

Water extraction for all 3 residuals. (24 hr., 37°C or specify time / temperature)

195000.1 **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.

195000.3 **EO Water Analysis**

Water extraction.
(24 hr., 37°C or specify time / temperature)

195000.6 **EO Water Analysis – Exhaustive**

Additional water extractions for exhaustive analysis.
(24 hr., 37°C or specify time / temperature)

195000.5 **EO Headspace Analysis**

Headspace extraction. (1 hr., 100°C or specify time / temperature)
3 extractions

195000.7 **EO, ECH (Water Extraction)**

Water extraction. (24 hr., 37°C or specify time / temperature)

195000.10 **EO (Headspace Extraction), ECH (Water Extraction)**

Headspace. (1 hr., 100°C or specify time / temperature) 3 extractions
Water extraction. (24 hr., 37°C or specify time / temperature)

195000.4 **ECH (Water Extraction)**

Water extraction. (24 hr., 37°C or specify time / temperature)

ENVIRONMENTAL MONITORING

In complex manufacturing environments, disruptions in production and unplanned downtime are inevitable. To support your environmental monitoring quality program, we focus on testing your water, air and surface samples.

Our team will coordinate with your manufacturing facility to quickly test and report results. Our scalability supports overflow sample collection as well as large-volume testing when the unexpected occurs.

The experts at WuXi AppTec understand how critical it is to deliver results quickly so you can move forward with production and release.

— Same-day sample receipt and reporting services are available for those instances when it is essential for production.
— Our approach is flexible and can be easily adapted to meet your validation requirements.
— Our program scalability and proven performance ensure peace of mind.

CONTROLLED ENVIRONMENT TESTING – MICROBIAL SAMPLING TESTS

1701000.1

Environmental Air and Surface Sample

Growth on each environmental air (plate or strip) or surface (contact plates) sample is enumerated. Gram stain and/or microbial identification are available.

SAMPLE REQUIREMENTS	Client provides air or surface sample(s) for incubation and enumeration.
PREFERRED SHIPPING	Overnight air. Protect from temperature extremes.

CONTROLLED ENVIRONMENT TESTING – MICROBIAL SAMPLING TESTS continued

Water System Counts

These assays are used as an indicator of the quality of water. Sample aliquots obtained from a water system are evaluated for number of viable microorganisms.

SAMPLE REQUIREMENTS

Client collects sample in sterile container, preferably screw-top, leak-resistant and made of material appropriate for the temperature of the water.
Within 2 hours of sample collection, pharmaceutical-grade water (per USP 1231) is required to be stored and shipped at 2-8 degrees Celsius.

PREFERRED SHIPPING

Overnight air. Too many ice packs might make the temperature drop below 2 degrees Celsius.

TEST CODE		MINIMUM SAMPLE SIZE
170300.1	**Microbial Counts**	100 mL
170300.2	**Microbial Counts**	1 mL
170300.3	**Microbial and Coliform Counts**	200 mL
170300.4	**Microbial and Pseudomonas Counts**	200 mL
170300.5	**Microbial, Coliform and Pseudomonas Counts**	300 mL
170300.6	**Coliform Counts**	100 mL
170300.7	**Pseudomonas Counts**	100 mL
170300.8	**Coliform and Pseudomonas Counts**	200 mL

SURFACE DISINFECTANT EFFICACY

Study designs commonly follow the USP <1072> regulatory guidelines. In addition, our standard methods (ASTM, AOAC, USP, ISO, etc.) can be modified, expanded or customized. Our program design evaluates the log reduction of a disinfection process on various surfaces that are cleaned. The study challenges a disinfectant, alone or in combination, with a variety of microorganisms and viruses.

We are the partner to work with to support the feasibility study and validation of the disinfectant(s) that works best for your surface material at your facilities. Our regulatory experts will work with you to design a validation to meet the latest regulations. Working with you, our team of technical experts leverages our custom study design knowledge with our understanding of microbiology to build a comprehensive study that best suits your needs.

We strive for continuous improvement and staying at the forefront of scientific learning and discovery. Please contact your Business Development Manager for additional services. This catalog provides a comprehensive view of the tests we offer, but it is by no means exhaustive. We look forward to working with you in support of your medical device product portfolio.

PACKAGE VALIDATION AND TESTING

Regulatory agencies' concern for labeling and packaging of a medical device leads to product quality scrutiny. Medical device package validations are a key component of all medical device design history files and regulatory submissions. Whether the device is sterile or nonsterile, packaging of the product is of the utmost importance to ensure it arrives as intended.

Our technical experts approach these validations by looking at the components of the packages both individually and as a whole. The packaging validation consists of three components: package and seal integrity testing, accelerated aging or shelf-life stability, and simulated distribution testing. Our validation and ongoing testing incorporates the aging of the product packaging to support shelf-life stability and product expiration labeling. In addition, our validation design will verify package integrity, seal strength and burst properties evaluation, and distribution of the final finished devices – whether boxes or cartons delivered remain intact.

OUR VALIDATION SERVICES INCLUDE:

- Seal Peel Strength
    - Package Integrity Testing
    - Burst / Creep Strength
    - Bubble Emission Test
    - Vacuum Leak
    - Dye Immersion / Dye Penetration
- Accelerated Aging / Shelf-Life Studies
- Simulated Distribution

Package design is a critical step of the device development phase. We want to work with you to confirm your packaging will safely deliver your product to the end user. The validation design considers your product and its unique characteristics. In addition, our testing services expand beyond package validations.

The test methods described in this section provide a comprehensive means of establishing that package integrity is compliant with International Standard ISO 11607, "Packaging for Terminally Sterilized Medical Devices."

IN THIS SECTION

SEAL INTEGRITY TESTING

Regulations dictate that the seal strength and specification limits be determined for pre-sterilization sealer performance verification (high, low and standard parameter settings) and seal strength consistency qualified for post-sterilization production, shipping and shelf-life qualifications.

