MEDICAL DEVICE TESTING SERVICES

PBL
Pacific BioLabs
The Service Leader in Bioscience Testing

CERTIFICATE OF ACCREDITATION

The ANSI National Accreditation Board

Hereby attests that

Pacific BioLabs

551 Linus Pauling Dr.
Hercules, CA 94547

Fulfills the requirements of

ISO/IEC 17025:2017

In the field of

TESTING

This certificate is valid only when accompanied by a current scope of accreditation document.
The current scope of accreditation can be verified at www.anab.org.

R. Douglas Leonard Jr., VP, PILR SBU

Expiry Date: 25 March 2023
Certificate Number: AT-2661

This laboratory is accredited in accordance with the recognized International Standard ISO/IEC 17025:2017.
This accreditation demonstrates technical competence for a defined scope and the operation of a laboratory quality management system (refer to joint ISO-ILAC-IAF Communiqué dated April 2017).

SCOPE OF ACCREDITATION TO ISO/IEC 17025:2017

Pacific BioLabs

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TESTING

Valid to: **March 25, 2023** Certificate Number: **AT-2661**

Biological

Specific Tests and/or Properties Measured	Specification, Standard, Method, or Test Technique	Items, Materials or Product Tested	Key Equipment or Technology
Biocompatibility			
Intramuscular Implant Test	ISO 10993-6 USP <88>	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Balance
Acute Systemic Toxicity Test	ISO 10993-11 USP <88>	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Incubators and Ovens Balance
Intracutaneous (Intradermal) Reactivity Test	ISO 10993-10 USP <88>	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Incubators and Ovens
Rabbit Pyrogen Test	ISO 10993-11; USP <151>, European Pharmacopoeia	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Thermometer
Safety Test for Biological Products	USP <88>	Biologics	Balance

Biological

Specific Tests and/or Properties Measured	Specification, Standard, Method, or Test Technique	Items, Materials or Product Tested	Key Equipment or Technology
Closed Patch Test for Delayed-Type Hypersensitivity Maximization Test for Delayed-Type Hypersensitivity Skin Sensitization-Buehler Method	ISO 10993-10 OECD 406	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Incubators and Ovens
Mucosa, Ocular, Dermal Irritation	ISO 10993-10, EPA/OPPTS 870.2500, EPA/OPPTS 870.2400, FHSA/16 CFR 1500.41, FSHA/16 CFR 1500.42, OECD 404, OECD 405	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Incubators and Ovens
Acute, Dermal, Oral Toxicity	ISO 10993-11, Iron Dextran Injection USP Monograph, EPA/OPPTS 870.1200, EPA/OPPTS 870.1100, FHSA, OECD 402, OECD 420, European Pharmacopoeia	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Incubators and Ovens
Bioassay			
Glucagon Assay	USP <123>	Pharmaceutical, Biologics	Clinical Chemistry Analyzer
Insulin Assay for Human Insulin – Bioidentity	USP <121>	Pharmaceutical, Biologics	Clinical Chemistry Analyzer
Cleaning & Disinfection Studies			
Medical Device Cleaning Validations	AAMI TIR12; AAMI TIR30	Medical Devices, Combination Devices,	Microplate Reader Spectrophotometer
Steam Sterilization Validation, Biological Indicators	ANSI/AAMI/ISO 17665-1 ANSI/AAMI/ISO 14161	Medical Devices, Combination Devices,	Incubators
Cytotoxicity			
Agar Diffusion	USP <87>; ANSI/AAMI/ISO 10993-5	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Incubators, Microscope

Biological

Specific Tests and/or Properties Measured	Specification, Standard, Method, or Test Technique	Items, Materials or Product Tested	Key Equipment or Technology
Elution	USP <87>; ANSI/AAMI/ISO 10993-5	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Incubators, Microscope
Direct Contact	USP <87>; ANSI/AAMI/ISO 10993-5	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Incubators, Microscope
LAL Bacterial Endotoxins	USP <85> and <161>; ANSI/AAMI ST72:2011; EP 2.6.14, Bacterial Endotoxins	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Incubating Absorbance Microplate Reader

