ASSESSING BIOCOMPATIBILITY

A GUIDE FOR MEDICAL DEVICE MANUFACTURERS

PBL
Pacific BioLabs
The Service Leader in Bioscience Testing

Biocompatibility Testing at Pacific BioLabs

Since 1982, Pacific BioLabs has conducted biocompatibility testing for the medical device and pharmaceutical industries. Our staff toxicologists have tested thousands of devices with a variety of configurations, applications and component materials.

Pacific BioLabs is located in a stunning 32,000 square foot facility in Hercules, CA. This state-of-the-art facility allows us to offer top quality testing services to our clients throughout the world. The vivarium contains a surgical suite, necropsy lab, radiation lab and several procedure rooms. The 26 animal rooms (including a separate SPF rodent suite) are served by a dedicated HEPA-filtered HVAC system. The vivarium has ample support areas, including a cage/rack washer, a separate clean cage storage room, and a dedicated sample prep lab.

Microbiology Services, Analytical Chemistry, Quality Assurance, Administration and facility support functions are housed in the second floor of the facility. The building site can also accommodate a planned 18,000 square foot expansion.

With ISO 17025:2017 accreditation from ANAB, AAALAC accredited facilities, and many years of experience, Pacific BioLabs is certain to meet your quality and regulatory requirements.

PBL's purpose built facility is 32,000 square feet with a 14,000 square foot vivarium.

Our experienced staff can help you design a cost-effective safety test program for your product. We provide quotes within 24 hours on most biocompatibility testing projects. And we are dedicated to providing you with clear, well-written reports and prompt, personalized service.

Please call Business Development at 510-964-9000 to discuss your testing requirements, or visit our website at PacificBioLabs.com.

Pacific BioLabs' testing capabilities for medical device companies include the following procedures.

BIOCOMPATIBILITY TESTING

- Cytotoxicity
- Sensitization
- Irritation or Intracutaneous Reactivity
  - Dermal Irritation
  - Ocular Irritation
  - Vaginal Irritation
  - Rectal Irritation
  - Penile Irritation
  - Hamster Cheek Pouch Irritation
- Acute Systemic Toxicity
- Material Mediated Pyrogenicity
- Subchronic Toxicity
- Genotoxicity
- Implantation/Degradation
- Hemocompatibility

MICROBIOLOGY TESTING

- Bioburden
- AAMI/ISO Dose Audits
- Biological Indicator Tests
- Environmental Monitoring
- Bacterial Endotoxin (LAL)
- Microbiology/Sterility Testing

CHEMICAL CHARACTERIZATION/ ANALYSIS

- GC/MS, LC/MS/MS, and ICP/MS
- FTIR, GC, HSGC, and HPLC
- USP Physiochemical Tests – Plastics or Elastomeric Closures
- Sterilant Residues
- Total Organic Carbon (TOC)
- Organic Solvent Residues
- Non-Volatile and Volatile Residues
- Colorant Analysis
- Extractables and Leachables Analysis

ADDITIONAL SUPPORT

- AAMI/ISO Sterilization Validation
- Cleaning and Disinfection Validations
- Accelerated Aging and Shelf-Life Testing
- Package Integrity Testing

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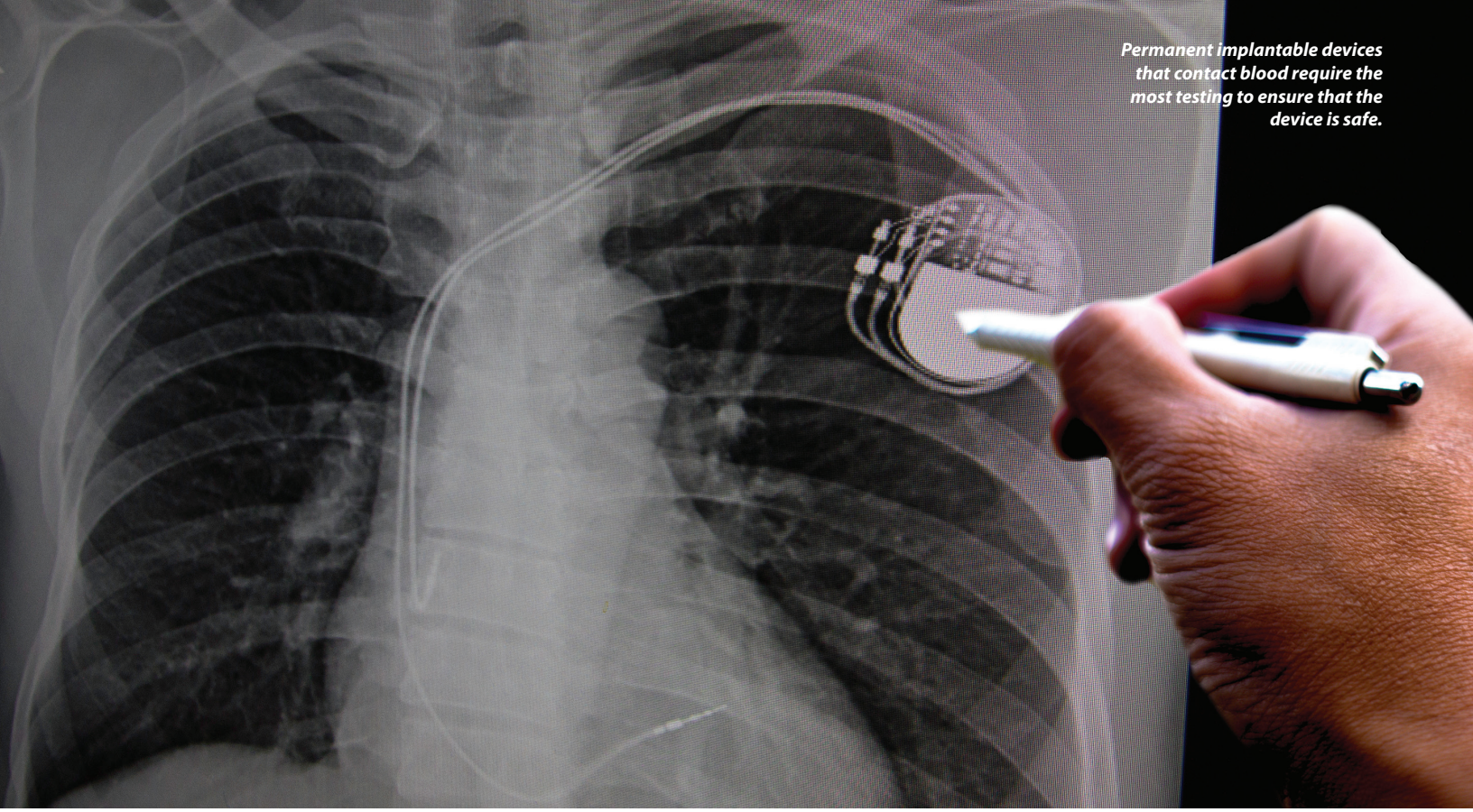


Permanent implantable devices that contact blood require the most testing to ensure that the device is safe.

INTRODUCTION TO BIOCOMPATIBILITY TESTING

What is Device Biocompatibility?

Device biocompatibility is determined by the interaction between a medical device and the tissues and physiological systems of the patient treated with the device. An evaluation of biocompatibility is one part of the overall safety assessment of a device. Biocompatibility of devices is investigated using analytical chemistry, *in vitro* tests, and animal models, *in vivo* tests. The biocompatibility of a device depends on several factors, including:

- the chemical and physical nature of its component materials
- the types of patient tissue that will be exposed to the device
- the duration of that exposure

Of course, the primary purpose of a device biocompatibility assessment is to protect patient and user safety. Manufacturers will also want to consider corporate regulatory goals and compliance risks in planning a biocompatibility testing program. Inevitably, evaluating the biocompatibility of a device is a risk assessment exercise. There is no risk-free device or device material. The goal of device designers is to minimize risk while maximizing benefit to patients.