38030.1

Seal Tensile Strength [ASTM F 88]

This method will determine the strength of a specific area of the seal for a medical device package. It may be used for pouch or tray / lid type packages having two components joined by an adhesive or heat seal process. The method does not measure seal continuity. Its most common application is for establishing process control parameters and package performance specifications, and to support package validation.

38039.1

Burst Strength [ASTM F 1140]

This method is used to determine a package's ability to resist internal pressure and is a measure of the strength of the package seals. Its most common application is for establishing process control parameters, package performance specifications, and to support package validation.

PACKAGE INTEGRITY TESTING

Regulations require the integrity of sterile packages be maintained during the production, shipping and shelf life of the product. Physical testing for package leaks has been shown to be more sensitive than the microbial challenge test, and is, generally, the preferred method.

38152.1

Bubble Emission Test (ASTM F 2096)

38152.2

Bubble Emission Test (FPA / SPMC 005-98)

This method, which covers the determination of gross leaks in flexible packaging, is applicable to nonporous packaging and to porous packaging that has its porous component sealed using a blocking agent. It is used to detect leakage of air through a channel in the seal or pin-hole in the package. The test is performed by submerging the package underwater and observing for leaks. This provides attribute data on the integrity of the primary package directly after production or after experiencing a dynamic or environmental-related event.

NOTE: For test code 38152.1, at least one (1) additional sample is needed for test setup.

PACKAGE INTEGRITY TESTING continued

30778.1

Compression Test [ASTM D 642]

This method covers compression tests on shipping containers (for example, boxes and drums) or components, or both. Shipping containers may be tested with or without contents. The procedure is used for measuring the ability of the container to resist external compressive loads applied to its faces, to diagonally opposite edges or to corners.

30779.1

Drop Test [ASTM D 5276]

This method is used in evaluating the capability of a container to withstand the sudden shock resulting from a free fall, or to evaluate the capability of a container and its inner packing to protect its contents during the sudden shock resulting from a free fall. The method is particularly suitable for containers that are normally handled manually during some part of their distribution cycle.

38038.1

Dye Penetration [ASTM F 1929]

This method, which covers the determination of gross leaks in flexible packaging, is applicable to porous and nonporous medical device packages. It is used to detect small leaks in materials or seals of packages where harmful biological or particulate contamination may enter. The method may be used to detect holes in package materials or channels in seals as small as 0.0025 inch. This provides attribute data on the integrity of the primary package directly after production or after experiencing a dynamic or environmental-related event.

38091.1

Liquid Dye Immersion [USP <1207.2> and USP <381>]

This method is used to detect failures, such as cracks, seams, and laminations through leaks or lack of fusion. The dye immersion method can be used on various types of materials such as nonporous, metallic materials (ferrous and non-ferrous) and nonmetallic materials (glazed ceramics, certain non-porous plastics, glass).

PACKAGE INTEGRITY TESTING continued

Microbial Barrier Performance Tests

38051.1

Whole Package Microbial Aerosol Challenge with Sterility Test

38059.1

Whole Package Microbial Talc Challenge with Sterility Test

This method is used to evaluate the ability of an intact, production package to maintain its sterile environment until it reaches its point of end use. The procedure includes preliminary test validation with the subject package, followed by an aerosol or talc challenge in the test chamber, package exterior decontamination, and subsequent sterility testing to determine the presence of the indicator organism inside the package or on the product. The aerosol may be performed under static or dynamic conditions. Dual-barrier packages may have one or both barriers validated for sterility.

38060.1

Microbial Ingress / Immersion Challenge

This method is used to assess the ability of a non-porous package to provide a microbial barrier. Packages containing sterile growth medium are immersed in a buffer solution containing a known concentration of an indicator organism. After the challenge, the packages are dried under laminar flow, then incubated and inspected for growth of the indicator organism. The method may be used for foil-lidded trays, foil pouches and rigid containers with closures.

TRANSPORTATION / DISTRIBUTION SIMULATION TESTING

Manufacturers must evaluate the ability of the package and shipper to protect the product adequately through the handling, shipping and distribution environment. Damage such as puncture, abrasion and seal failure may result.

38052.F

Distribution Simulation Shipper Test [ASTM D 4169 – DC 13]

This test method is performed by subjecting shipping units to a test plan consisting of a sequence of hazard elements (e.g., shock, drop, vibration, compression) that are encountered in various distribution environments. The test plan provides a uniform basis of evaluating, in a controlled and repeatable laboratory environment, the ability of the shipping units and contents to withstand the distribution environment. The test plan uses established test methods at levels representative of those encountered in actual distribution. The Distribution Cycle (DC) most commonly used for medical device packages is DC 13, Assurance Level I, which is designed for the small parcel and overnight shipping mode. Customized distribution cycles can be designed when the anticipated distribution of the product is well understood and defined.

SAMPLE REQUIREMENTS One or more shippers

NOTE: The ASTM procedure is the method of choice as it provides a more realistic simulation of the distribution environment and uses test levels that are more indicative of actual occurrences.

38057.F

Transportation Simulation Test [ISTA Project 1A, 2A and 3A]

These tests provide a means for a manufacturer to predetermine the probability of the safe arrival of their packaged products at their destination through the utilization of tests developed to simulate the shocks and stresses normally encountered during handling and transportation.

SAMPLE REQUIREMENTS One or more shippers

311729.1

Thermal Controlled Transport Packaging Test [ISTA 7D]

This method covers the thermal performance testing of packaged products to evaluate the effects of external temperature exposure.

SAMPLE REQUIREMENTS One or more shippers

30659.1

ISTA Environmental Conditioning [ISTA Series]

Temperature Cycling Sequence

1. Frozen or winter ambient -29°C for 72 hours, no RH control
2. Tropical wet then dry 38°C @ 85% RH for 72 hours, then 60°C @ 30% RH for 6 hours

SAMPLE REQUIREMENTS Varies

30660.1

ASTM Environmental Conditioning [ASTM D4332]

This practice is used to simulate particular field conditions that a container, package or packaging component may encounter during its life or testing cycle.

