CURTISS-WRIGHT

IMR TEST LABS

MITIGATING BIOCOMPATIBILITY RISKS IN MEDICAL DEVICE MANUFACTURING

Cleanliness Testing and Cytotoxicity Analysis for Medical Applications

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The medical devices and surgical tools used daily in the medical industry are subject to strict testing standards dictated by the FDA and other regulatory bodies using ASTM and ISO methodologies. Ensuring that these items are free from harmful residues left behind by manufacturing or cleaning processes is essential to maintaining patient health. As such, medical device manufacturers must test the materials they use and the products they fabricate to make sure they are safe for biological contact with patients.

Medical device cleanliness testing ensures that materials used in medical implants – as well as surgical, diagnostic, and therapeutic tools – won't have adverse toxic effects when utilized for patient treatments. A range of chemical and metallurgical examinations can assess the performance of these materials in relation to their potential impact on patient well-being.

In addition to the testing processes for medical device cleanliness, manufacturers must also determine that tools and equipment that will come into contact with human tissue will not produce unexpected cytotoxic reactions in patients. While cytotoxic chemicals can have positive medical benefits – chemotherapy drugs are cytotoxic agents that kill cancer cells, for example – unexpected cytotoxic agent exposure during surgery, treatment, or long-term device exposure can cause serious medical complications or death.

Medical Device Testing

The medical industry stringently adheres to strict quality standards, and for good reason. When materials are coming into direct contact with mammalian tissue – or going so far as to be implanted on a lasting basis – quality simply cannot be compromised.

Accredited materials testing labs provide analytics to manufacturers of a wide range of medical and dental implants. Thorough testing assures biocompatibility and lasting material performance, and also isolates and investigates failures. Verifying raw materials, supporting research and development, and final testing on finished products all play a key role in creating safe, reliable products. Just a few of the materials subject to evaluation include:

- Metals
- Powders
- Polymers and elastomers
- Coatings
- Ceramics
- Finished composite products
- Platings and anodizings
- Porous materials
- Process solutions

Medical Cleanliness

In the same vein as maintaining strict standards for device manufacturing, those in the medical field must also adhere to strict standards of cleanliness for the tools or components they use to treat patients or conduct research. Manufacturing and cleaning processes must follow very rigorous guidelines to eliminate the risk of contamination, which could adversely affect patients.

Diverse testing options are frequently used by the medical sector to ensure medical cleanliness in manufacturing and cleaning processes, such as:

ICP-MS Analysis

The ICP-MS instrument is designed to detect and identify a large variety of heavy metals, such as lead, mercury, and cadmium. Exposure to these metals leads to buildup in the organs and fatty tissue in the body, and can be poisonous when accumulated in the system to certain levels. Medical devices such as dental appliances and stents are often fabricated using nickel alloys. Inductively-coupled plasma mass spectrometry (ICP-MS) tests help manufacturers confirm that device users will not be at risk from unsafe levels of nickel exposure during a device's recommended service life.

TOC/IC Analysis

Medical devices are repeatedly exposed to a range of cleaning solutions throughout their service life. Total Organic Carbon (TOC) or Ion Chromatography (IC) testing are used to detect residue from detergents and other cleaning supplies to ensure that any residue left behind is within safe levels.

Polar/Non-Polar Extractions

During manufacturing, medical devices and tools may be exposed to a range of oils from machining processes and detergents from cleaning processes. To guarantee medical cleanliness, laboratories use Extractable Material testing to ensure that end-use devices are free of contaminants. This is part of the preparatory protocol for TOC/IC analysis.

Leaching Extractions

Medical devices may break down over time due to lengthy exposure to the body's organic material. Leaching tests simulate the body's internal chemistry, establishing accurate predictions of how a medical device will interact with the body over time. This is part of the preparatory protocol for ICP-MS analysis.