Microbiological

Specific Tests and/or Properties Measured	Specification, Standard, Method, or Test Technique	Items, Materials or Product Tested	Key Equipment or Technology
Antimicrobial Effectiveness	USP <51>	Chemicals, Pharmaceuticals, Biologics	ISO Class 5 Biosafety Cabinets
Bacteriostasis / Fungistasis Sterility	USP <71>	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Membrane Filtration/Direct Transfer
Bioburden	USP <61>; ANSI/AAMI/ISO 11737-1	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	Laminar Air Flow Hood
Sterility Assurance	Sterility AAMI TIR 33, Sterility ANSI/AAMI/ISO 11137-2 Method 1, Sterility ANSI/AAMI/ISO 11137-2, Sterility AAMI/ISO TIR 15844, ANSI/AAMI/ISO 11737-2	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	ISO Class 5 Biosafety Cabinets, ISO 5 through 8 Areas
Microbial Enumeration Testing for Specified Microorganisms	USP <61>; USP <62>; USP <1111> EP/BP	Medical Devices, Combination Devices, Chemicals, Pharmaceuticals, Biologics	ISO Class 5 Biosafety Cabinets, Incubators

Chemical

Specific Tests and/or Properties Measured	Specification, Standard, Method, or Test Technique	Items, Materials or Product Tested	Key Equipment or Technology
Conductivity	USP <645>	Pharmaceutical Water	Conductivity Analyzer
Total Organic Carbon	USP <643>	Pharmaceutical Water	Total Organic Carbon Analyzer
Extractable Leachable Testing	ISO 10993-18	Medical Devices, Combination Medical Devices	ICP-MS HPLC GC-MS

Note:

1. This scope is formatted as part of a single document including Certificate of Accreditation No. AT-2661.

R. Douglas Leonard Jr., VP, PILR SBU

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To view this booklet online, please go to PacificBioLabs.com.

May 2019

PBL is FDA registered and ISO 17025:2017 accredited by ANAB. Our animal science operations are accredited by AAALAC.

THE SERVICE LEADER AMONG DEVICE CROs

Since 1982, **Pacific BioLabs**, a non-clinical GMP/GLP CRO, has provided biological and analytical testing designed to support both growing and established medical device companies. As *The Service Leader in Bioscience Testing*, our goal is to provide our clients with a combination of expertise, rigor in our quality systems, and personalized attention that is unique among CROs.

Facility and Location

Pacific BioLabs is housed in a 32,000 square foot facility in Hercules, CA. This state-of-the-art laboratory/vivarium allows us to offer top quality testing services to our clients throughout the world.

Completed in 2000, all major building systems and equipment have been validated to cGMP and GLP standards. A generator supplies back-up electrical service for all critical utilities and equipment. A monitoring system provides 24-hour alerts of any deviations or outages, allowing for rapid resolution, and ensuring optimal facility operation.

Quality Systems

Pacific BioLabs is a cGMP and GLP laboratory that has a world class quality system based on ISO 17025:2017, requirements similar to those in the medical device Quality System Regulation (QSR-21 CFR 820) and incorporates by reference ISO 9001:2015. PBL has an excellent track record of positive outcomes from FDA inspections, hosts over 50 client audits per year and has a culture committed to quality.

- GLP and cGMP compliant
- FDA Registered
- ISO 17025 Accredited by ANAB
- Electronic SOPs