SAMPLE REQUIREMENTS Varies

SHELF-LIFE EXPIRATION DATING STUDIES

Accelerated aging is a key component of the overall packaging validation for medical devices. Following ISO 11607, a package validation is accelerated aging and the corresponding integrity testing as well as simulated distribution and its subsequent integrity testing.

A comprehensive packaging validation looks at accelerated aging and simulated distribution as separate components and each requires its own set of samples. The total package validation will pool the data from accelerated aging and simulated distribution in order to provide device manufacturers a complete validation of their package configurations.

Accelerated aging serves as key interim data to support product shelf-life dating until real-time data is available. If chamber space and time allow, we can also provide aging additional samples. This additional aging may be useful in the future to support extending a shelf life or supplemental data in the event of an issue.

In addition, our technical experts continue to leverage their experience with a broad range of products and industry experience to provide education on test strategies or suggestions as to how to approach a reported test failure. As is true with our approach to custom studies, our services are a holistic approach and partnership consulting with you to understand your product and recommend a strategy that is best for you.

ACCELERATED AGING TESTING

SAMPLE REQUIREMENTS

— Volume of Material
— Expiration Date
— Test Temperature
— Ambient (Storage) Temperature
— Aging Factor (Q10) [The most common Q10 is 2.0]

ACCELERATED AGING TESTING continued

NOTE: For accelerated and real-time aging, we offer a wide variety of temperature and relative humidity options. Contact your Business Development Manager if you need specific parameters not shown below.

38034.1

Accelerated Aging @ 55°C / 1 year

Condition primary packages at a test temperature of 55°C for a period of 1 year of equivalent real-time aging. This test may include exposure to high humidity and low humidity to provide maximum stress to packages. Ambient storage temperature = 22°C.

TEST DURATION 38 days = 1 year RTE (Real-Time Equivalent)

38034.3

Accelerated Aging @ 60°C / 1 year

Condition primary packages at a test temperature of 60°C for a period of 1 year of equivalent real-time aging. This test may include exposure to high humidity and low humidity to provide maximum stress to packages. Ambient storage temperature = 22°C.

TEST DURATION 27 days = 1 year RTE (Real-Time Equivalent)

38034.4

Accelerated Aging – Custom

Condition primary packages at a custom test temperature for an equivalent real-time aging period to be determined. Environmental factors may be considered.

TEST DURATION Equation is used to determine RTE (Real-Time Equivalent)

We strive for continuous improvement and staying at the forefront of scientific learning and discovery. Please contact your Business Development Manager for additional services. This catalog provides a comprehensive view of the tests we offer, but it is by no means exhaustive. We look forward to working with you in support of your medical device product portfolio.

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WuXi AppTec

MICROBIOLOGY TESTING

Microbial assays involve a variety of tests, from the determination of the numbers and types of organisms naturally present on a product to the assessment of controlled environments. With our comprehensive menu of microbiology services, WuXi AppTec Medical Device Testing provides testing across the product development lifecycle and beyond, from R&D and screening to in-process release, validations and finished product delivery.

IN THIS SECTION

BACTERIAL ENDOTOXIN (LAL)

Pyrogens are fever-producing materials that most often originate from Gram-negative bacterial cell walls, but can also originate as leachates from some chemicals and materials. Pyrogens from bacterial cell walls (the most commonly encountered type of pyrogen) are referred to as bacterial endotoxins and are readily detected by Limulus Amebocyte Lysate (LAL) testing systems.

LAL gel clot testing is a semi-quantitative method for testing of most medical devices/products. This method has been replaced in most cases by the more sensitive kinetic methods. The kinetic chromogenic LAL method provides direct quantification of the detected endotoxin level and is especially useful for very low-level detection, determining the endotoxin reduction of various production processes, monitoring the quality of water systems, and providing endotoxin levels for lot release of products. The kinetic turbidimetric method is similar to the chromogenic method and is used where there may be color interferences (e.g., blood-containing product). We follow the FDA, USP and AAMI guidelines when performing LAL tests.

Each time a new device/product is produced, or a significant change in material formulation is made on an existing device/product, a validation is recommended to be performed on samples from three production lots. The purpose of this is to ensure that the materials used in the construction of the device do not impart an inhibiting or enhancing effect on the LAL test system. Other changes, such as a change in the testing laboratory, may only require a single lot validation.

Sample requirements for both the validation testing and routine testing are typically determined by the size of the production lots from which the samples are selected.

NOTE: Chemical pyrogens, also called materials-mediated pyrogens, can be detected only by using the USP Rabbit Pyrogen Test or Materials-Mediated Test. (See the Biocompatibility section.)

BACTERIAL ENDOTOXIN (LAL) continued

130601.1
Kinetic Chromogenic

130802.1
Kinetic Turbidimetric

LAL Test Validation (Inhibition / Enhancement)

Validation of the inhibition or enhancement properties of materials on the test system.

SAMPLE REQUIREMENTS PER PRODUCTION LOT [USP <161> AND ANSI / AAMI ST72]
For lots of less than 30 units – 2 sample devices
For lots of 30-100 units – 3 sample devices
For lots of 101 units or greater – 3 % of lot, up to maximum of 10

[It is recommended that samples be sterile.]

NOTE: Validation testing can be performed at the same time and on the same samples as the lot release (finished product) testing.

130501.1
Kinetic Chromogenic

130801.1
Kinetic Turbidimetric

LAL Limit Test – Finished Product Testing

Quantitative determination of endotoxin level for finished devices or other materials.

SAMPLE REQUIREMENTS
For lots of less than 30 units – 2 sample devices
For lots of 30-100 units – 3 sample devices
For lots of 101 units or greater – 3% of lot, up to maximum of 10

[It is recommended that samples be sterile.]

130701.1
Kinetic Chromogenic

130801.2
Kinetic Turbidimetric

LAL Liquid Test

Endotoxin testing of water system samples or other non-biological liquids.

SAMPLE REQUIREMENTS
Minimum of 1 mL in sealed endotoxin-free polystyrene or glass container.