Cytotoxic Reactions

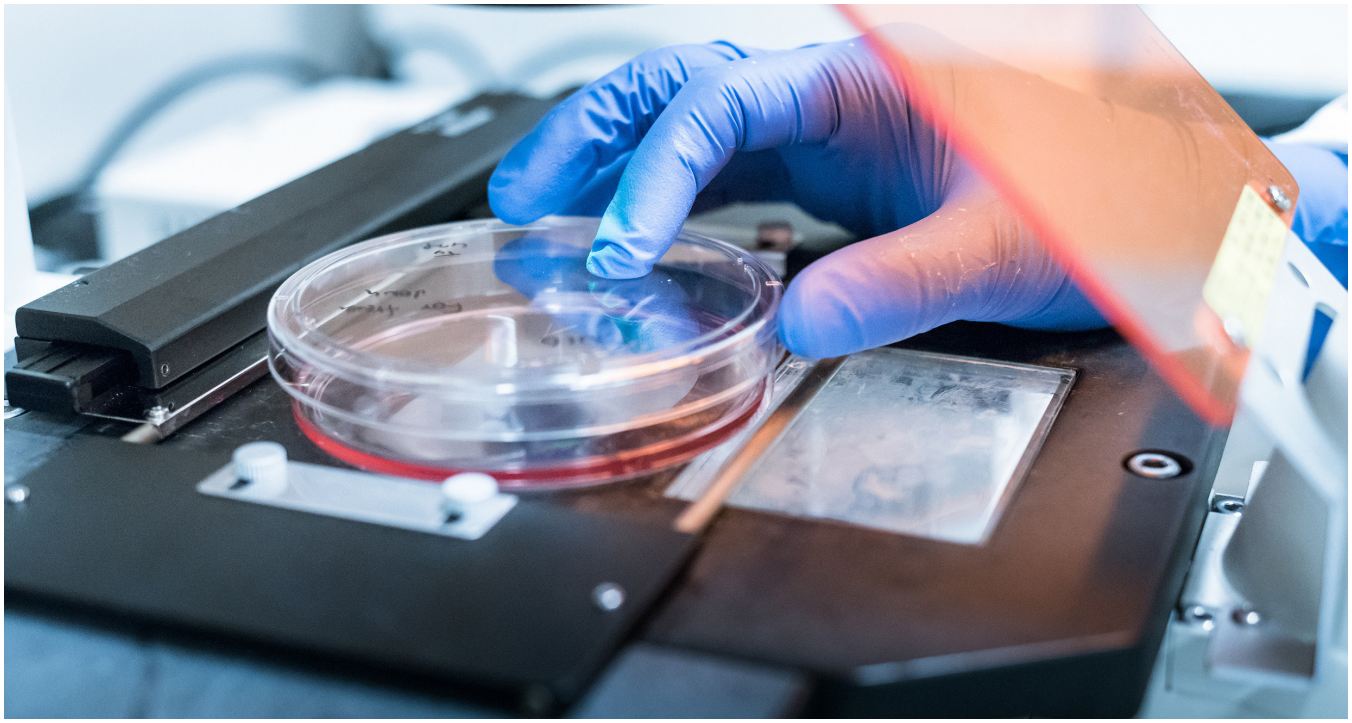
As medical device manufacturing standards and cleanliness assessments prevent the risks associated with potentially hazardous residual contamination, biocompatibility testing safeguards patients from harmful reactions between medical equipment and human tissue. Such exposure can result in critical medical complications or even potential fatalities.

There are a number of ways in which a cell can respond when exposed to a cytotoxic compound.

Necrosis, a form of cell death, causes the cell to lose its membrane integrity and rapidly die. The cell's metabolism shuts down, causing it to swell rapidly before the membrane is compromised and intracellular material exits the cell. A rapid reaction, necrosis overrides the natural processes in a cell's genetic code that would typically recycle material from a dying cell.

Apoptosis, another form of cell death, is triggered by innate genetics. A cytotoxin activates the program for controlled death protocol, provoking a series of defined molecular events including nuclear condensation, cytoplasmic shrinkage, and the cleavage of DNA. Eventually, the process results in secondary necrosis.

Decreased cell viability may not actually kill the cell in question, but it will cease to grow, thrive, and divide. Cells with reduced viability have a limited ability to heal from the damage caused by cytotoxic agents.



Testing Methods for Biocompatibility

If a cytotoxic element on a medical device is exposed to healthy living cells around a wound, the healing process can be dramatically compromised — this is why sterilization and clean rooms are so important in medical facilities. Implants, particularly man-made medical devices, demand the highest possible degree of cleanliness to ensure minimal complications.

Some of the common tests in evaluating biocompatibility include:

- Cytotoxicity and tissue culture analysis
- Sensitization assays
- Acute systemic toxicity evaluations
- Irritation tests
- Sub-cutaneous and genotoxicity
- Hemocompatibilty
- Implantation tests
- Carcinogenesis bioassays
- Pharmacokinetics
- Histopathology evaluations
- Preclinical safety testing
- Reproductive and developmental toxicity tests

Common Cytotoxicity Testing Methods

In vitro – or non-animal, test tube-based – cytotoxicity testing has become a popular and ethical method of assessing how a material interacts with living mammalian cells. A highly efficient pre-cursor to toxicology testing, it avoids potentially unsafe in vivo testing while still ensuring a thorough analysis.

