

BIOCOMPATIBILITY TESTING AT PACIFIC BIOLABS

For 30 years, Pacific BioLabs has conducted biocompatibility testing for the medical device and pharmaceutical industries. Our staff toxicologists have tested hundreds 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, 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 9001:2008 and ISO 13485:2003 certified operations, AAALAC accredited facilities, and 30 years of experience, Pacific BioLabs is certain to meet your quality and regulatory requirements.

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 Tests	QA/QC Testing	Validation Support	Extractable Material Characterization
<ul style="list-style-type: none"> • Cytotoxicity • Sensitization • Irritation • Systemic Toxicity • Genotoxicity • Implantation • Hemocompatibility • Surgical Models • Subchronic Toxicity • Chronic Toxicity 	<ul style="list-style-type: none"> • Bioburden • AAMI/ISO Dose Audits • Biological Indicator Tests • Environmental Monitoring • Bacterial Endotoxin (LAL) • Microbiology/ Sterility Testing 	<ul style="list-style-type: none"> • AAMI/ISO Sterilization Validation • Reusable Device • Cleaning, Disinfection, and Sterilization Validation • Accelerated Aging and Stability Testing • Package Integrity Testing 	<ul style="list-style-type: none"> • USP Physiochemical Tests – Plastics or Elastomeric Closures • Sterilant Residues • AA, IR, GC, HPLC • Total Organic Carbon (TOC) • Organic Solvent Residues • Non-Volatile Residues

ASSESSING BIOCOMPATIBILITY

A GUIDE FOR MEDICAL DEVICE MANUFACTURERS

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

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EXECUTIVE SUMMARY

PURPOSE OF BIOCOMPATIBILITY TESTING

Biocompatibility is, by definition, a measurement of how *compatible* a device is with a *biological* system. The purpose of performing biocompatibility testing is to determine the fitness of a device for human use, and to see whether use of the device can have any potentially harmful physiological effects. As stated by the International Organization of Standards:

“The primary aim of this part of ISO 10993 is the protection of humans from potential biological risks arising from the use of medical devices.”
(ISO 10993-1:2009)

The overall process of determining the biocompatibility of any medical device involves several stages. One should begin by collecting data on the materials comprising the device, then perform *in vitro* screening (often only on components of the device), and finally conduct confirmatory *in vivo* testing on the finished device. It is essential to make sure that the finished device is challenged to ensure that human use of the device does not result in any harmful effects.

BIOCOMPATIBILITY TEST PLANNING

The primary goal of a biocompatibility screening program is the protection of humans. However, since animal testing is necessary for many biocompatibility tests, a secondary goal is to eliminate unnecessary testing and minimize the number and exposure of test animals. With this in mind, it is important to conduct research beforehand to document all relevant data on the component materials of the device and on similar devices with an established clinical history. Existing data may be sufficient to demonstrate biological safety of parts or of the entire device, thus precluding the need to conduct certain tests.

The required tests will also depend on the use of the device and the manner and duration in which it will interact with the body. In test planning it is important to note whether the device is a surface device, an external communicating device, or an implant device, and what tissues the device will contact. (Implant devices interacting with the blood, for instance, will require more thorough testing than a surface device with an expected contact time of only a few days.)

When planning, it is also important to note that Good Laboratory Practice (GLP) compliance is required for certain biocompatibility regulatory submissions. Because of this, it is generally a good idea to conduct biocompatibility testing according to GLP to allow for the maximum regulatory flexibility and compliance.

CONDUCTING TESTS

Typically, material characterization and analysis of the device's components are conducted prior to any biological testing. This involves extracting leachable materials from the device or components at an elevated temperature, and analyzing the leachable extracts for potentially harmful chemicals or cytotoxicity.

Once *in vitro* testing has been completed, *in vivo* biological testing can be done based upon the device's intended use. This testing can range from skin irritation testing to hemocompatibility and implantation testing. Turnaround time for tests can range from three weeks to greater than several months, depending on the specific test data needed. Subchronic or chronic implantation testing can last even longer.