STERILITY METHOD SUITABILITY (Bacteriostasis / Fungistasis)

The Sterility Method Suitability Test (B / F) is necessary to demonstrate that there are no substances produced by the test materials (in the specified volume of test medium) that would cause inhibition of bacterial or fungal growth in a sterility test (i.e., a false negative interpretation). Testing is performed by inoculating sterility test samples in media with low levels of selected organisms to ensure growth. The parameters for the Sterility Method Suitability Test (B / F) are based on USP, and ISO/AAMI requirements.

190105.1 Immersion

190104.1 Membrane Filtration

190109.1 Fluid Path

Sterility Method Suitability Test (B / F) – Two Media [USP]

Sample device or material in the sterility test medium is tested for growth inhibition using the current USP organisms for Soybean-Casein Digest Medium (SCDM) and Fluid Thioglycollate Medium (FTM). (Additional organisms available upon request.)

SAMPLE REQUIREMENTS 6 sterile product samples

190106.1 Immersion

190107.1 Membrane Filtration

190108.1 Fluid Path

Sterility Method Suitability Test (B / F) – One Medium

Sample device or material in the sterility test medium is tested for growth inhibition using the current USP organisms for Soybean-Casein Digest Medium (SCDM). This method is used when only SCDM (TSB) is used for sterility testing products. (Additional organisms available upon request.)

SAMPLE REQUIREMENTS 3 sterile product samples

190111.1 Immersion

190112.1 Membrane Filtration

Sterility Method Suitability Test (B / F) – Per Organism, Per Medium

Sample device or material in the sterility test medium is tested for growth inhibition using selected organisms in specified media.

SAMPLE REQUIREMENTS 1 sterile product sample, per organism, per medium

PRODUCT STERILITY

Product sterility testing is typically performed in the validation of sterilization processes and, in some cases, for monitoring sterilization cycles. Sterility tests involve total immersion, membrane filtration or a fluid pathway fill method. The number of samples tested, the growth medium used and the incubation conditions are based on the particular standard or regulatory requirement – USP, AAMI / ISO or FDA / CFR.

110100.1
≤ 500 mL of media

110100.3
600-1000 mL of media

110100.5
1200-2500 mL of media

AAMI / ANSI / ISO Sterility Immersion

This test is used in sterilization validations (e.g., radiation, EO). Products are tested in Soybean-Casein Digest Medium (SCDM) at 30° ± 2°C for 14 days.

SAMPLE REQUIREMENTS Dependent on method used (e.g., AAMI 11137 Method 1 requires 100 samples, VDmax requires 10 samples).

122500.1

AAMI / ANSI / ISO Sterility Membrane Filtration

This test is used in sterilization validations (e.g., radiation, EO). Products are tested in Soybean-Casein Digest Medium (SCDM) at 30° ± 2°C for 14 days.

SAMPLE REQUIREMENTS Dependent on method used (e.g., AAMI 11137 Method 1 requires 100 samples, VDmax requires 10 samples).

110100.2
≤ 500 mL of media

110100.4
600-1000 mL of media

110100.6
1200-2500 mL of media

USP Sterility Immersion

This testing is used to monitor sterilization loads. Products are tested in both Soybean-Casein Digest Medium (SCDM) and Fluid Thioglycollate Medium (FTM) per USP guidelines.

SAMPLE REQUIREMENTS Up to 40 product samples.

122500.2

USP Sterility Membrane Filtration

This testing is used to monitor sterilization loads. Products are tested in both Soybean-Casein Digest Medium (SCDM) and Fluid Thioglycollate Medium (FTM) per USP guidelines.

SAMPLE REQUIREMENTS Up to 40 product samples.

122950.1
</= 500 mL of media

122950.2
600-100 mL of media

122950.3
1200-1500 mL of media

AAMI Sterility Fluid Path

This test is used in sterilization validations and for routine dose audit testing for devices with pathways labeled sterile. Products are tested utilizing Soybean-Casein Digest Medium (SCDM) at 30° +/- 2°C for 14 days.

SAMPLE REQUIREMENTS Dependent on method used (e.g., AAMI 11737 Method 1 requires 100 samples, VDMax requires 10 samples).

122950.1
</= 500 mL of media

122950.2
600-100 mL of media

122950.3
1200-1500 mL of media

USP Sterility Fluid Path

This test is used to monitor sterilization loads for devices with pathways labeled sterile. Products are tested utilizing both Soybean-Casein Digest Medium (SCDM) and Fluid Thioglycollate Medium (FTM) per USP guidelines.

SAMPLE REQUIREMENTS Up to 40 product samples.

1228810.1
300 mL of media

1228810.2
800 mL of media

Pyronema Screening

This test is used to determine the presence of *Pyronema* in sterilized products. Products are tested in Soybean-Casein Digest Medium (SCDM) at 20°C-25°C for 28 days.

SAMPLE REQUIREMENTS 100 samples.

BIOBURDEN

Bioburden testing is an assessment of the numbers and types of microorganisms present on a product, and is used for assessment of incoming materials, as an indicator of manufacturing conditions and to support sterilization validations. A determination of the recovery efficiency and characterization (grouping micro-organisms into categories) are both required for compliance with bioburden standards. All aspects of bioburden testing – test parameters, characterization and recovery efficiency — performed according to specified ISO, AAMI, USP or FDA requirements.

1606000.1

Aerobe Bioburden

Aerobe microflora count. (Test conditions may recover mold and yeasts as well as bacteria.)

1604000.1

Fungi Bioburden

Mold and yeast count. Extracts are plated using media designed to select for yeast and mold organisms (fungi).

1605500.1

Spore Bioburden

Aerobic spore count. Extracts are heat shocked to eliminate vegetative cells but recover spores.

1605600.1

Anaerobe Bioburden

Anaerobe microflora count. Extracts are incubated under anaerobic conditions. (Test conditions may recover facultative organisms as well.)