- **The MEM elution method,** also known as **Extraction Testing**, directly exposes the monolayers of cells to test fluid extracted from the test object or material. Ideal for medical devices, this method is useful for testing isolated components or parts for cytotoxic reactions. This method is the most widely recognized and broadly accepted testing method.
- **Direct Contact Testing** is most effective on low density testing materials. The process exposes a piece of test material directly to cells growing on a culture or other medium. The cells are then incubated and observed for any potential diffusion or reactivity caused by the material sample.
- **Agar Diffusion**, also referred to as **Agar Overlay Testing**, works indirectly, cushioning cell monolayers with agar against the material being tested. An especially effective solution for transparent materials, agar diffusion is excellent for contact lenses and other clear plastic parts.

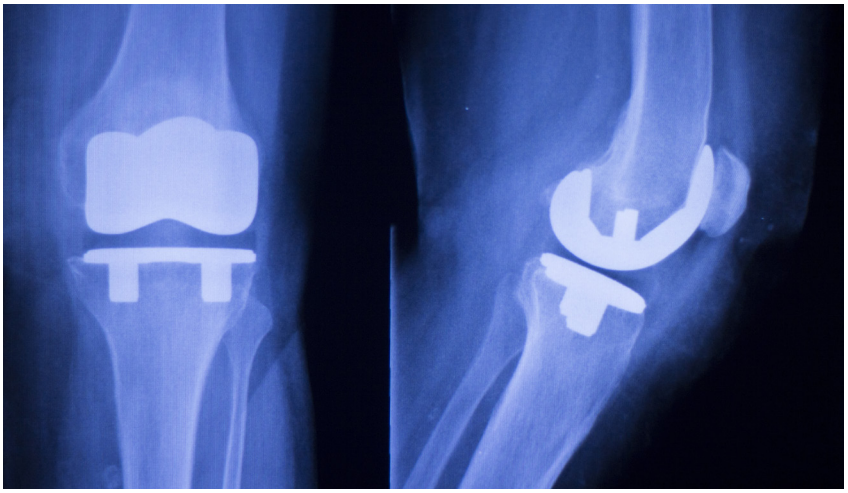
- **MTT Assay for Quantitative Cytotoxicity** uses a colorimetric procedure to assess the metabolic activity of cells. Performed either by extracts or direct contact, this method is purely quantitative; There is no analyst interpretation involved. It is an excellent tool to evaluate the cytotoxicity of extractable materials in medical devices, potential anti-cancer medicines, toxic compounds and environmental pollutants, and antibodies.

Medical Device and Cytotoxicity Testing at IMR

Supported by our chemical, metallurgical, corrosion, and failure analysis departments, IMR offers both characterization and quantification of residues and particulates to help you quickly eliminate sources of contamination.

With a range of techniques including FTIR, Total Organic Carbon, Ion Chromatography, GC/MS, ICP-MS / ICP-AES, optical and scanning electron microscopy (SEM, SEM-EDX), IMR is equipped to test for contaminants including:

- Cutting Fluids
- Particulates
- Detergents/Cleaning Solutions
- Oils
- Anions/Cations
- Halogens
- Mold Release Agents
- Plasticizers



Our new Cytotoxicity Lab is built for thorough, reliable analysis. We specialize in MEM Elution testing, the most widely recognized and accepted test methodology available for cytotoxicity testing. Our team understands the major risks and stringent regulations involved in developing high-quality, effective healthcare solutions and is here to help you succeed.

IMR's well-equipped lab conducts the most accurate testing available. We handle sterile mammalian cell cultures for testing on a wide range of tools, contaminants, and implantable devices. Our analysts assemble thorough evaluations, meticulously analyzing your device for any biocompatibility hazards.

Testing with the IMR Team

At IMR Test Labs, we offer a full array of the latest techniques in chemical analysis. We carefully evaluate the potential particulates, oils, contaminants, and detergents, that can be left behind from the manufacturing, handling, and packaging processes, and obtain a complete, precise analysis of any potential compromise to your product's safety and performance.

As an international testing firm, IMR offers a full scope of materials testing services in addition to biocompatibility tests. Our experts work across industries, providing complete chemical analysis, cleanliness testing, mechanical testing, corrosion testing, metallurgical analysis, failure analysis, fatigue testing, and more.

Our labs are ISO/IEC 17025 accredited for all our service offerings. At IMR, you'll find skilled metallurgists, technicians, chemists, engineers, and materials scientists — all ready to help. To learn more about how we can help you create safe and sanitary products, request a quote or contact us.

ABOUT US

We're an international firm offering a complete scope of materials testing services, including chemical analysis, cleanliness testing, corrosion testing, mechanical testing, metallurgical analysis, failure analysis, fatigue testing and much more.

We have five facilities, located in Ithaca, New York; Louisville, Kentucky; Portland, Oregon; Singapore; and Suzhou, China. IMR demonstrates an on-going commitment to serve our clients' analytical needs, wherever they may be.

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