EVALUATING THE DATA

After tests are completed and all data has been collected, it is recommended that an expert assessor interpret the data and test results. This will provide insight on whether additional tests need to be conducted, or whether the existing data provide enough information for an overall biological safety assessment of the device.

INTRODUCTION TO BIOCOMPATIBILITY TESTING

WHAT IS DEVICE BIOCOMPATIBILITY?

The word biocompatibility refers to 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 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 EU/ISO REQUIREMENTS FOR BIOCOMPATIBILITY TESTING?

The best starting point for understanding biocompatibility requirements is ISO Standard 10993, Biological Evaluation of Medical Devices. Part 1 of the standard is the Guidance on Selection of Tests, Part 2 covers animal welfare requirements, and Parts 3 through 19 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 11.)

Testing strategies that comply with the ISO 10993 family of documents are acceptable in Europe and Asia. In 1995, FDA issued a Blue Book Memorandum G95-1, which replaced the *Tripartite Guidance* (the previous biocompatibility testing standard). FDA has substantially adopted the ISO guideline, although in some areas FDA's testing requirements go beyond those of ISO.

The specific ISO test procedures vary slightly from the USP procedures historically used for FDA submissions. The ISO procedures tend to be more stringent, so companies planning to register their product in both Europe and the U.S. should follow ISO test methods. FDA requirements should be verified since additional testing may be needed. Japanese procedures for sample preparation and testing are slightly different from either USP or ISO tests.

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 devices that have significant tissue contact. Refer to the flow chart from ISO 10993-1 (page 13) 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 is 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 is 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 and hemocompatibility studies).
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. Section 18 of ISO 10993, Chemical Characterization of Materials, gives some guidance on this process.
(See also pages 22 -23.)

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 of the device in question or from clinical experience with predicate devices or devices containing similar components or materials.

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 22 for specifics of such a program.

Biological testing is probably the most critical step in a biocompatibility evaluation. The ISO materials biocompatibility matrix (page 13) 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.

Device designers should generally consult with an experienced device toxicologist and their clinical investigators to determine how best to meet the requirements of the materials biocompatibility matrix. For each biological effect category, the rationale for the testing strategy should be documented. This is especially true when a manufacturer decides not to perform testing for an effect specified by the matrix for their category of devices.

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. In addition, you should definitely 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
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 materials that could compromise device safety. Inexpensive non-animal studies (such as cytotoxicity and hemocompatibility tests) provide an additional screen for material safety. Material screening tests also help insure 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 lend themselves to testing of composite samples. Due to physical limitations, agar overlay or direct contact cytotoxicity tests and 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) procedures. GLP treatment is explicitly required for IDE and PMA submissions. FDA reviewers indicate they strongly prefer GLP treatment for studies supporting 510(k)s. In addition, manufacturers of device components and materials should have their biocompatibility studies done 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 and the 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 research processes

When implementing biocompatibility testing for medical devices, certain GLP requirements should be kept in mind. Relative to the main points above:

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.