1605000.1

Total Bioburden Panel Aerobe / Anaerobe / Spore / Fungi

Intended for items for which a full characterization of the bioburden is needed.

Additional combined bioburden testing is available. Separate microorganism counts are provided.

1607000.1	Aerobe / Fungi
1608000.1	Aerobe / Spore
1608100.1	Aerobe / Anaerobe
1603010.1	Aerobe / Fungi / Spore
1607500.1	Aerobe / Anaerobe / Fungi
1604500.1	Aerobe / Anaerobe / Spore

BIOBURDEN continued

1601000.1

Bioburden Recovery Efficiency – Repetitive Recovery Method

Devices are extracted multiple times to determine overall efficiency of the first extraction. The percent efficiency and the correction factor are calculated for use in future bioburden evaluations performed on the product. This method is not recommended for items that typically display a very low bioburden (e.g., less than 50 CFU per device).

SAMPLE REQUIREMENTS 5 non-sterile devices.

1602000.1

Bioburden Recovery Efficiency – Spore Inoculation Method

Devices are inoculated with a known quantity of bacterial spores and then subjected to the established bioburden procedure. The recovered spores are counted and a correction factor is calculated for use in future bioburden evaluations.

SAMPLE REQUIREMENTS 3 sterile devices.

200040.1

Most Probable Number (MPN) 3-Tube Method

The MPN method is a well-established and fully documented method for estimating the number of viable microorganisms in a product in which the microorganisms are randomly distributed. The method is particularly appropriate for a product having bioburden of a low mean number.

Additional MPN testing is available.

200040.3

Most Probable Number (MPN) 10-Tube Method – Per Sample

BIOLOGICAL INDICATORS

Biological indicators (BIs) are carriers, such as a paper strip, that are inoculated with a specified level of a particular organism (typically *Bacillus* species). BIs are used to validate and/or monitor certain sterilization processes. Testing is performed according to either manufacturer's recommended BI or USP, ISO or AAMI requirements.

120100.3

Biological Indicator Direct Transfer

Individual spore strips are transferred from their primary package to Soybean-Casein Digest Medium (SCDM) and incubated for recovery of the indicator organism.

SAMPLE REQUIREMENTS
Spore strips.
Client-provided positive control recommended.

SHIPPING
Overnight air.
Protect from temperature extremes.

120100.2

Biological Indicator within Product

Spore strips that have been placed within a product or its package are retrieved from the product or package and transferred to Soybean-Casein Digest Medium (SCDM) for recovery of the indicator organism.

SAMPLE REQUIREMENTS
Spore strips.
Client-provided positive control recommended.

SHIPPING
Overnight air.
Protect from temperature extremes.

120100.1

Biological Indicator – Self-Contained

Self-contained BIs that have been placed within a product or its package are removed, activated (if required) and incubated for the recovery of the indicator organism.

SAMPLE REQUIREMENTS
Self-Contained Biological Indicator Vials or Ampoules.
Client-provided positive control recommended.

SHIPPING
Overnight air.
Protect from temperature extremes.

INOCULATED PRODUCT

Inoculated product consists of actual devices or materials that have been inoculated with a specified level of a liquid biological indicator (BI) suspension. Inoculated products are used to validate and/or monitor certain sterilization processes. Testing is performed by product immersion using either the manufacturer's BI parameters or those found in USP, ISO or AAMI standards.

1902000.2
B. subtilis

Product Inoculation

Devices are inoculated (usually in a location determined as most difficult to sterilize) with an indicator organism appropriate to the sterilization system in use.

SAMPLE REQUIREMENTS No minimum.

Indicate required population and sterilization method.

160210.1

Spore Count for Inoculated Product

After devices are cleaned per manufacturer's instruction, a bioburden test is performed to evaluate the effectiveness of the cleaning. Results are reported as a percent reduction.

SAMPLE REQUIREMENTS 4 product samples (1 to be used as positive control).

Biological Indicator within Product

Spore strips that have been placed within a product or its package are retrieved from the product or package and transferred to Soybean-Casein Digest Medium (SCDM) for recovery of the indicator organism.

SAMPLE REQUIREMENTS Spore strips.
Client-provided positive control recommended.

SHIPPING Overnight air.
Protect from temperature extremes.

1221010.1 ≤ 500 mL of media
1221010.2 600-1000 mL of media
1221010.3 1100-2500 mL of media

Inoculated Product Sterility

Product that has been inoculated with a liquid spore solution and exposed to a sterilization process is tested in Soybean-Casein Digest Medium (SCDM) to detect surviving organisms.

SAMPLE REQUIREMENTS Dependent on method and sterilizer volume.

120200.1

USP Biological Indicator: Total Viable Spore Count (Suspension)

Liquid samples, including spore suspensions and inoculated liquids, are enumerated to confirm spore population.

SAMPLE REQUIREMENTS Dependent upon expected population.

DOCUMENT REQUIREMENTS Manufacture's Certification of Analysis (CoA).

INOCULATED PRODUCT continued

190300.1

USP Biological Indicator: Total Viable Spore Count (Composite of 4 BIs)

Before using a new lot of BIs for sterilization load monitoring, the average population per unit should be independently confirmed per USP regulations or manufacturer's instructions.

SAMPLE REQUIREMENTS	Dependent on selected test.
DOCUMENT REQUIREMENTS	Manufacture's Certification of Analysis (CoA).
SHIPPING	Overnight air. Protect from temperature extremes.

190300.2

Biological Indicator: Total Viable Spore Count – per Manufacturer's Instructions

Before using a new lot of BIs for sterilization load monitoring, the average population per unit should be independently confirmed per USP regulations or manufacturer's instructions.

SAMPLE REQUIREMENTS	Dependent on selected test.
DOCUMENT REQUIREMENTS	Manufacture's Certification of Analysis (CoA). Manufacture instruction for population assay (if accessible).
SHIPPING	Overnight air. Protect from temperature extremes.

MICROBIAL IDENTIFICATION

This series of tests offers the ability to identify the microbial strain present.