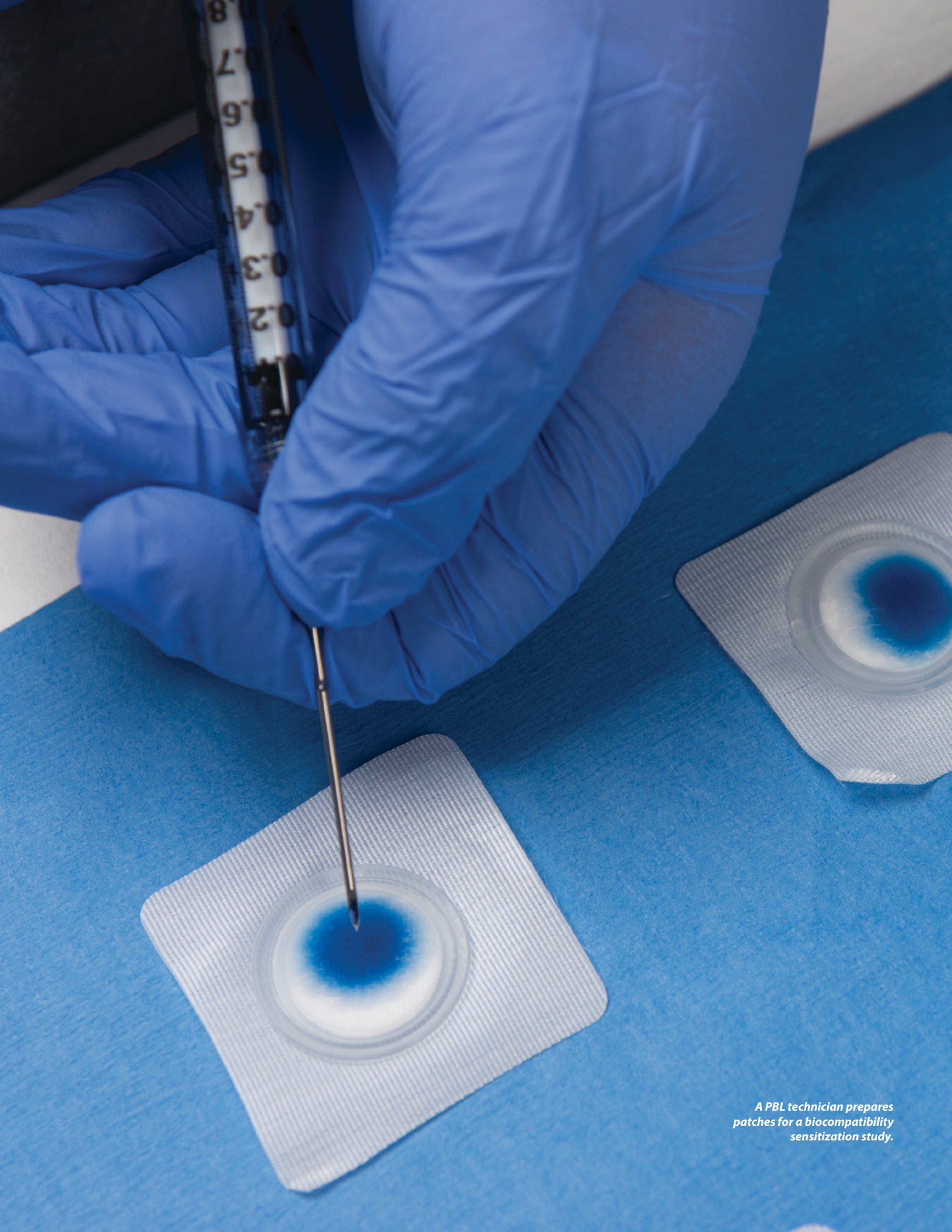
TESTING SERVICES

Device Development Support

- Biocompatibility Testing
- Chemical Characterization
- USP Class Plastics
- Material Mediated Pyrogenicity
- Latex Testing
- Complement Activation
- Cytotoxicity
- Contact Lens Solution Testing
- Sterilization Validation
- Shelf Life Testing
- Reusable Device Cleaning and Disinfection Validations

Device Manufacturing Support

- Bioburden and Sterility Testing
- LAL / Endotoxin Testing
- Residual Analysis
- Package Integrity Testing
- Environmental Monitoring



A PBL technician prepares patches for a biocompatibility sensitization study.

BIOCOMPATIBILITY TESTING

Pacific BioLabs offers both *in vitro* and *in vivo* biocompatibility testing from our San Francisco Bay Area location. Our skilled technicians can help plan your project and ensure a smooth testing process. PBL has been assisting medical device companies with FDA 510K and IDE, as well as international regulatory submissions for over 30 years. We offer testing performed according to ISO 10993 and compliant with all major regulatory bodies. Our animal programs are AAALAC accredited, and we carry ISO 17025 accreditation.

Cytotoxicity

- Agarose Overlay
- MEM Elution
- Direct Contact
- MTT (quantitative)

Sensitization

- Maximization Test
- Closed Patch (Buehler)

Irritation / Intracutaneous Reactivity

- Intracutaneous Reactivity
- Mucosal Irritation (Vaginal, Rectal, Oral, Penile)
- Ocular Irritation
- Intraocular Irritation
- Dermal Irritation (Intact or Abraded Skin)

Systemic Toxicity / Pyrogenicity

- Acute Systemic Toxicity
- USP/CFR Pyrogen Test
- ISO Rabbit Pyrogen - Material Mediated

Subacute / Subchronic Toxicity

- Mice, Rats, New Zealand White Rabbits
- 14-30 Day
- 90 Day
- 180 Day

Hemocompatibility

- JP Hemolysis Test
- ASTM Hemolysis

Implantation Testing

- ISO and USP Intramuscular Implantation
- Subcutaneous Implantation

EPA / OECD Testing

- Acute Dermal Toxicity (Limit Test)
- Acute Dermal Irritation
- Acute Oral Toxicity (Limit Test)
- Acute Eye Irritation
- Buehler Method

A PBL analyst prepares an extraction solution for a medical device extractable/leachable study.