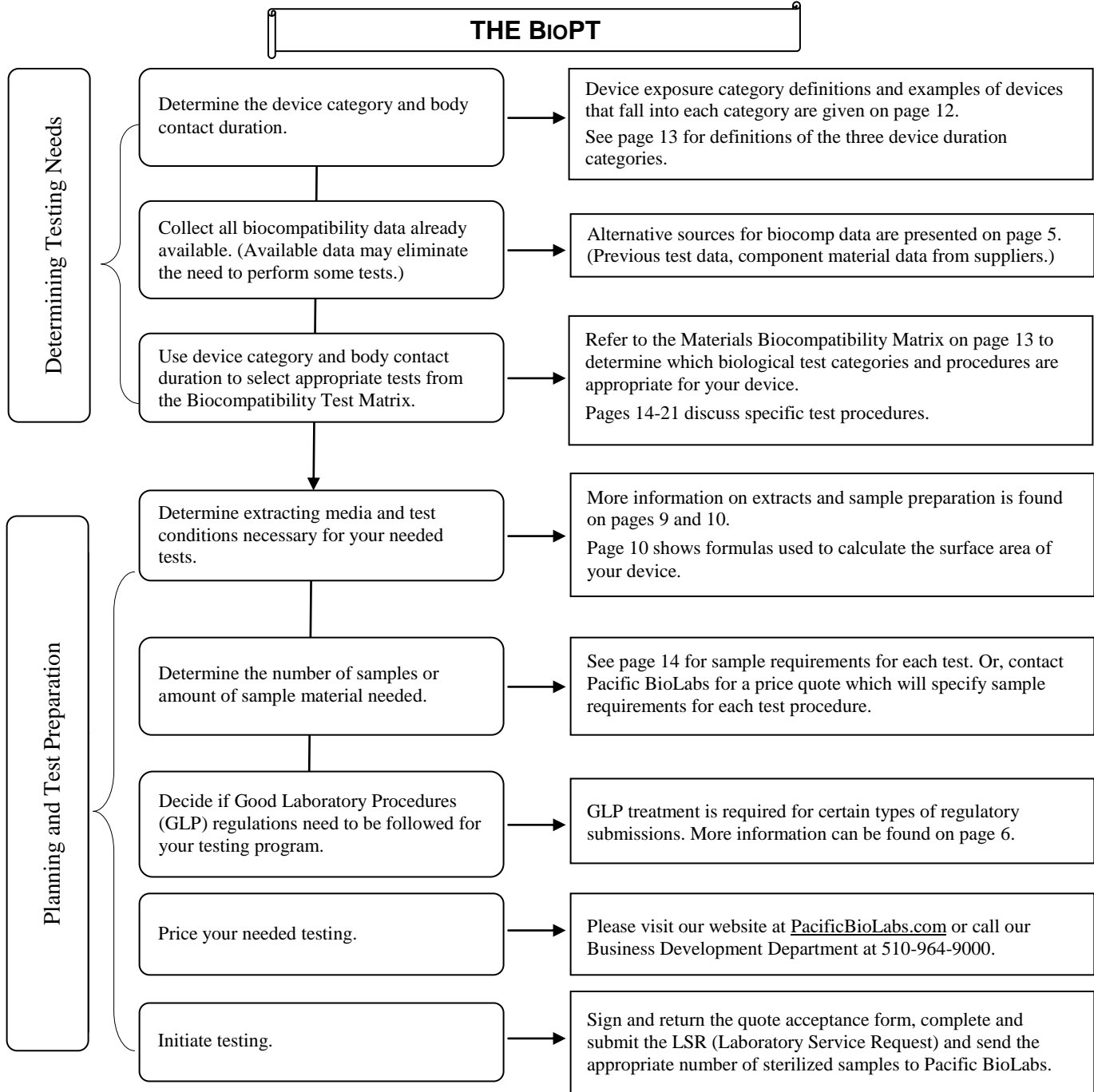
2. **Characterization.** For non-clinical studies intended to evaluate safety, it is necessary that the Study Director have detailed knowledge about the properties of the test item. Characteristics such as identity, potency, composition, stability, and impurity profile, as they apply to medical devices, 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, 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 22, *Materials Characterization and Analytical Testing of Biomaterials*. 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. **Rules.** 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.** 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 charged with assuring management that 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 and that these off-site QAU units 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 processes.

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 gives you an overview of the process. Follow the page references to get more detail on each specific topic. For information on materials characterization & analytical testing of devices, see page 22-23.