Gram Stain

Differential staining technique used to categorize microorganisms.

Colony Morphology

Description of an organism's macroscopic (colony) appearance, including shape, color and texture.

190630.1

Gram Stain and Colony Morphology

Description of an organism's macroscopic (colony) appearance, including shape, color and texture, plus differential staining to determine organism category.

190401.1

Bacterial / Microbial Identification

Identification of a microbial isolate to at least the *genus* level.

MICROBIOLOGICAL EXAMINATION

Microbiological Examination Tests, as outlined in USP <61> and <62>, are designed to provide an estimate of the number of viable aerobic microorganisms, both bacteria and fungi, and/or to screen for specific target microbial species. These test methods can be applied to pharmaceutical articles, both finished and raw materials, and may also be useful for evaluating the presence of organisms on materials used in medical devices or biologics.

161402.1

Microbial Enumeration Tests – Suitability (USP <61>)

Test should be performed at least once (and, as circumstances require, subsequently) to demonstrate the test sample does not inhibit recovery or multiplication, under test conditions, of microorganisms that may be present. Aliquots of the diluted sample are inoculated with separate, diluted cultures of: *Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans* and *Aspergillus brasiliensis*. Confirmed inoculum counts are compared to counts recovered in the presence of the test material to determine whether the method provides for satisfactory neutralization of any inhibitory properties from the test material and appropriate recovery of the inoculum organisms.

161400.1

Microbial Enumeration Tests – Testing of Products (USP <61>)

Test is designed to determine total aerobic microbial count, and total yeast and mold count that can be recovered from the test material under the conditions and by the methods outlined in USP <61>.

161405.1
Single organism

161403.1
Organisms as listed

Tests for Specified Microorganisms – Suitability (USP <62>)

Test should be performed at least once (and, as circumstances require, subsequently) to demonstrate the test sample does not inhibit recovery or multiplication, under test conditions, of microorganisms that may be present. Aliquots of the diluted sample are inoculated with separate, diluted cultures of: *Staphylococcus aureus, Pseudomonas aeruginosa*, *Escherichia coli, Salmonella enterica, Candida albicans* and/or *Clostridium sporogenes*. Confirmed inoculum counts are compared to counts recovered in the presence of the test material to determine whether the method provides for satisfactory neutralization of any inhibitory properties from the test material and appropriate recovery of the specified organisms.

161404.1
Single organism

161401.1
Organisms as listed

Tests for Specified Microorganisms – Testing of Products (USP <62>)

Test is designed to demonstrate freedom of the test material from Bile-tolerant Gram-Negative Bacteria, *Escherichia coli, Salmonella, Pseudomonas aeruginosa, Staphylococcus aureus, Clostridia* and *Candida albicans.*

GROWTH PROMOTION

Prepared media must be tested prior to use to ensure it will support the growth of low levels of microorganisms. We offer this testing per USP requirements as well as customized per client request.

190411.1

Growth Promotion for Liquid Media (3 orgs per USP <71>)

Sterility Test Medium is tested for growth promotion using the current USP <71> organisms for Soybean-Casein Digest Medium (SCDM) or Fluid Thioglycollate Medium (FTM). (Additional organisms available upon request.)

SAMPLE REQUIREMENTS

3 samples per media type.
Negative control inoculated upon request. 1 additional sample needed for Negative Control, if requested.

190412.1
Solid Media

190412.2
Liquid Media

Growth Promotion for Solid / Liquid Media (Up to 5 orgs per USP <61>)

Growth Medium is tested for growth promotion using the current USP <61> organisms in agar or broth for Soybean-Casein Digest Medium (SCDM) or Sabouraud Dextrose Medium. (Additional organisms available upon request.)

SAMPLE REQUIREMENTS

5 samples per media type (liquid media).
10 samples per media type (solid media).
Negative control inoculated upon request. 1 additional sample needed for Negative Control, if requested.

190410.1

Growth Promotion per Organism

Growth Medium is tested for growth promotion using selected organisms in specified media.

SAMPLE REQUIREMENTS

1 sample per organism.
Client to specify test organisms.

We strive for continuous improvement and staying at the forefront of scientific learning and discovery. Please contact your Business Development Manager for additional services. This catalog provides a comprehensive view of the tests we offer, but it is by no means exhaustive. We look forward to working with you in support of your medical device product portfolio.

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ANTIMICROBIAL TESTING

Antimicrobial studies are used to evaluate the efficacy of an antimicrobial product feature or agent. WuXi AppTec Medical Device Testing's comprehensive efficacy testing program provides relevant data that can speed formulation selection, verify product performance, and confirm the efficacy of antimicrobial agents when combined with devices.

THE PROGRAM FEATURES

- *In Vitro* tests
  - Quickly evaluate activity and potency of antimicrobial agents
- Biofilm quantification studies
  - Evaluate candidate materials and dose levels to determine impact on biofilm formation
- *In Vivo* studies
  - Evaluate the antimicrobial effectiveness of final product candidates in a biologic system

Also offered are antimicrobial assays used to determine or confirm the effectiveness of treatments applied to commercial textiles and other industrial products.

IN THIS SECTION

ANTIMICROBIAL EFFICACY TESTING – *IN VITRO* ASSAYS

We offer the following assays to quantitatively or semi-quantitatively evaluate the antimicrobial activity of medical devices, components or other materials treated with antimicrobial agents. Many of the standard test methods listed here may be modified to include different or additional organisms as well as different or additional exposure times based on product application, claims and characteristics, activity of medical devices, components or other materials treated with antimicrobial agents.

190670.1

USP <51> Antimicrobial Effectiveness

Determines the effectiveness of antimicrobial (preservative) substances for the following products: injections and other parenterals including emulsions, otic products, sterile nasal products and ophthalmic products made with aqueous bases or vehicles; topically used products made with aqueous bases or vehicles, nonsterile nasal products, and emulsions, including those applied to mucous membranes; oral products other than antacids, made with aqueous bases or vehicles; antacids made with an aqueous base. Typically conducted prior to conducting microbial recovery assays involving products with potential inhibitory or microbicidal activity.