MEDICAL DEVICE CHEMICAL CHARACTERIZATION

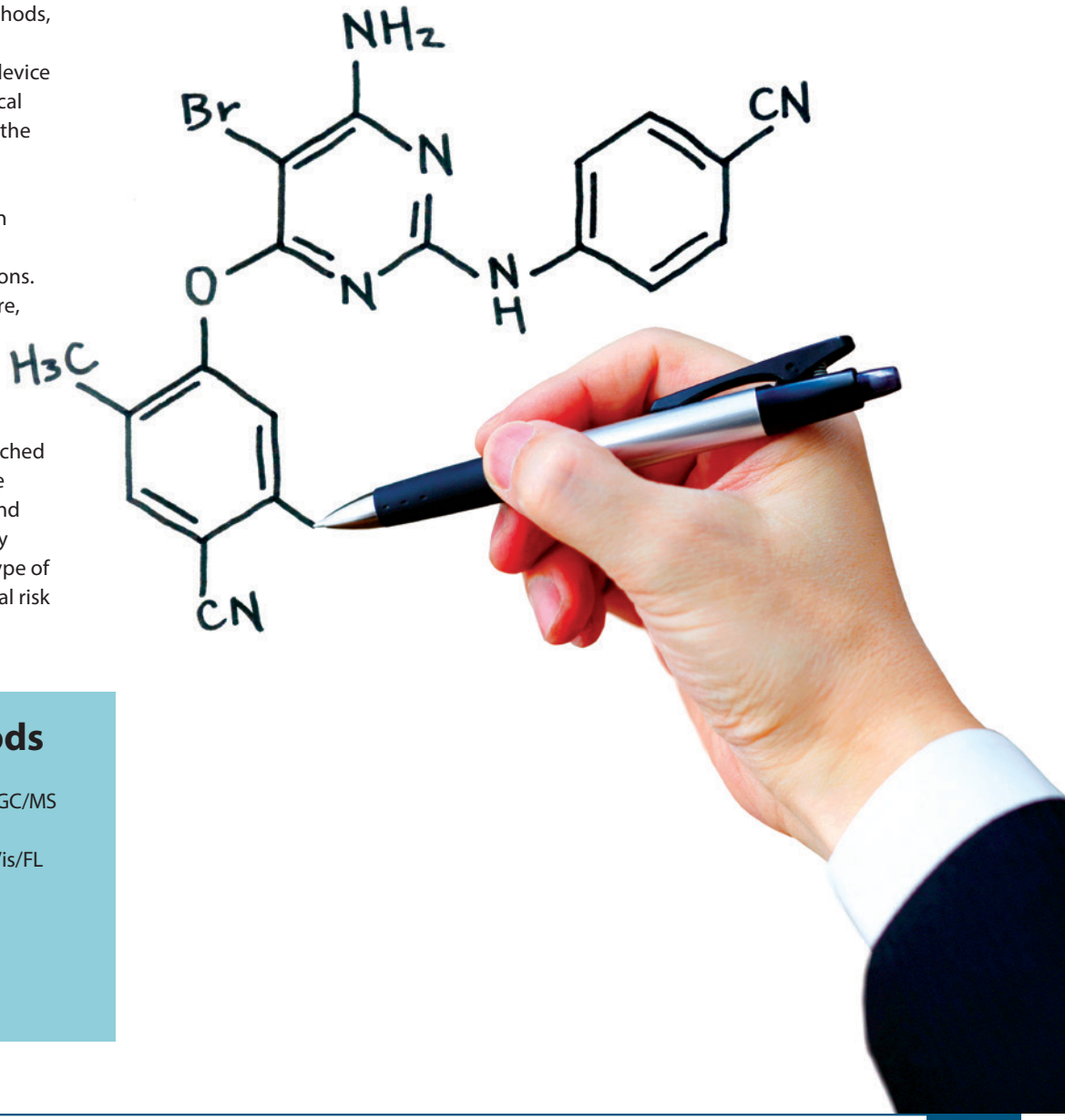
Chemical Characterization and Biocompatibility

Establishing the biocompatibility of a medical device is a key part of ensuring the safety of any device. Historically, biocompatibility has been assessed primarily through *in vivo* testing. However, FDA and international regulators are placing an increasing emphasis on using analytical methods to identify and quantitate the chemicals that can be extracted from, or leach out of, devices. The resulting data from these extractable/leachable studies is used to construct a more complete picture of device safety.