What are the FDA and ISO Requirements for Biocompatibility Testing?

The best starting point for understanding biocompatibility requirements is the ISO 10993 guideline, Biological Evaluation of Medical Devices. Part 1 of the standard is evaluation and testing within a risk management process, Part 2 covers animal welfare requirements, and Parts 3 through 20 are guidelines for specific test procedures or other testing-related issues. A list of the individual sections of ISO 10993 can be found on page 10.

Testing strategies that comply with the ISO 10993 family of documents are acceptable in Europe and most of Asia. In 2016, FDA issued a guidance titled, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and Testing within a risk management process"*, which replaced Blu*e Book Memorandum G95-1* (the previous FDA biocompatibility testing standard). FDA has substantially adopted the ISO guideline, although in some areas FDA's testing requirements go beyond those of ISO.

Pacific BioLabs highly recommends discussing your proposed biocompatibility testing plan with an FDA reviewer before initiating testing.

Do I Need Biocompatibility Data?

Biocompatibility data of one kind or another is almost always required for medical devices. Refer to the flow chart from ISO 10993-1 (page 6) to help determine if your device needs biocompatibility testing.

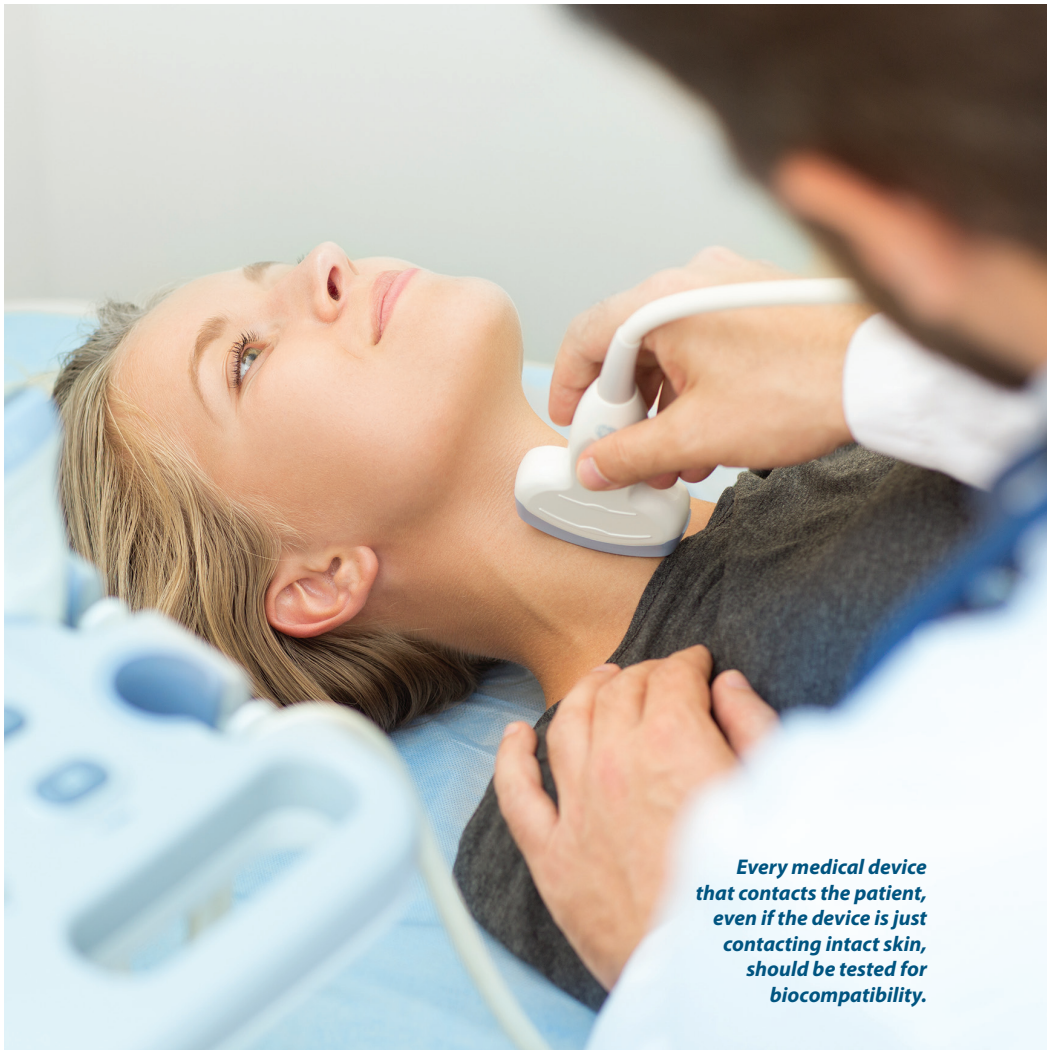
Most commonly, companies arrange for their own biocompatibility studies. You may be able to reduce the amount of testing you will need on a specific device if you have some or all of the following types of biocompatibility data.

1. ***Data from previous submissions*** – If data are available from a previous submission, consider the following points as you apply it to your current device. You will need to perform confirmatory testing if there are significant changes in any of these areas.
   - **a.** Materials selection
   - **b.** Manufacturing processes
   - **c.** Chemical composition of materials
   - **d.** Nature of patient contact
   - **e.** Sterilization methods

2. ***Data from suppliers of materials or components*** – If vendor data are used, manufacturers should obtain copies of the original study reports. It is important that the laboratory that generated the reports had an experienced staff, a strong track record of cGMP/GLP compliance, and an AAALAC accredited animal science program. Usually manufacturers will want to conduct at least some confirmatory testing of their own (e.g., cytotoxicity biocompatibility and chemical analysis).

3. ***Analytical data*** – Manufacturers may use analytical data to help demonstrate that a device has a low overall risk or a low risk of producing a given biological effect. Part 18 of ISO 10993, Chemical Characterization of Materials, provides some guidance on this process (also see pages 13 – 14).

4. ***Clinical data*** – Clinical data can be used to satisfy some biological effects categories from the ISO 10993-1 test selection matrix. The data may come from clinical trials using the device in question or from clinical experience with predicate devices or devices containing similar components or materials.