CHOOSING EXTRACTION MEDIA

Medical device biocompatibility problems are most often caused by toxins that leach out of the device into the surrounding tissues or body fluids. Consequently, in the laboratory, extracts of device materials (leachables) 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 extraction studies allow the chemist to identify and quantitate specific leachable moieties. This data can in turn help 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. 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 (SCI) extract approximates the aqueous, hydrophilic fluids in the body. It also permits the use of extreme temperatures in preparing the extracts, thus simulating certain sterilization conditions.

Tissue culture media may even more closely approximate aqueous body fluids, but cannot be used for high temperature extractions. Vegetable oils are non-polar, hydrophobic solvents and simulate 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 SCI 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 vegetable 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, you will want to choose the highest extraction temperature that does not melt or fuse the material or cause chemical changes. To provide some margin of safety for use conditions, Pacific BioLabs 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 common extraction conditions.

TABLE 1: EXTRACTING MEDIA

Sodium Chloride for Injection, USP (SCI)
Vegetable Oil
1:20 Alcohol in SCI
Polyethylene Glycol 400 (PEG)
DMSO
Clinically Relevant Solvents

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 (<i>justification required</i>)

**For most devices, only saline and vegetable oil extracts are needed.*

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 both 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/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. 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 CAD

program 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 14 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 cm²/mL or 3 cm²/mL, depending on the thickness of the test material). For some types of materials, the ratio used for USP Elastomeric Closures for Injections (1.25 cm² per mL) is preferred.

FORMULAS FOR SURFACE AREA CALCULATION

Device Shape	Formula
Square or Rectangle	$A = L \times W$
Hollow Cylinder	$A = (ID + OD) \pi \times L$
Disk	$A \text{ (one side)} = \pi r^2$
Ellipse	$A = (\pi \times X \times Y)/4$
Regular Polygon	$A = (b \times h \times n)/2$

Device Shape	Formula
Solid Cylinder (including ends)	$A = (OD \times \pi \times L) + (2 \pi r^2)$
Triangle	$A = (b \times h)/2$
Sphere	$A = 4 \times \pi r^2$
Trapezoid	$A = (h \times [p + q])/2$
Circular Ring	$4 \pi^2 R_r r_c$

LEGEND

A = surface area
OD = outer diameter
W = width
R _R = 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
r _o = ½ OD

ID = inner diameter
L = length
R = radius
r _c = cross section radius (circular ring)
π = 3.14
b = base length
n = number of sides of a polygon
r _i = ½ ID

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

Part	Topic
1	Evaluation and Testing
2	Animal Welfare Requirements
3	Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity
4	Selection of Tests for Interactions with Blood
5	Tests for Cytotoxicity – <i>In Vitro</i> Methods
6	Tests for Local Effects after Implantation
7	Ethylene Oxide Sterilization Residuals
8	Selection and Qualification of Reference Materials for Biological Test
9	Framework for Identification & Quantification of Potential Degradation Products
10	Test for Irritation and Sensitization
11	Test for Systemic Toxicity
12	Sample Preparation and Reference Materials
13	Identification and Quantification of Degradation Products from Polymers
14	Identification and Quantification of Degradation Products from Ceramics
15	Identification and Quantification of Degradation Products from Coated and Uncoated 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	Physicochemical, Mechanical and Morphological Characterization (Draft)
20	Principles and Methods for Immunotoxicology Testing of Medical Devices (Draft)

* = The United States ISO Member Body, ANSI/AAMI, is considering a version of this document for use in the U.S.

DEVICE CATEGORIES – DEFINITIONS & EXAMPLES

Device Categories		Examples
Surface Device	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 intrainestinal 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 communicating	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. Regulatory agencies rarely require biocompatibility testing for such devices.