Chemical Characterization Studies at PBL

Chemical characterization studies (analogous to leachables and extractables studies), following ISO 10993-18 methods, look at the types and amounts of chemicals that may migrate from a device during use. From this specific chemical profile, an overall risk assessment of the safety of the device can be created.

Pacific BioLabs' team of chemists can work with clients to determine the most appropriate extraction conditions. Parameters such as time, temperature, solvent choice, and nature of the device will be considered. Compounds extracted from the device can often be identified using mass spectrometry or FTIR data. Leached or extracted residual solvents can be analyzed by GC and GC/MS. Trace and heavy metal analysis is conducted by ICP-MS. Based on the amount and type of compounds extracted, a toxicological risk assessment is conducted.



Available Methods

- Volatiles & Organics by GC & GC/MS
- Headspace GC
- Spectrophotometry by UV/Vis/FL
- Identity/Purity by HPLC
- ICP-MS Elemental Analysis
- FTIR
- TOF-MS
- LC/MS/MS

An analyst removes extraction fluid during a USP class plastics test.

USP CLASS PLASTICS

USP <88> Class Plastic Tests are designed to assess the biological reactivity of various types of plastics materials *in vivo*. Originally developed to test drug containers, the USP class plastics tests are often performed on unmolded plastic resins as well as containers. Class plastics testing is not a substitute for testing performed according to ISO standards, but is often used by manufacturers to classify/certify materials. The USP defines six plastics classes, from class I to class VI with class VI being the most rigorous and most frequently requested certification.

Why Perform USP Class Plastics Testing?

Many plastics manufacturers find it advantageous to have their materials classified, especially if their plastic resins are a likely candidate to be used in medical devices. A plastic material that has passed the USP Class Plastics tests is expected to be more likely to produce favorable biocompatibility results.

Testing Services

- USP Class Plastics I-VI
- USP Systemic Injection Test
- USP Intracutaneous Test
- USP Implant Test
- USP Safety Test

How Do You Perform USP Class Plastics Testing?

There are three *in vivo* tests involved in the classification of plastics. The Systemic Injection Test and the Intracutaneous Test are designed to determine the systemic and local biological responses to plastics and other polymers by the single-dose injection of specific extracts prepared from a sample. The third test, the Implantation Test, is designed to evaluate the reaction of living tissue to a test material. The testing for the six different class plastics levels is done using different combinations of these three tests using different extraction liquids.

Quarterly dose audits require bioburden testing, which this PBL microbiologist is conducting for a medical device client.

MEDICAL DEVICE STERILITY ASSURANCE

Sterilization Services and Validations

PBL provides steam sterilization services, and can work with radiation or ethylene oxide sterilization facilities to perform the microbiology work needed for sterilization validations.

- Steam Sterilization and Validation Testing
- Liquid Chemical Sterilization
- Dry Heat Sterilization and Depyrogenation
- Gamma, E-Beam, and Ethylene Oxide Sterilization Validation Testing

Sterility Testing

The Pacific BioLabs facility contains a dedicated sterility testing suite. The HEPA-filtered HVAC maintains a positive pressure cascade from the core cleanroom through a gowning room, a sample disinfection room, and an ambient pressure entrance area. Walk-in and reach-in incubator rooms are also integrated into the sterility testing suite.

Additional Services

- Bioburden Validation
- Bacteriostasis/Fungistasis
- AAMI/ISO Dose Audit
- Sample Item Portion (SIP) Preparation

Bioburden

A bioburden test determines how many microbes are on the medical device. The bioburden level is often used in radiation sterilization validations to calculate the radiation dose. Additionally, as part of quality control, quarterly bioburden testing is done to determine whether the microbiological load on a device has changed.

A PBL analyst performs a cleaning validation by using the worst-case parameters from the manufacturer's IFU.

REUSABLE DEVICE VALIDATION

Reusable Device Validation Testing

The skilled technicians at Pacific BioLabs have been performing reuse validations for many years on devices ranging from simple forceps to complex and sensitive surgical equipment. PBL can prepare a validation protocol for the cleaning, disinfection or sterilization of your reusable device and then perform the validation to test the effectiveness of the reprocessing procedure.