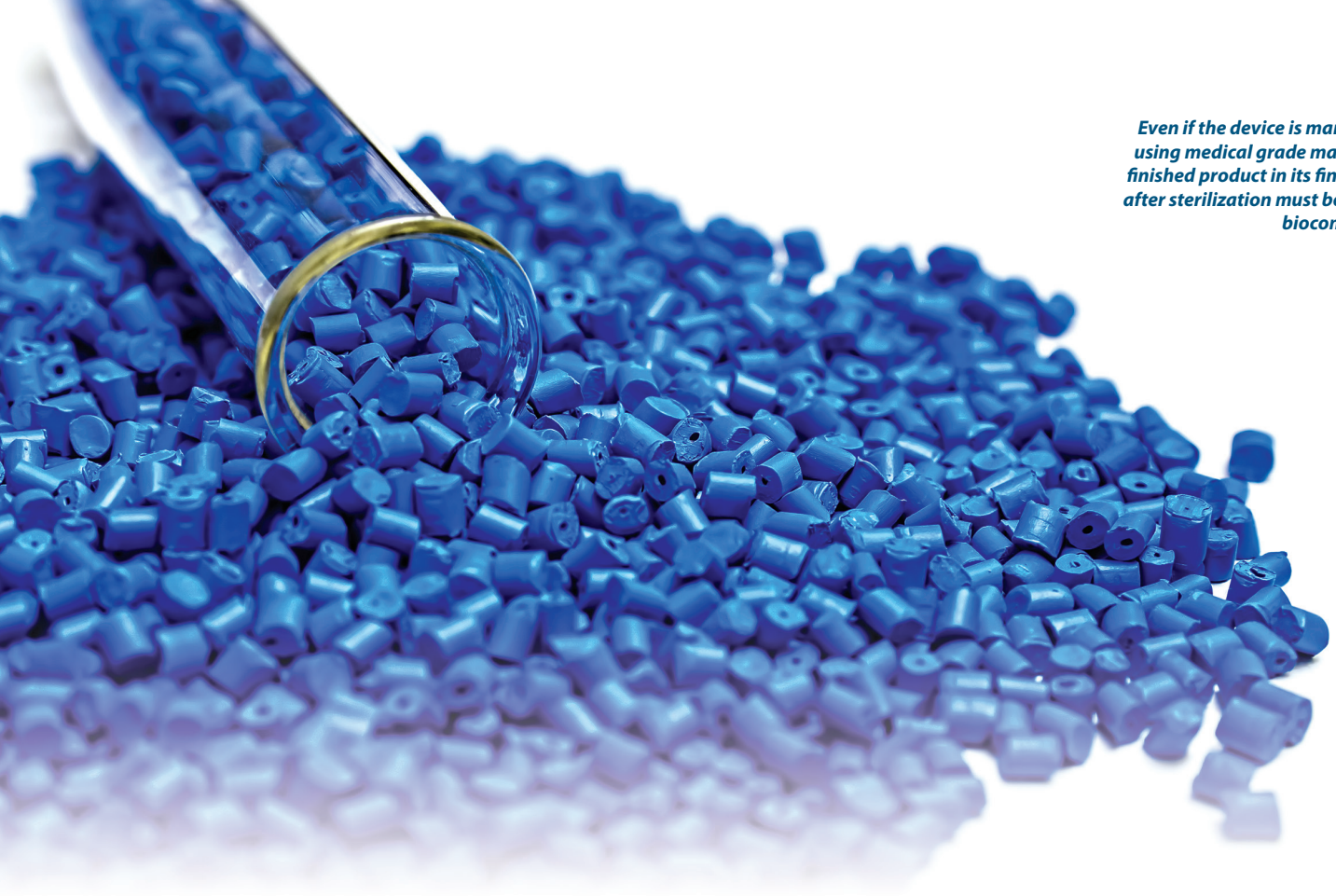
Every medical device that contacts the patient, even if the device is just contacting intact skin, should be tested for biocompatibility.

How Do I Determine Which Tests I Need?

The core of the ISO Standard is confirmation of the fitness of the device for its intended use. The first step in this process is chemical characterization of device components. See page 13 for specifics of such a program.

Biological testing is probably the most critical step in a biocompatibility evaluation. The ISO endpoints biocompatibility matrix (page 11) categorizes devices based on the type and duration of body contact. It also presents a list of potential biological effects. For each device category, certain effects must be considered and addressed in the regulatory submission for that device. ISO 10993-1 does not prescribe a specific battery of tests for any particular medical device. Rather, it provides a framework that can be used to design a biocompatibility testing program. Developing a biological evaluation plan (BEP) is recommended to assess the risks associated with the device and to develop a testing plan that mitigates those risks.

Device designers should generally consult with an experienced device toxicologist or regulatory group and their clinical investigators to develop a BEP and determine how best to meet the endpoints in the biocompatibility matrix. For each biological effect category, the rationale for the testing strategy should be documented, usually in a biological evaluation report. Justification is especially needed when a manufacturer decides not to perform testing for specified in the biocompatibility matrix for their category of devices. All justifications for test exclusions will need to be provided during the submission to the regulatory body.



Even if the device is manufactured using medical grade materials, the finished product in its finished form after sterilization must be tested for biocompatibility.

Should I Test Device Materials, Or Only a Composite of the Finished Device?

As a manufacturer, you should gather safety data on every component and material used in a device. Typically raw material providers will screen their plastic materials for biocompatibility following USP guidelines. In addition, the device manufacturer should conduct testing on the finished device as specified by ISO 10993-1. Generally, the best approach is to:

1. Assemble vendor data on candidate materials . If possible, select medical grade materials.

2. Conduct analytical and *in vitro* screening of materials.

3. Conduct confirmatory testing on a composite sample from the finished device.

There is a risk in testing the finished device without developing data on component materials. If an adverse result occurs, it can be difficult to track down the component that is causing the problem. You may end up delaying your regulatory submission while you repeat testing on the individual components.

Screening device materials minimizes this risk. The initial chemical characterization should detect leachable or extractable chemicals that could compromise device safety. Inexpensive non-animal studies (such as cytotoxicity tests) provide an additional screen for material safety. Material screening tests also help ensure that you will not be forced to redesign your device due to biocompatibility test failures. Many manufacturers assemble data on a library of qualified materials used in their products.

Some test procedures do not allow testing of composite samples. For example, due to physical limitations, agar overlay, direct contact cytotoxicity tests or implant studies require separate testing of each device component.

For all biocompatibility studies, test samples should be sterilized using the same method as will be used for the finished device.

Is GLP Treatment Required for Biocompatibility Testing?

As a general rule, all studies designed to assess the safety of a medical product in nonclinical models (including biocompatibility studies for medical devices) should be conducted according to Good Laboratory Practice (GLP). GLP treatment is explicitly required for IDE, 510(k), and PMA submissions. In addition, manufacturers of device components and materials should have their biocompatibility studies conducted per GLP so that their clients can use the data in any type of regulatory submission.

GLP procedures are similar across geographical boundaries and examples include the United States 21 CFR Part 58 (FDA) and 40 CFR part 160 (EPA) and the European OECD ENV/MC/CHEM(98)17. A good review of GLP procedures can be found in the WHO Handbook on Good Laboratory Practices (WHO, 2009).

GLP procedures stress the importance of the following:

- **Resources**: organization, personnel, facilities and equipment
- **Characterization:** test items and test systems
- **Rules:** protocols, standard operating procedures (SOPs)
- **Results:** raw data, final report and archives
- **Quality Assurance:** independent monitoring of study conduct

When implementing biocompatibility testing for medical devices the following GLP requirements must be satisfied:

1. **Resources.** The Study Director occupies a pivotal point of control for the study, is appointed by the test facility management, and assumes full responsibility for the GLP compliance of all activities within the study. The Study Director must therefore be aware of all events that may influence the quality and integrity of the study. Even when certain phases or parts of the study are delegated to other test sites, the Study Director retains overall responsibility for the entire study, including the parts delegated. This responsibility is reflected in a signed and dated GLP Compliance Statement which is included in all study reports.

2. **Characterization.** For non-clinical studies intended to evaluate safety, it is required that the Study Director have detailed knowledge about the properties of the test item. Characteristics such as identity, composition, strength, purity, stability and uniformity profile, as they apply to medical devices, should be known for the test item and should be provided to the Study Director. Documentation of test article characterization is often found in a Certificate of Analysis or comparable formal document signed by Quality Assurance or other responsible personnel, which should be included in the final report of study results. Additional information related to the requirement for characterization of test materials can be found on page 14 and 15. The manufacturer's batch record for the lot from which test samples are pulled can also be a good source of data on device characterization.

3. **Protocol.** The principal steps of studies conducted in compliance with GLP are described in the study Protocol. The Protocol must be approved and signed by the Study Director before the study starts. Alterations to the study design can only be made through a formal amendment to the Protocol. Adherence to a Protocol ensures that the study can be reconstructed at a later point in time.

4. **Results and Interpretation.** GLP study results are interpreted by the Study Director based on the study design and actual conduct of the study. The GLP principles do not include allowance for the Out of Specification (OOS) process that is commonly employed in evaluation of study results for cGMP processes (e.g. manufacturing). However, confounding or contributing factors that could result in misinterpretation of study results can be noted by the Study Director.