Samples are inoculated with known levels of microorganisms and are evaluated for degree of inhibition over a 28-day period.

190662.1

USP <1227> Validation of Microbial Recovery (Neutralization Validation)

Evaluates the method chosen to neutralize the antimicrobial properties of any product with inhibitory or microbicidal activity. The purpose of the assay is to ensure the validity of test results achieved during the USP <51> Antimicrobial Effectiveness test and other microbial recovery tests. It is conducted prior to estimating the number of viable microorganisms.

190655.1

ISO 22196

Specifies the testing methods to quantitatively evaluate antimicrobial activity and antimicrobial efficacy of bacteria on the surface of antimicrobial products. Recommended test organisms are *Staphylococcus aureus* and *Escherichia coli*. Triplicate samples are inoculated and evaluated for antimicrobial activity over a defined time period (usually 24 hours).

110790.1

ZONE OF INHIBITION / KIRBY-BAUER SUSCEPTIBILITY

Demonstrates activity / potency of antimicrobials or antibiotics, based on measuring the zone of inhibition observed for specified microorganisms. Areas of particular application include materials treated or infused with an antimicrobial agent that leaches out of the material.

ANTIMICROBIAL EFFICACY TESTING – *IN VITRO* ASSAYS continued

110780.1

ASTM E-2149 – Dynamic Contact

Quantitatively evaluates the effectiveness of a sample treated with a non-leaching antimicrobial by shaking in an organism suspension. The typical challenge organism is *Klebsiella pneumoniae*. Samples are exposed to the challenge organism in a liquid suspension for 1 hour under continuous agitation. The percent reduction of the challenge organism is then calculated.

110775.1

ASTM E-2180 – Bound Antibacterial Activity

Quantitatively evaluates the effectiveness of an antimicrobial agent incorporated into hydrophobic polymeric material. Recommended challenge organisms are *Staphylococcus aureus* and *Pseudomonas aeruginosa* (or *Klebsiella pneumoniae*). An aqueous-based bacterial inoculum remains in close contact with the treated material as a "pseudo-biofilm." Treated and non-treated (control) samples are compared for determination of percent reduction over a defined time period.

CUSTOM

ASTM E-2315 – Time-Kill Procedure

Duplicate samples are inoculated with the selected challenge microorganisms and changes in that inoculum population are evaluated at time points selected based on intended use of the material or over a longer period of time to develop a kill model for the material.

1625510.1

Microbial Barrier / Strikethrough

This test method evaluates the ability of the test material to provide a barrier to microbial penetration. A portion of test material is placed on the surface of an agar plate.

ANTIMICROBIAL EFFICACY TESTING – *IN VIVO* STUDIES

Antimicrobial studies are used to evaluate the efficacy of an antimicrobial product feature or agent. WuXi AppTec Medical Device Testing's comprehensive efficacy testing program provides relevant data that can speed formulation selection, verify product performance, and confirm the efficacy of antimicrobial agents when combined with devices.

CUSTOM

Antimicrobial Efficacy (AME) – *In Vivo* Studies

FDA-accepted animal models (developed by WuXi AppTec) test the efficacy of antimicrobial components of medical devices in an infectious agent-challenge study. Each antimicrobial efficacy (AME) study is custom designed, using clinically relevant bacterial strains and several implant and infection-delivery methodologies to produce a consistent and non-lethal *in vivo* device infection. Analyses of infection at device explant include assessment of remaining bacteria from device and surrounding tissue, imaging and identification of viable bacterial strain from the resulting infection.

BACTERIAL STRAINS

Our library of bacterial strains continues to expand. The bacterial strains most commonly administered during *in vivo* device infection studies include:

– *Acinetobacter baumannii*
– *Escherichia coli*
– Methicillin-resistant *Staphylococcus aureus* (MRSA)
– *Pseudomonas aeruginosa*
– *Staphylococcus aureus*
– *Staphylococcus capitis*
– *Staphylococcus epidermidis*
– Vancomycin-resistant *Enterococcus faecium/faecalis* (VRE)
– Other isolates suggested or provided by the Sponsor

ADDITIONAL ANALYSES

– *In vitro* antimicrobial tests, including Zone of Inhibition
– Histopathology to assess local response, microscopic evidence of bacterial infection, device characteristics, etc.
– Biochemical and/or DNA identification of recovered bacterial strains
– Hematology and clinical chemistry analyses to assess disease progression
– Chemistry / drug elutions analysis of serum and tissue samples
– Imaging analysis of explanted device surfaces, including scanning electron microscopy and confocal laser scanning microscopy

BIOFILM STUDIES

110783.1

ASTM E-2196 Rotating Disk Reactor

This method is designed to generate a biofilm under “medium fluid shear” conditions where the shear is caused by the continuous movement of the test sample surface over a low-nutrient medium in a continuously stirred flow reactor.

110797.1

ASTM E-2562 CDC Reactor

This method is designed to generate a biofilm under “high shear” conditions where the shear is caused by the continuous flow of nutrients over the surface of the sample where the flow of nutrients is controlled in a continuously stirred flow reactor.

INDUSTRIAL PRODUCT ANTIMICROBIAL ASSAYS

Antimicrobial assays are used to determine or confirm the effectiveness of treatments applied to commercial textiles and other industrial products. Test methods for measuring antimicrobial activity include ASTM, AATCC and other standard or modified methods. Testing includes antibacterial and antifungal activity, with both qualitative and quantitative assays available.

Test parameters in the following descriptions are those found in the standard method referenced. Many test methods allow modifications to these parameters based on product application, claims and characteristics.

110700.1

AATCC Method 30, Part III

Samples are inoculated with *Aspergillus brasiliensis* and evaluated for the degree of growth over a 7-day period.

110710.1

AATCC Method 100

Samples are inoculated with *Staphylococcus aureus* and *Klebsiella pneumoniae* and evaluated for percent reduction of the bacteria over selected contact periods between 1 to 24 hours.