Cleaning Validations

A medical device cleaning validation requires that the device is soiled with biological material in a manner that is clinically relevant. The soil will often depend on the type of device being tested, but typically is a mixtures of proteins, hemoglobin, and carbohydrates. Once soiled, the medical device will be cleaned according to the manufacturer's instructions and any remaining soil will be extracted from the device. The process is considered validated if a series of at least three cleaning tests show that the markers (such as protein and hemoglobin) are below levels prescribed in AAMI TIR 12:2010 *Designing, Testing and Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities: A Guide for Medical Device Manufacturers*.

Disinfection Validations

Medical device disinfection validations are performed differently depending on the level of disinfection required; high level disinfection, intermediate level disinfection or low level disinfection. However, all disinfection validations require that the device be inoculated with microorganisms and then exposed to the disinfectant. Any remaining microbes are extracted from the device and grown on plates in a manner similar to a bioburden test.

Reusable Device Validation Services

- Protocol Development
- Cleaning and Disinfection Validations
- Sterilization Validations
- Automated Cleaning/Disinfection
- Manual, Mechanical, and Ultrasonic Cleaning

A PBL microbiologist performs a package integrity test using the edge dip method.

SHELF-LIFE AND PACKAGE TESTING

Shelf Life Studies

Medical device manufacturers wishing to gather data on the shelf life of their products may subject their devices to long-term stability studies or accelerated aging studies. There are many different endpoints that can be used to assess the shelf life of a medical device, including functionality and package integrity, so it is important that endpoints and test methodology are decided upon before testing is begun.

The GMP microbiological labs at Pacific BioLabs can provide clients with temperature and humidity controlled chambers for storing samples for various types of medical device shelf life and aging studies on both products and packaging. All chambers are monitored 24/7 by a Rees or Visalia environmental monitoring system.

Arrhenius Equation

The accelerated aging technique is based on the assumption that the chemical reactions involved in the deterioration of materials follow the Arrhenius reaction rate function. This function states that rises in temperature of 10°C will double the rate of a chemical reaction. This function is expressed as a Q_{10} factor – i.e. the ratio of the rate of a reaction at two temperatures 10°C apart. If the rate of the reaction is doubled then $Q_{10} = 2$. This is the most common approach used to perform accelerated aging of medical devices.

Package Integrity Testing

Pacific BioLabs performs the dye penetration and the microbial challenge package integrity tests. Package integrity tests are used to detect packaging problems that could adversely affect the sterility of a medical device. Sterile products are subjected to an environmental stress intended to simulate extreme conditions that a product might encounter in shipping or storage. The product packaging is then subjected to microbial challenge or dye penetration testing to determine if it has retained its properties as a microbial barrier.

The PBL environmental monitoring team can travel to your facility and sample the air, surface and compressed gas systems for viable organisms.

ENVIRONMENTAL MONITORING

For the production of safe medical devices, manufacturing environment conditions are of paramount importance. By controlling and monitoring the manufacturing environment, potential bioburden contamination can be limited, helping to ensure a high sterility assurance level for finished products.

EM Sampling

Pacific BioLabs' microbiology lab has experience in working with manufacturers to develop and implement effective environmental monitoring programs, including air and surface sampling as well as process water testing. Our microbiologists can visit your facility to gather samples, or train your personnel in proper sample collection technique. Additionally, we can provide the necessary supplies for routine sampling and monitoring.

Air Samples

Both viable (microbial) air samples and non-viable air samples can be taken. Typically, viable air samples are collected using a Rotary Centrifugal Air Sampler (RCS) using TSA air strips. Viable air samples can also be taken from a facility's compressed gas systems. Non-viable particles are measured using a laser diode instrument with the ability to simultaneously measure particles of various sizes including the two most commonly used particle limits in the medical device industry of ≥ 0.5 µm and ≥ 5.0 µm.

Surface Sampling

Surface samples are taken using contact plates or swabs. Contact plates are small petri dishes containing agar media in a convex shape that can be pressed against a flat surface. Any microbes on the surface being sampled will stick to the agar and when incubated will grow into a colony that can be visually counted. Swabs are used to sample areas that contact plates would not be able to sample, such as corners or irregular shaped surfaces. Any microbes attached to the swab are then extracted using an extraction fluid. The extraction fluid is then filtered leaving the microorganisms on the filter. The filter is placed on a petri dish containing agar and incubated. During the incubation period each individual microbe on the filter will grow into an observable colony.

EM Services

- Viable Air Sampling
- Non-Viable Air Sampling
- Viable Compressed Gas Sampling
- Surface Sampling
- Water Testing

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