5. **Quality Assurance.** The Quality Assurance Unit (QAU) is an independent unit that assures management GLP compliance has been attained in the test facility as a whole and in each individual study. For GLP studies where various aspects of an individual study are conducted at multiple sites (e.g. test article characterization, clinical chemistry analysis, histopathology, etc.), it is required that the additional sites have a functioning QAU. These off-site QAU units must also provide assurance in the form of a written report to the Study Director that these off-site aspects of the study have been conducted according to the protocol, and that they are in compliance with GLP.

THE PACIFIC BIOLABS BIOCOMPATIBILITY PLANNING TOOL (BIOPT)

Device companies spend a tremendous amount of time, money and energy developing and implementing biocompatibility testing programs. Pacific BioLabs has developed the **BioPT** (Biocompatibility Planning Tool) to guide you through the basic concepts of device testing and to help manufacturers select testing procedures to comply with current regulatory requirements.

The chart below provides an overview of the process. Follow the page references for more detail on each topic. For information on chemical characterization & analytical chemistry testing, see page 14-15.

The BioPT

DETERMINING TESTING NEEDS

Determine the device category and body contact duration.	Device exposure category definitions and examples of devices that fall into each category are given on page 10. See page 10 for definitions of the three device duration categories.
Collect all biocompatibility data already available. (Available data may eliminate the need to perform some tests.)	Alternative sources for biocomp data are presented on page 4. (Previous test data, component material data from suppliers.)
Chemical Characterization	More information on chemical characterization can be found on pages 13-14.
Use device category and body contact duration to select appropriate tests from the Biocompatibility Test Matrix.	Refer to the Materials Biocompatibility Matrix on page 11 to determine which biological test categories and procedures are appropriate for your device. Pages 15-20 discuss specific test procedures.

PLANNING AND TEST PREPARATION

Determine extracting media and test conditions necessary for your needed tests.	More information on extracts and sample preparation is found on pages 7 and 8. Page 8 shows formulas used to calculate the surface area of your device.
Determine the number of samples or amount of sample material needed.	See page 12 for sample requirements for each test. Or, contact Pacific BioLabs for a price quote which will specify sample requirements for each test procedure.
Decide if Good Laboratory Practices (GLP) regulations need to be followed for your testing program.	GLP treatment is required for most types of regulatory submissions. More information can be found on page 5.
Price your needed testing.	To obtain a quote visit our website at PacificBioLabs.com or call our Business Development Department at 510-964-9000.
Initiate testing.	Sign and return the quote acceptance form, complete and submit the LSR (Laboratory Service Request) and send the appropriate number of samples to Pacific BioLabs.

Selection of Extraction Media

Medical device biocompatibility problems are most often caused by chemicals that leach out of the device into the surrounding tissues or body fluids. Consequently, in the laboratory, extracts of device materials (extractables) are often used in assessing biocompatibility. These extracts are generally prepared using exaggerated conditions of time and temperature to allow a margin of safety over normal physiological conditions.

Analytical extractable/leachable studies allow the chemist to identify and quantitate specific extractable and leachable chemicals. This data helps the device toxicologist or risk assessor determine the worst case scenario for patient exposure and the risk to patient health.

Extracts are also used in many of the biological tests specified by ISO 10993 guideline. Table 1 at the bottom of this page lists the most commonly used extracting media.

Extracts are selected on the basis of the biological environment in which the test material is to be used. A saline extract approximates the aqueous, polar, hydrophilic fluids in the body. It also permits the use of extreme temperatures in preparing the extracts, thus simulating certain sterilization conditions.

Cell culture media may even more closely approximate aqueous body fluids, but cannot be used for high temperature extractions. Cotton seed oil is a non-polar, hydrophobic solvent and simulates the lipid fluids in the body. For technical reasons, DMSO extracts are often used in certain genotoxicity and sensitization tests. Two other common extracting media – Alcohol in saline and PEG – should be used only if they approximate the solvent properties of drugs or other materials that will contact the device during its normal use. For most devices, however, extracts using saline and cotton seed oil are sufficient.

Extraction conditions (temperature and time) should be at least as extreme as any conditions the device or material will encounter during sterilization or clinical use. Generally, the highest extraction temperature that does not melt or fuse the material or cause chemical changes is used. To provide some margin of safety for use conditions, regulatory bodies recommends an extraction condition of at least 50°C for 72 hours. For devices that are susceptible to heat, an extraction condition of 37°C for 72 hours may be acceptable. Table 2 lists extraction conditions recommended by ISO 10993-12 guidelines.

Table 1: Extracting Media

Sodium Chloride for Injection, USP
Cotton Seed Oil
1:20 Alcohol in Saline
Polyethylene Glycol 400 (PEG)
DMSO
Cell Culture Media
Clinically Relevant Solvents

Note: For most devices, only saline and vegetable oil extracts are needed

Table 2: Extraction Conditions

37°C for 72 hours
50°C for 72 hours
70°C for 24 hours
121°C for 1 hour
Other Conditions (justification required)

Sample Preparation

Typically, the standard surface area of your device is used to determine the volume of extract needed for each test performed. This area includes the combined area of all sides of the device but excludes indeterminate surface irregularities. If the surface area cannot be determined due to the configuration of the device, a mass per volume of extracting fluid can be used. In either case, the device is cut into small pieces before extraction to enhance exposure to the extracting media and achieve complete immersion. In some cases, it is not appropriate to cut the device; such devices are tested intact.

The simplest method for determining the surface area of a device is usually to use the engineering diagrams from the design engineering group. Typically the surface area can be calculated with just a few keystrokes. Alternatively, you can calculate the surface area using the equations below. Or you can submit a sample device and/or an engineering drawing to Pacific BioLabs, and our staff will perform the calculations.

The table on page 13 lists the amount of sample required for many procedures. Generally, we recommend using the ratio of sample to extracting media specified in ISO 10993-12 (i.e. either 6 cm^2/mL or 3 cm^2/mL, depending on the thickness of the test material). For some types of materials, the ratio used for Elastomeric Closures for Injections (1.25 cm^2 per mL) is preferred.

The surface area of the device is needed to determine the extraction volume.

Formulas for Surface Area Calculation

DEVICE SHAPE	FORMULA
Square or Rectangle	A (one side) = L x W
Hollow Cylinder	A = (ID + OD) π x L
Disk	A (one side) = π r^2
Ellipse	A = (π x X x Y)/4
Regular Polygon	A = (b x h x n)/2
Solid Cylinder (including ends)	A = (OD x π x L) + (2 π r^2)
Triangle	A = (b x h)/2
Sphere	A = 4 x π r^2
Trapezoid	A = (h x [p + q])/2
Circular Ring	4 $π^2$Rrrc

LEGEND

A = surface area
OD = outer diameter
W = width
RR = ring radius (circular ring)
X, Y = longest and shortest distances through the center of an ellipse
h = height
p, q = length of the parallel sides of a trapezoid
ID = inner diameter
L = length
R = radius
rc = cross section radius (circular ring)
π = 3.14
b = base length
n = number of sides of a polygon

ISO 10993 - BIOLOGICAL EVALUATION OF MEDICAL DEVICES LISTING OF INDIVIDUAL PARTS

PART	TOPIC
1	Evaluation and Testing Within a Risk Management Process
2	Animal Welfare Requirements
3	Tests for Genotoxicty, Carcinogenicity, and Reproductive Toxicity
4	Selection of Tests for Interactions with Blood
5	Tests for In Vitro Cytotoxicity
6	Tests for Local Effects after Implantation
7	Ethylene Oxide Sterilization Residuals
8	Selection and Qualification of Reference Materials for Biological Tests
9	Framework for Identification & Quantification of Potential Degradation Products
10	Test for Irritation and Skin Sensitization
11	Test for Systemic Toxicity
12	Sample Preparation and Reference Materials
13	Identification and Quantification of Degradation Products from Polymeric Medical Devices
14	Identification and Quantification of Degradation Products from Ceramics
15	Identification and Quantification of Degradation Products from Metals and Alloys
16	Toxicokinetic Study Design for Degradation Products and Leachables
17	Establishment of Allowable Limits for Leachable Substances
18	Chemical Characterization of Materials
19	Physico-chemical, Morphological and Topographical Characterization of Materials
20	Principles and Methods for Immunotoxicology Testing of Medical Devices
22	Guidance on Nanomaterials