ISO MATERIALS BIOCOMPATIBILITY MATRIX

Medical Device Categorization		Biological Effect													
Category	Contact	Contact Duration A - Limited (≤ 24 hours) B - Prolonged (24 hours-30 days) C - Permanent (> 30 days)	Initial Evaluation Tests								Supplementary Evaluation Tests				
			Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Systemic Toxicity (acute)	Subchronic Toxicity (Subacute Toxicity)	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental ³	Biodegradation ³	
Surface Device	Skin	A	•	•	•										
		B	•	•	•										
		C	•	•	•										
	Mucosal Membrane	A	•	•	•										
		B	•	•	•	F	F		F						
		C	•	•	•	F	•	•	F				F		
	Breached or Compromised Surface	A	•	•	•	F									
		B	•	•	•	F	F		F						
		C	•	•	•	F	•	•	F				F		
External Communicating Device	Blood Path, Indirect	A	•	•	•	•						•			
		B	•	•	•	•	F					•			
		C	•	•	F	•	•	•	F	•			•	•	
	Tissue/Bone/Dentin ¹	A	•	•	•	F									
		B	•	•	•	•	•	•	•						
		C	•	•	•	•	•	•	•				•	•	
	Circulating Blood	A	•	•	•	•			F ²				•		
		B	•	•	•	•	•	•	•	•					
		C	•	•	•	•	•	•	•	•			•	•	
Implant Device	Tissue/Bone	A	•	•	•	F									
		B	•	•	•	•	•	•	•						
		C	•	•	•	•	•	•	•				•	•	
	Blood	A	•	•	•	•	•			•	•				
		B	•	•	•	•	•	•	•	•					
		C	•	•	•	•	•	•	•	•			•	•	

This table is only a framework for the development of an assessment program for your device and is not a checklist. Adopted from ISO 10993-1:2009 and FDA 510(k) Memorandum - #G95-1 Tables 1 and 2 (2009)

• = ISO Evaluation Tests for Consideration
 F = Additional Tests which may be required for US submissions

Note¹ Tissue includes tissue fluids and subcutaneous spaces

Note² For all devices used in extracorporeal circuits

Note³ Depends on specific nature of the device and its component materials

Consult with the FDA before performing any biocompatibility testing if you are submitting an IDE or you have a device/drug combination.

TEST TURNAROUND TIME AND SAMPLE REQUIREMENTS

REQUIREMENT	TEST NAME	SAMPLE AMOUNT			ESTIMATED TURN AROUND (in weeks)
		Surface Area Double amounts for materials < 0.5 mm in thickness	Irregular, powders or liquids		
			Gram s	mL	
Cytotoxicity	ISO Agar Overlay	1 x 3 pieces			4
	ISO MEM Elution	60 cm ²			
	ISO Direct Contact	60 cm ²	4	20	
	ISO MTT	60 cm ²			
	ISO Colony Formation	60 cm ²			
Sensitization	ASTM Murine Local Lymph Node Assay (LLNA)	N/A	16	30	5
	Maximization Test	60 cm ² x 6 devices	24	60	7
	Closed Patch Test	1 in ² x 130 devices	60	80	8
Irritation	ISO Intracutaneous Test	60 cm ² x 2 devices	8	40	5
	ISO Dermal Irritation	60 cm ² x 2 devices	4	10	5
	ISO Ocular Irritation	60 cm ² x 2 devices	2	5	5
	Mucous Membrane Irritation	Varies	Varies	Varies	Varies
Systemic Toxicity	Material Mediated Pyrogen Test	60 cm ² x 5 devices	24	120	5
	ISO Acute Systemic Test	60 cm ² x 2 devices	8	40	5
	Subacute	Varies	Varies	Varies	Varies
	Subchronic	Varies	Varies	Varies	Varies
	Chronic	Varies	Varies	Varies	Varies
Genotoxicity	Ames Test	120 cm ² x 2 devices	8	40	8 – 9
	Mouse Lymphoma Assay	240 cm ² x 2 devices	16	80	15 – 17
	Mouse Micronucleus Assay	1200 cm ² x 2 devices	40	200	15 – 17
	Chromosomal Aberration Test	120 cm ² x 2 devices	8	40	12 – 14
Implantation	Implantation Test (Local effects) (All ISO Implant Tests Include Histopathology) (7 days or greater)	12 strips 1 x 10 mm			varies
Hemocompatibility	Hemolysis – ASTM Direct and Indirect Contact	6 devices / 160 cm ²	12	20	4
	<i>In Vivo</i> Thrombogenicity	6 – 2 ½ “ long pieces			10 - 12
	<i>In Vitro</i> Platelet Aggregation Assay	120 cm ² x 2 devices	20	Inquire	6 - 8
	Partial Thromboplastin Time (PTT)	60 cm ²	4	N/A	6 - 8
	Prothrombin Time (PT)	60 cm ²	4	N/A	6 - 8
	Complement Activation	60 cm ² x 2 devices	8	Inquire	8 - 9
Carcinogenesis	Lifetime Toxicity	Inquire			Inquire
Analytical Tests	USP Physicochemical Tests	720 cm ²	N/A		6
	Other Procedures	Inquire			Inquire