110720.1

AATCC Method 147

Samples placed in direct contact with *Staphylococcus aureus* and *Klebsiella pneumoniae* inoculum streaks are evaluated for inhibition of growth and zones of inhibition within 24 hours.

110730.1

AATCC Method 174, Part 1

This method is utilized to provide a qualitative antibacterial assessment of carpets. It is designed for assessment of new carpets and must not be used for carpets that have been laid down and worn. Separate agar plate surfaces are inoculated with *Staphylococcus aureus* and *Klebsiella pneumoniae*. A 25 mm x 50 mm piece of carpet is placed onto the surface of each plate. Both the fiber and backing of each carpet sample are tested. Following 18-24 hours of incubation, the zone of inhibition is measured.

110740.1

AATCC Method 174, Part 2

This method provides a quantitative procedure for evaluation of the degree of antibacterial activity. It may be utilized to determine the effects of repeated washings on the antimicrobial activity. It is designed for assessment of new carpets and must not be used for carpets that have been laid down and worn. Carpet samples are inoculated with a known concentration of two test organisms, *Staphylococcus aureus* and *Klebsiella pneumoniae*. A 48 mm disk of carpet is used for each organism and the fiber side is inoculated. Following 24 hours of incubation, carpet samples are neutralized with Letheen Broth and serial dilutions performed. The number of bacteria present is determined and the percent reduction is calculated.

INDUSTRIAL PRODUCT ANTIMICROBIAL ASSAYS continued

110750.1

AATCC Method 174, Part 3

This method is utilized to provide a qualitative antifungal assessment of carpet. It is designed for assessment of new carpets and must not be used for carpets that have been laid down and worn. Two 38 mm disks of carpet are placed onto inoculated agar plates containing *Aspergillus niger*. An aliquot of inoculum is also pipetted on top of the carpet samples. Both the fiber side and the backing side are tested. Following 7 days of incubation, the carpet sample is rated for growth / no growth.

110785.1

ASTM E-2471 – Antimicrobial Activity in Carpet

Qualitatively evaluates (both stereomicroscopically and visually) antibacterial and antifungal activity at the fiber layer and at the primary backing layer of carpet when challenged with *Aspergillus brasiliensis, Serratia marcescens* and *Staphylococcus aureus*.

110760.1

ASTM G-21 Antifungal, Semi-Quantitative

Semi-quantitatively evaluates ability of synthetic polymeric test material to support the growth of a mixture of 5 fungi. Synthetic polymeric test material is usually provided in the form of molded and fabricated articles, tubes, rods, sheets and film materials. Samples are inoculated with the fungi mixture and evaluated for the degree of growth for up to 28 days.

Additional testing applicable to industrial products listed below.
Please refer back as these tests are listed previously in this catalog.

- ASTM E-2149 – Dynamic Contact
- ASTM E-2180 – Bound Antibacterial Activity
- ASTM E-2315 – Time-Kill Procedure
- Zone of Inhibition / Kirby-Bauer

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TISSUE PRODUCT TESTING

WuXi AppTec Medical Device Testing offers a comprehensive program of services for tissue-based products – built on our unequaled experience and expertise.

To support product development through commercialization of your tissue-based product, our testing transitions seamlessly through each phase. We offer viral inactivation studies, efficacy studies and lot release testing to support the product from development through commercialization.

IN THIS SECTION

TISSUE-BASED PRODUCT TESTING

WuXi AppTec Medical Device Testing offers a comprehensive program of services for tissue-based products – built on our unequaled experience and expertise.

DBM Lot Release Assays (cGMP)

OSTEOINDUCTIVITY *(In Vivo)*

In Vivo assays in nude mice or rats are used to definitively prove the ability of a DBM product to induce ectopic bone formation. The study is performed by intra- or inter-muscular implantation of product followed by histopathology.

In this catalog, please reference Microbiology Bacterial Endotoxin (LAL) for more information.

The kinetic chromogenic LAL method provides direct quantification of detected endotoxin levels to determine existing level of endotoxin on the product or endotoxin reduction of a production process.

Viral Clearance Studies

For over 25 years, we have provided proven performance at all levels of viral clearance studies.

Our extensive expertise, unparalleled suite capacity, comprehensive database mining and collection of ultra-pure, high-titer virus stocks make us the clear industry leader.

PROCESSES EXPERIENCE

Our experience spans a broad range of different processes, including:

INACTIVATION
- Heat / Pasteurization
- Low and high pH
- Solvent / Detergent
- Irradiation
- Sterilization
- High-energy light
- Alcohols
- Disinfectants
- Liquid chemical sterilization
- Gas / Plasma / CO_2 processes

CLEANING
- Kinetics of inactivation
- Coupon studies

Quality Control and Ongoing Product Testing

We have a wide range of expertise in all areas of quality testing used for processed tissue and tissue-based products. The tests listed below are highlighted in detail within each section noted.

TEST OFFERINGS INCLUDE

MICROBIOLOGY
- Bioburden
- Endotoxin (LAL)
- Sterility

CHEMISTRY
- Residual Moisture
- Residual Calcium

VALIDATION
- Environmental Monitoring
- Water Quality

PACKAGE TESTING
- Package Testing
- Accelerated Aging
- Cold Chain Studies

PACKAGE TESTING
- Validation of Sterilization Procedures
- Validation of Decontamination Procedures
- Process Change Validations

In-Vivo Small Animal Models

OTHER CUSTOM SERVICES

Additional customized studies that complement a tissue testing program, including biocompatibility testing and cell-based potency assays.

We strive for continuous improvement and staying at the forefront of scientific learning and discovery. Please contact your Business Development Manager for additional services. This catalog provides a comprehensive view of the tests we offer, but it is by no means exhaustive. We look forward to working with you in support of your medical device product portfolio.

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WuXi AppTec

US TESTING LOCATIONS | SAINT PAUL, MN | ATLANTA, GA

MEDICALDEVICE.WUXIAPPTEC.COM

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