DEVICE CATEGORIES – DEFINITIONS & EXAMPLES

DEVICE CATEGORIES		EXAMPLES
Surface Device	**Intact Skin**	Devices that contact intact skin surfaces only. Examples include electrodes, external prostheses, fixation tapes, compression bandages and monitors of various types.
	Mucous membrane	Devices communicating with intact mucosal membranes. Examples include contact lenses, urinary catheters, intravaginal and intraintestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gastroscopes), endotracheal tubes, bronchoscopes, dental prostheses, orthodontic devices and IUD's.
	Breached or compromised surfaces	Devices that contact breached or otherwise compromised external body surfaces. Examples include ulcer, burn and granulation tissue dressings or healing devices and occlusive patches.
External Communicating Device	**Blood path indirect**	Devices that contact the blood path at one point and serve as a conduit for entry into the vascular system. Examples include solution administration sets, extension sets, transfer sets, and blood administration sets.
	Tissue/bone/ dentin	Devices communicating with tissue, bone, and pulp/dentin system. Examples include laparoscopes, arthroscopes, draining systems, dental cements, dental filling materials and skin staples. This category also includes devices which contact internal tissues (rather than blood contact devices). Examples include many surgical instruments and accessories.
	Circulating blood	Devices that contact circulating blood. Examples include intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, hemoadsorbents and immunoabsorbents.
Implant Device	**Tissue/bone**	Devices principally contacting bone. Examples include orthopedic pins, plates, replacement joints, bone prostheses, cements and intraosseous devices. Devices principally contacting tissue and tissues fluid. Examples include pacemakers, drug supply devices, neuromuscular sensors and stimulators, replacement tendons, breast implants, artificial larynxes, subperiosteal implants and ligation clips.
	Blood	Devices principally contacting blood. Examples include pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts and stents, internal drug delivery catheters, and ventricular assist devices.

Non-Contact Devices

These are devices that do not contact the patient's body directly or indirectly. Examples include in vitro diagnostic devices, sterilization accessories, and urine collection bottles. Regulatory agencies rarely require biocompatibility testing for such devices.

Endpoints to be Addressed in a Biological Risk Assessment

MEDICAL DEVICE CATEGORIZATION BY			ENDPOINTS OF BIOLOGICAL EVALUATION														
NATURE OF BODY CONTACT		CONTACT DURATION															
Category	Contact	A - limited (≤24 h) B - prolonged (>24 h to 30 d) C - permanent (>30 d)	Physical and/or Chemical Information	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Material-Mediated Pyrogenicity[a]	Acute Systemic Toxicity[b]	Subacute Toxicity[b]	Subchronic Toxicity[b]	Chronic Toxicity[b]	Implantation Effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/Developmental Toxicity[d]	Degradation[f]
Surface Medical Device	Intact Skin	A	X[g]	E[h]	E	E											
		B	X	E	E	E											
		C	X	E	E	E											
	Mucosal Membrane	A	X	E	E	E											
		B	X	E	E	E		E	E			E					
		C	X	E	E	E		E	E	E	E	E		E			
	Breached or Compromised Surface	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E	E		
External Communicating Medical Device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue/bone/dentin[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulated blood	A	X	E	E	E	E	E					E	E[j]			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
Implant Medical Device	Tissue/bone[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Blood	A	X	E	E	E	E	E				E	E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

Table obtained from ISO 10993-1:2018.

a Refer to ISO 10993-11:2017, Annex F. **b** Information obtained from comprehensive implantation assessments that include acute systemic toxicity, subacute toxicity, subchronic toxicity and/or chronic toxicity may be appropriate if sufficient animals and timepoints are included and assessed. It is not always necessary to perform separate studies for acute, subacute, subchronic, and chronic toxicity. **c** Relevant implantation sites should be considered. For instance medical devices in contact with intact mucosal membranes should ideally be studied/ considered in contact with intact mucosal membranes. **d** If the medical device can contain substances known to be carcinogenic, mutagenic and/or toxic to reproduction, this should be considered in the risk assessment. **e** Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, medical devices with relevant target populations (e.g. pregnant women), and/or medical devices where there is the potential for local presence of device materials in the reproductive organs. **f** Degradation information should be provided for any medical devices, medical device components or materials remaining within the patient, that have the potential for degradation. **g** X means prerequisite information needed for a risk assessment. **h** E means endpoints to be evaluated in the risk assessment (either through the use of existing data, additional endpoint-specific testing, or a rationale for why assessment of the endpoint does not require an additional data set). If a medical device is manufactured from novel materials, not previously used in medical device applications, and no toxicology data exists in the literature, additional endpoints beyond those marked "E" in this table should be considered. For particular medical devices, there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated. **i** Tissue includes tissue fluids and subcutaneous spaces. For gas pathway devices or components with only indirect tissue contact, see device specific standards for biocompatibility information relevant to these medical devices. **j** For all medical devices used in extracorporeal circuits.

TEST TURNAROUND TIME AND SAMPLE REQUIREMENTS

REQUIREMENT	TEST NAME	ESTIMATED SAMPLE AMOUNT REQUIREMENTS			ESTIMATED TURN AROUND (In Weeks)
		Surface Area Double Amounts for Material < 0.5 mm in thickness	Irregular, Powders or Liquids		
			Grams	mL	
Cytotoxicity	Agar Diffusion MEM Elution Direct Contact MTT	1 cm^2 x 3 pieces 60 cm^2 1 cm^2 x 3 pieces 60 cm^2	4	20	3 - 4 (GLP) 2 (non-GLP)
Sensitization	Maximization Test Closed Patch Test	60 cm^2 x 6 devices/pieces 2.5 cm^2 x 116 pieces	24 60	60 80	6 - 7 7 - 8
Irritation or Intracutaneous Reactivity	Intracutaneous Test Dermal Irritation Test Ocular Irritation Test Vaginal Irritation Test Penile Irritation Test Rectal Irritation Test Hamster Cheek Pouch Irritation Test	60 cm^2 per extract 2.5 cm x 2.5 cm x 6 pieces 60 cm^2 per extract 10 devices 10 devices 10 devices Varies	4 2 2 4 4 4 4	20 10 10 20 20 20 5	4 - 5 4 - 5 4 - 5 6 - 7 6 - 7 6 - 7 Varies
Acute Systemic Toxicity	Material Mediated Pyrogen Test Acute Systemic Test	360 cm^2 60 cm^2 per extract	20 8	100 20	4 - 5 4 - 5
Genotoxicity	Ames Test Mouse Micronucleus Assay Chromosomal Aberration Test	20 cm^2 per extract 60 cm^2 per extract 30 cm^2 per extract	8 8 10	10 40 20	7 - 8 7 - 8 7 - 8
Implantation	Implantation Test (Local effects) *(All Implant Tests Include Histopathology)* *(7 days or greater)*	12 - 16 strips 1 x 10 mm			Varies
Hemocompatibility	Hemolysis - ASTM Direct and Indirect Contact Platelet and Leukocyte Counts Partial Thromboplastin Time (PTT)	60 cm^2 x 6 devices/pieces 3 devices 60 cm^2	12 Inquire 4	20 Inquire	6 - 7 7 - 8 7 - 8
Immunotoxicity	Complement Activation	120 cm^2 x 2 devices/pieces	8	Inquire	7 - 8
Chemical Characterization of Extractables and Leachables	FTIR Material Identification UV/Vis Spectroscopy for Colorants GC/MS for Volatiles/semi-Volatiles LC/MS for Non-Volatiles Heavy Metal Analysis by ICP/MS	Inquire Inquire Inquire Inquire Inquire	Inquire Inquire Inquire Inquire Inquire		3 - 4 3 - 4 Inquire Inquire Inquire

CHEMICAL CHARACTERIZATION & ANALYTICAL TESTING

Analytical procedures provide the initial means for investigating the biocompatibility of medical device materials. Knowledge of device materials and their propensity for releasing leachable matter will help manufacturers assess the risks of in vivo reactivity and preclude subsequent toxicology problems with finished devices.