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 (TISSUE 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.

Quantitative cytotoxicity tests are preferred by regulatory agencies and institutions.

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. (See page 9 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-dimethylthiazol-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 IC_{50} 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 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 (CFA) to enhance the skin sensitization response.

The *Closed Patch Test* involves multiple topical doses and is recommended for devices that will contact unbroken skin only.

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 Langerhans 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. *From an animal welfare perspective, this test is preferable to the Guinea Pig Maximization or the Closed Patch Test, and it allows for faster turnaround time. However, if a negative result is seen in the LLNA test, a Guinea Pig Maximization test must be conducted.*

IRRITATION TESTS

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 intact natural channels or tissues. These studies often use extracts rather than the material itself. Some common procedures include vaginal, cheek pouch and eye irritation studies. (See page 9 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 Materials Biocompatibility Matrix recommends this test for all blood contact devices. It may also be appropriate for any other device that contacts internal tissues.

The *Material Mediated Pyrogen* test evaluates the potential of a material to cause a pyrogenic response, or fever, when introduced into the blood. Lot release testing for pyrogenicity is done *in vitro* using the *bacterial endotoxin (LAL)* test. It 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.

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 protocols for subchronic testing that are appropriate for many devices. They may use *intraperitoneal* administration of an extract of the device or device material or an *intravenous* route of administration. Implant tests are often performed for different durations appropriate to assess subchronic toxicity of devices and device materials.

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

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*, which have been selected for their sensitivity to mutagens. The Mouse Lymphoma and the HGPRT assays are common procedures using mammalian cells to detect point mutations. The *Mouse Lymphoma* assay is also able to 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-term exposure require an Ames test and two *in vivo* methods, usually the *Chromosomal Aberration* and *Mouse Micronucleus* 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.*

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, 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. More information on histopathology service is available on page 21.

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.

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 activation 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.

DEVICES OR COMPONENTS WHICH CONTACT CIRCULATING BLOOD AND THE CATEGORIES OF APPROPRIATE TESTING — EXTERNAL COMMUNICATING DEVICES

Device Examples	Test Category				
	Thrombosis	Coagulation	Platelets	Hematology	Complement System
Catheters in place for less than 24 hours (Atherectomy devices)	x ^a			x ^b	
Blood monitors	x ^a			x ^b	
Blood storage and administration equipment, blood collection devices, extension sets		x	x	x ^b	x ^c
Catheters in place for more than 24 hours: guidewires, intravascular endoscopes, Intravascular ultrasound, laser systems, Retrograde coronary perfusion catheters.	x ^a			x ^b	x
Cell savers		x	x	x ^b	
Devices for absorption of specific substances from blood		x	x	x	x
Donor and therapeutic apheresis equipment and cell separation systems		x	x	x	x
Extracorporeal membrane oxygenator systems, haemodialysis/haemofiltration equipment, percutaneous circulatory support devices	x ^a			x	x
Leukocyte removal filter		x	x	x ^b	x

^a Thrombosis is an in-vivo or ex-vivo phenomenon. Coagulation and platelet response are involved in this process. The manufacturer must decide if testing in coagulation and platelet testing are appropriate. ^b Haemolysis testing only. ^c Only for aphaeresis equipment.