Increasingly, FDA has been asking for analytical characterization of device materials and potential leachables per ISO 10993-18. Many firms also use analytical procedures for routine QC of raw materials or finished products.

The degree of chemical characterization required should reflect the nature and duration of the clinical exposure and should be determined based on the data necessary to evaluate the biological safety of the device. It will also depend on the nature of the materials used, e.g. liquids, gels, polymers, metals, ceramics, composites or biologically sourced material.

The following strategy is suggested as a sound program for chemical characterization of a device material:

1. Determine the qualitative composition of each device component or material. This information should be available from the material vendor, or it can be determined through laboratory testing. The list of constituents should include
   - **a.** the identity of the matrix (i.e. the major component such as the specific polymer, alloy, or metal)
   - **b.** all plasticizers, colorants, anti-oxidants, fillers, etc. deliberately added during fabrication of the material
   - **c.** impurities such as unreacted monomers and oligomers
   - **d.** manufacturing materials such as solvent residues, slip agents, and lubricants.

2. Estimate the potential for patient exposure for each item on the material constituent list. Use literature searches of toxicological databases to assess the likelihood of tissue reactivity. For potentially toxic constituents, design and conduct laboratory studies to determine the extractable levels of those constituents. Use exaggerated conditions of time and temperature, and consider appropriate detection limits. Additional studies may be needed to assess levels of extractables released in actual use conditions.

3. Data generated from this characterization process can be used to create a material data file. The information can then be used as a reference for continued testing of device materials to ensure consistency of future production lots. This may in turn reduce the need for routine biological testing.

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

Additional uses of analytical characterization data might include:

1. An assessment of the overall biological safety of a medical device.

2. Measurement of the level of any extractable and leachable substance in a medical device in order to allow the assessment of compliance with the allowable limit derived for that substance from health based risk assessment.

3. Judging equivalence of a proposed material to a clinically established material.

4. Judging equivalence of a final device to a prototype device to check the relevance of data on the latter to be used to support the assessment of the former.

5. Screening of potential new materials for suitability in a medical device for a proposed clinical application.

Traditional Extractable and Leachable Material Characterization

- USP Physicochemical Tests – Plastics
- USP Physicochemical Test Panel for Elastomeric Closures for Injections
- USP Polyethylene Containers Tests – Heavy Metals and Non-volatile Residues
- Indirect Food Additives and Polymers Extractables (21CFR Part 177)
- Sterilant Residues – Ethylene Oxide, Ethylene Chlorohydrin, Ethylene Glycol

Tests Procedures for Extractable and Leachable Material

- UV/Visible Spectroscopy
- Gas Chromatography
- Liquid Chromatography
- Infrared Spectroscopy (IR)
- Mass Spectrometry
- Residual Solvents
- Atomic Absorption Spectroscopy (AAS)
- Inductively-coupled Plasma Mass Spectroscopy (ICP/MS)

PBL's SCIEX TripleTOF 5600 mass spec system, generates high resolution MS and MS/MS spectra essential for extractable leachable studies.

Bulk Material Characterization

- Infrared Spectroscopy Analysis for Identity and Estimation of Gross Composition
  - Reflectance Spectroscopy
  - Transmission Spectroscopy
- Atomic Absorption Spectroscopy (AAS)
- Inductively-coupled Plasma Mass Spectroscopy (ICP/MS)
- Thermal Analysis

Surface Characterization

- IR Reflectance Spectroscopy
- Scanning Electron Microscopy (SEM)
- Energy-dispersive X-ray Analysis (EDX)

BIOLOGICAL TEST METHODS

The following pages describe some of the specific procedures recommended for biocompatibility testing. This listing does not imply that all procedures are necessary for any given material, nor does it indicate that these are the only available tests.

Cytotoxicity (Cell Culture)

Cell culture assays are used to assess the biocompatibility of a material or extract through the use of isolated cells *in vitro*. These techniques are useful in evaluating the toxicity or irritancy potential of materials and chemicals. They provide an excellent way to screen materials prior to *in vivo* tests.

There are two categories of cytotoxicity evaluation: qualitative and quantitative. Both quantitative and qualitative cytotoxicity tests are accepted by regulatory agencies.

There are three cytotoxicity tests commonly used for medical devices. The ***Direct Contact*** procedure is recommended for low density materials, such as contact lens polymers. In this method, a piece of test material is placed directly onto cells growing on culture medium. The cells are then incubated. During incubation, leachable chemicals in the test material can diffuse into the culture medium and contact the cell layer. Reactivity of the test sample is indicated by malformation, degeneration and lysis of cells around the test material.

The ***Agar Diffusion*** assay is appropriate for high density materials, such as elastomeric closures. In this method, a thin layer of nutrient-supplemented agar is placed over the cultured cells. The test material (or an extract of the test material dried on filter paper) is placed on top of the agar layer, and the cells are incubated. A zone of malformed, degenerative or lysed cells under and around the test material indicates cytotoxicity.

The ***MEM Elution*** assay uses different extracting media and extraction conditions to test devices according to actual use conditions or to exaggerate those conditions. Extracts can be titrated to yield a semi-quantitative measurement of cytotoxicity. After preparation, the extracts are transferred onto a layer of cells and incubated. Following incubation, the cells are examined microscopically for malformation, degeneration and lysis of the cells.

Cytotoxicity testing can be used as a fast and inexpensive screen before moving into in vivo testing.

(See page 7 for more information on the selection of extracting media and conditions). Two quantitative cytotoxicity tests have been internationally tested for chemicals and medical devices:

The ***MTT Cytotoxicity Test*** measures the viability of cells by spectrophotometric methods. This colorimetric method measures the reduction of the yellow, water-soluble MTT [3-(4,5 dimethyl-thiazol-2-yl)-2,5-diphenyl tetrazolium bromide] by mitochondrial succinate dehydrogenase. A minimum of four concentrations of the test material are tested. This biochemical reaction is only catalyzed by living cells.

The ***Colony Formation Cytotoxicity Test*** enumerates the number of colonies formed after exposing them to the test material at different concentrations. This is a very sensitive test since the colony formation is assessed while the cells are in a state of proliferation (logarithmic phase), and thus more susceptible to toxic effects. A concentration-dependence curve evaluating the induced inhibition of the test material can be created, and the IC50 value (concentration of the test material that provides 50% inhibition) can be calculated. The quantitative tests can be performed on extracts and by direct contact.

At least one type of cytotoxicity test, qualitative or quantitative, should be performed on each component of any device.

Sensitization Assays

Sensitization studies help to determine whether a material contains chemicals that cause adverse local or systemic effects after repeated or prolonged exposure. These allergic or hypersensitivity reactions involve immunologic mechanisms. Studies to determine sensitization potential may be performed using either specific chemicals from the test material, the test material itself, or most often, extracts of the test material. The Materials Biocompatibility Matrix (see page 11) recommends sensitization testing for all classes of medical devices.

The ***Guinea Pig Maximization Test*** (Magnusson-Kligman Method) is recommended for devices that will have externally communicating or internal contact with the body or body fluids. In this study the test material is mixed with complete Freund's adjuvant to enhance immunological response.

The *Closed Patch Test* involves multiple topical doses and is recommended for devices that will only contact unbroken skin or for materials that are not suitable to be injected intradermally.

The ***Murine Local Lymph Node Assay*** (LLNA) determines the quantitative increase in lymphocytes in response to a sensitizer. If a molecule acts as a skin sensitizer, it will induce the epidermal Langherhans cells to transport the allergen to the draining lymph nodes, which in turn causes T-lymphocytes to proliferate and differentiate. This method may only be used for chemicals that come into direct contact with intact skin or are transported through the skin. Additionally, this method can only reliably detect moderate to strong sensitizers. The FDA intends to evaluate the use of LLNA tests for medical devices in a case by case basis. PBL does not recommend performing this test.

Skin irritation is present on a patient after wearing an arm brace. Proper biocompatibility testing may have prevented this occurrence.

Irritation Tests or Intracutaneous Reactivity

These tests estimate the local irritation potential of devices, materials or extracts, using sites such as skin or mucous membranes, usually in an animal model. The route of exposure (skin, eye, mucosa) and duration of contact should be analogous to the anticipated clinical use of the device, but it is often prudent to exaggerate exposure conditions somewhat to establish a margin of safety for patients.

In the ***Intracutaneous Test***, extracts of the test material and blanks are injected intradermally. The injection sites are scored for erythema and edema (redness and swelling). This procedure is recommended for devices that will have externally communicating or internal contact with the body or body fluids. It reliably detects the potential for local irritation due to chemicals that may be extracted from a biomaterial.

The ***Primary Skin Irritation*** test should be considered for topical devices that have external contact with intact or breached skin. In this procedure, the test material or an extract is applied directly to intact and abraded sites on the skin of a rabbit. After a 24-hour exposure, the material is removed and the sites are scored for erythema and edema.

Mucous Membrane Irritation Tests are recommended for devices that will have externally communicating contact with mucous membranes. Some common procedures include vaginal, rectal, penile and hamster cheek pouch studies. (See page 7 for more information on extracts.)

Acute Systemic Toxicity

By using extracts of the device or device material, the ***Acute Systemic Toxicity*** test detects leachables that produce systemic (as opposed to local) toxic effects. The extracts of the test material and negative control blanks are injected into mice (intravenously or intraperitoneally, depending on the extracting media). The mice are observed for toxic signs just after injection and at four other time points. The Endpoints Matrix (see page 11) recommends this test for all blood contact devices. It may also be appropriate for any other device that contacts internal tissues.

Material-Mediated Pyrogen Test

The ***Material Mediated Pyrogen*** test evaluates the potential of a material to cause a pyrogenic response, or fever, when introduced into the blood. Pharmaceutical lot release testing for pyrogenicity is performed *in vitro* using the ***bacterial endotoxin (LAL)*** test and the test must be validated for each device or material. However, for assessing biocompatibility, the rabbit pyrogen test is preferred. The rabbit test, in addition to detecting bacterial endotoxins, is sensitive to material-mediated pyrogens that may be found in test materials or extracts.

Subacute/Subchronic Toxicity

Tests for ***subchronic toxicity*** are used to determine potentially harmful effects from longer-term or multiple exposures to test materials and/or extracts during a period of up to 10% of the total lifespan of the test animal (e.g. up to 90 days in rats). Actual use conditions of a medical device need to be taken into account when selecting an animal model for subchronic toxicity. Appropriate animal models are determined on a case-by-case basis.

Pacific BioLabs offers two approaches for subchronic testing that are appropriate for many devices via implantation of the device materials or injection of extracts of the device materials. Extracts may be administered by ***intraperitoneal*** or/and an ***intravenous*** route of administration. Implant tests are often performed for different durations appropriate to assess subchronic toxicity of devices and device materials.

Subchronic toxicity tests are required for all permanent devices and should be considered for those with prolonged contact with internal tissues.

Extracts are injected into test animals for a subchronic toxicity test.

Implantation Tests

Implant studies are used to determine the biocompatibility of medical devices or biomaterials that directly contact living tissue other than skin (e.g. sutures, surgical ligating clips, implantable devices, intraocular lenses, etc.). These tests can evaluate devices, which, in clinical use, are intended to be implanted for either short-term or long-term periods. Implantation techniques may be used to evaluate both absorbable and non-absorbable materials. To provide a reasonable assessment of safety, the implant study should closely approximate the intended clinical use.

The dynamics of biochemical exchange and cellular and immunologic responses may be assessed in implantation studies, especially through the use of histopathology. Histopathological analysis of implant sites greatly increases the amount of information obtained from these studies.

Degradation Tests could be performed in conjunction with implantation tests. According to ISO 10993-13, a degradation product is a chemical compound derived from the breakdown of the polymeric material, including any compound produced by consecutive chemical reactions. An accelerated test can be done using a temperature of 70 ± 2°C to detect degradation products but if the identification and quantification of the degradation products are insufficient for a risk analysis, then real-time testing should be performed. If the device is designed to be absorbable, the FDA recommends that degradation assessments be conducted in an appropriate animal model. If an adverse biological response is observed *in vivo*, an *in vitro* assessment should be conducted to identify the source of the toxicity.

Genotoxicity

Genotoxicity evaluations use a set of *in vitro* and *in vivo* tests to detect mutagens, substances that can directly or indirectly induce genetic damage directly through a variety of mechanisms. This damage can occur in either somatic or germline cells, increasing the risk of cancer or inheritable defects. A strong correlation exists between mutagenicity and carcinogenicity.

Genotoxic effects fall into one of three categories: point mutations along a strand of DNA, damage to the overall structure of the DNA, or damage to the structure of the chromosome (which contains the DNA). A variety of tests have been developed to determine if damage has occurred at any of these levels. These assays complement one another and are performed as a battery.

The most common test for mutagenicity, the Ames test, detects point mutations by employing several strains of the bacteria *Salmonella typhimurium* and *Escherichia coli* which have been selected for their sensitivity to mutagens. The ***Mouse Lymphoma*** assay is a common procedure using mammalian cells to detect point mutations and it can also detect clastogenic lesions in genes (chromosome damage). Assays for DNA damage and repair include both *in vitro* and *in vivo* Unscheduled DNA Synthesis (UDS). Cytogenetic assays allow direct observation of chromosome damage. There are both *in vitro* and *in vivo* methods, including the ***Chromosomal Aberration*** and the ***Mouse Micronucleus*** assays.

ISO 10993-1 specifies an assessment of genotoxic potential for permanent devices and for those with prolonged contact (>24 hours) with internal tissues and blood. Extracorporeal devices with limited contact (<24 hours) may require a genotoxicity evaluation. Generally, devices with long-tem exposure require an Ames test and two *in vivo* methods, usually the Chromosomal Aberration and Mouse Lymphoma tests. Devices with less critical body contact may be able to be tested using only the Ames test.

When selecting a battery of genotoxicity tests, you should consider the requirements of the specific regulatory agency where your submission will be made. *Because of the high cost of genotoxicity testing, Pacific BioLabs strongly recommends that you consult your FDA reviewer before you authorize testing.*

All blood contacting devices must be tested for hemocompatibility.

Hemocompatibility

Materials used in blood contacting devices (e.g. intravenous catheters, hemodialysis sets, blood transfusion sets, vascular prostheses) must be assessed for blood compatibility to establish their safety. In practice, all materials are to some degree incompatible with blood because they can either disrupt the blood cells (hemolysis) or activate the coagulation pathways (thrombogenicity) and/or the complement system.

The ***hemolysis assay*** is recommended for all devices or device materials except those which contact only intact skin or mucous membranes. This test measures the damage to red blood cells when they are exposed to materials or their extracts, and compares it to positive and negative controls.