DEVICES OR COMPONENTS WHICH CONTACT CIRCULATING BLOOD AND THE CATEGORIES OF APPROPRIATE TESTING — IMPLANT DEVICES

Device examples	Test Category				
	Thrombosis	Coagulation	Platelets	Hematology	Complement System
Annuloplasty rings, mechanical heart valves	x ^a			x ^b	
Intra-aortic balloon pumps	x ^a			x	x
Total artificial hearts, ventricular-assist devices	x ^a			x	
Embolization devices	x ^a			x ^b	x
Endovascular grafts	x ^a			x ^b	
Implantable defibrillators and cardioverters	x ^a			x ^b	
Pacemaker leads	x ^a			x ^b	x
Prosthetic (synthetic) vascular grafts and patches, including arteriovenous shunts	x ^a			x ^b	
Stents	x ^a			x ^b	
Tissue heart valves	x ^a			x ^b	
Tissue vascular grafts and patches, including arteriovenous shunts	x ^a			x ^b	
Vena cava filters	x ^a			x ^b	

^a Thrombosis is an in-vivo or ex-vivo phenomenon. Coagulation and platelet response are involved in this process. The manufacturer must decide if testing in coagulation and platelet testing are appropriate. ^b Haemolysis testing only.

CARCINOGENESIS BIOASSAYS

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 negotiate an alternative to full scale 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. They are often required for devices with permanent contact with internal tissues.

PHARMACOKINETICS

Pharmacokinetic or ADME (Absorption/Distribution/Metabolism/Excretion) studies are used to investigate the metabolic processes of absorption, distribution, biotransformation, and elimination of toxic leachables and potential degradation products from test materials and/or extracts. They are especially appropriate for bioabsorbable materials or for drug/device combinations. The toxicology team at Pacific BioLabs is happy to work with you in setting up the appropriate PK or ADME study for your product.

PRECLINICAL SAFETY TESTING

The objectives of preclinical safety studies are to define pharmacological and toxicological effects not only prior to initiation of human studies but throughout clinical development. Both *in vitro* and *in vivo* studies can contribute to this characterization. Pacific BioLabs has extensive experience in designing and running successful preclinical safety studies.

HISTOPATHOLOGY SERVICES

Implant studies are often the most direct evaluation of device biocompatibility. The test material is placed in direct contact with living tissue. After an appropriate period, the implant site is recovered and examined microscopically for tissue reaction. The histopathologist can detect and describe many types of tissue and immune system reactions.

Similarly, in subchronic and chronic studies, various organs and tissues are harvested at necropsy and evaluated microscopically for toxic effects. Many of these studies also call for clinical chemistry analysis of specimens or serum samples from the test animals.

MATERIALS CHARACTERIZATION & ANALYTICAL TESTING OF BIOMATERIALS

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 10993-17 and 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.

Additional uses of analytical characterization data might include:

1. Use in an assessment of the overall biological safety of a medical device.
2. Measurement of the level of any 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 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 MATERIAL

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

BULK MATERIAL CHARACTERIZATION

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

SURFACE CHARACTERIZATION

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

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, sterility assurance, microbiology and preclinical toxicology/pharmacology services.

SERVING THE BIOSCIENCE INDUSTRY SINCE 1982

Pacific BioLabs clients range from small start-ups to Fortune 500 companies. 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 audit all aspects of lab operations and administer our world class CAPA (corrective and preventive action) 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 EPA 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 Intertek to ISO 9001:2008 and ISO 13485:2003. Our animal science program is AAALAC accredited.

REFERENCES

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NOTES

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