Coagulation assays measure the effect of the test article on human blood coagulation time. They are recommended for all devices with blood contact. The ***Prothrombin Time Assay (PT)*** is a general screening test for the detection of coagulation abnormalities in the **extrinsic** pathway.

The ***Partial Thromboplastin Time Assay (PTT)*** detects coagulation abnormalities in the **intrinsic** pathway.

The most common test for thrombogenicity is the *in vivo* method. For devices unsuited to this test method, ISO 10993-4 requires tests in each of four categories: coagulation, platelets, hematology, and complement system.

Immunotoxicity

Complement activation testing is recommended for implant devices that contact circulatory blood. This *in vitro* assay measures complement activation in human plasma as a result of exposure of the plasma to the test article or an extract. The measure of complement actuation indicates whether a test article is capable of inducing a complement-induced inflammatory immune response in humans.

Other blood compatibility tests and specific *in vivo* studies may be required to complete the assessment of material-blood interactions, especially to meet ISO requirements.

Circulating Blood-Contacting Devices or Device Components and the Categories of Appropriate Testing for Consideration – External Communicating Devices and Implant Devices

DEVICE EXAMPLES	TEST CATEGORY						
	HAEMOLYSIS		THROMBOSIS				
			in vitro				*in vivo/ ex vivo*[a]
	Material-induced	Mechanically-induced	Coagulation	Platlet activation	Complement[d]	Haemotology	
EXTERNAL COMMUNICATING DEVICES							
Blood monitors (temporary/ex vivo)[b]	X		X	X		X	
Blood storage and administration equipment (e.g. infusion/transfusion sets), blood collection devices, extension sets	X		X	X		X	
Catheters in place for less than 24 hours (e.g. atherectomy devices, intravascular ultrasound catheters, antegrade/ retrograde coronary perfusion catheters, guide wires); cannulae	X		X[c]	X[c]		X[c]	X[c]
Catheters in place for more than 24 hours (e.g. parenteral nutrition catheters, central venous catheters); cannulae	X		X[c]	X[c]		X[c]	X[c]
Cell Savers[b]	X		X	X			
Devices for absorption of specific substances from blood[b]	X	X	X	X	X		
Donor ant therapeutic aphaeresis equipment and cell separation systems[b]	X	X	X	X	X		
Cardiopulmonary bypass system[b]	X	X	X[c]	X[c]	X	X[c]	X[c]
Haemodialysis/haemofiltration equiment[b]	X	X	X[c]	X[c]	X	X[c]	X[c]
Leukocyte removal filter[b]	X		X[c]	X[c]	X	X[c]	X[c]
Percutaneous circulatory support devices[b]	X	X	X[c]	X[c]	X	X[c]	X[c]
IMPLANT DEVICES							
Annuloplasty rings, mechanical heart valves	X	X					X
Embolization devices	X						X
Endovascular grafts	X						X
Implantable defibrillator and cardiovascular leads	X						X
Intra-aortic balloon pumps[b]	X	X					X
Pacemaker leads	X						X
Prosthetic (synthetic) vascular grafts and patches, including arteriovenous shunts	X						X

Table obtained from ISO 10993-4:2017

a Thrombosis is an *in-vivo* or *ex-vivo* phenomenon, but can be stimulated with *in-vitro* conditions. *In vivo* or *ex vivo* testing might not be necessary if clinically relevant *in vitro* thrombosis testing is performed.

b Direct or indirect blood contacting components only. For components that have only indrirect blood contact, *in vivo* thrombogenesis and mechanical haemolysis or complement activation might not be necessary.

c It is recognized that coagulation, platelet and leucocyte responses are primarily involved in the process of thrombosis. Therefore it is up to the manufacturer to decide specific testing in the coagulation, platelet and haemotology test categories as an alternate *in vivo* testing.

d See also ISO/TS 10993-20 for more information on when complement activation should be considered for other end points such as anaphylaxis.

Reproductive and developmental toxicity studies should be conducted if the medical device is intended to be used by a relevant target populations (such as pregnant women) or if the device contacts reproductive organs.

Chronic Toxicity

Chronic Toxicity tests are longer term toxicity test, typically between six and twelve months. The FDA recommends evaluating chronic effects for devices having an exposure period of longer than thirty days.

Carcinogenicity Studies

These assays are used to determine the tumorigenic potential of test materials and/or extracts from either a single or multiple exposures, over a period consisting of the total lifespan of the test system (e.g. two years for rat, 18 months for mouse, or seven years for dog).

Carcinogenicity testing of devices is expensive, highly problematic, and controversial. Manufacturers can almost always utilize an alternative approach to carcinogenicity testing of their devices.

Reproductive and Developmental Toxicity

These studies evaluate the potential effects of test materials and/or extracts on fertility, reproductive function, and prenatal and early postnatal development. It is recommended that this test be performed for novel materials, materials with a known reproductive or developmental toxicity, devices with relevant target populations (such as pregnant women) and for devices where there is the probability for the local presence of device materials in the reproductive organs.

THE PACIFIC BIOLABS ADVANTAGE

THE SERVICE LEADER IN BIOSCIENCE TESTING

Pacific BioLabs (PBL) is an independent laboratory offering GLP/GMP testing services to the medical device and pharm/biopharm industries. PBL specializes in biocompatibility, chemical characterization, sterility assurance, microbiology, reusable device validations and preclinical toxicology/pharmacology services.

SERVING THE BIOSCIENCE INDUSTRY SINCE 1982

Pacific BioLabs clients range from small start-ups to Fortune 500 giants. Our staff is widely recognized for their experience, technical competence and commitment to client service. Over the years, PBL has gained a national reputation for quality in service and excellence in science.

STATE OF THE ART VIVARIUM AND LABS

Pacific BioLabs conducts its operations in a stunning 32,000 square foot facility in Hercules, CA, overlooking the San Francisco Bay. The building houses a 12,000 square foot vivarium with a surgery suite, necropsy lab, radiation lab, procedure rooms, and ample support areas. The semi-barrier SPF rodent suite has a HEPA-filtered air supply and dedicated procedure space. Animal facilities and critical equipment are monitored 24/7. Emergency power is supplied by an on-site generator. The site can accommodate a planned 18,000 square foot facility expansion.

RIGOROUS REGULATORY COMPLIANCE

In the regulatory science arena, quality means compliance. PBL has an outstanding track record in audits by FDA, EPA, MHRA, and other agencies, not to mention hundreds of client auditors.

At Pacific BioLabs we conduct all testing in accordance with applicable Good Manufacturing Practice (cGMP) and Good Laboratory Practice (GLP) regulations. To insure data integrity, our Quality Assurance Unit staff routinely audits all aspects of lab operations and administer our world class CAPA system. PBL's extensive body of Standard Operating Procedures is at the core of a thorough, documented training system which ensures that all technical staff can capably perform their assigned procedures.

For most biocompatibility submissions, the FDA and EU require that testing be performed in accordance with GLP regulations. It is the client's responsibility to determine when GLP treatment is required for their product and to inform PBL in writing of this requirement at the time of sample submission. (An additional fee for GLP treatment will be incurred, typically 10-20% of total test costs.)

Pacific BioLabs is FDA-registered and certified by ANAB to ISO/IEC 17025:2017. Our animal science program is AAALAC accredited.

REFERENCES

- 21 CFR Part 58. Code of Federal Regulations Title 21, Chapter 1, Subchapter A, Part 58; Good Laboratory Practice For Nonclinical Laboratory Studies
- 40 CFR Part 160. Code of Federal Regulations Title 40, Chapter 1, Subchapter E, Part 160; Good Laboratory Practice Standards
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PBL

Pacific BioLabs

The Service Leader in Bioscience Testing

www.PacificBioLabs.com InfoPBL@PacificBioLabs.com
551 Linus Pauling Drive, Hercules, CA 94547
(510) 964-9000