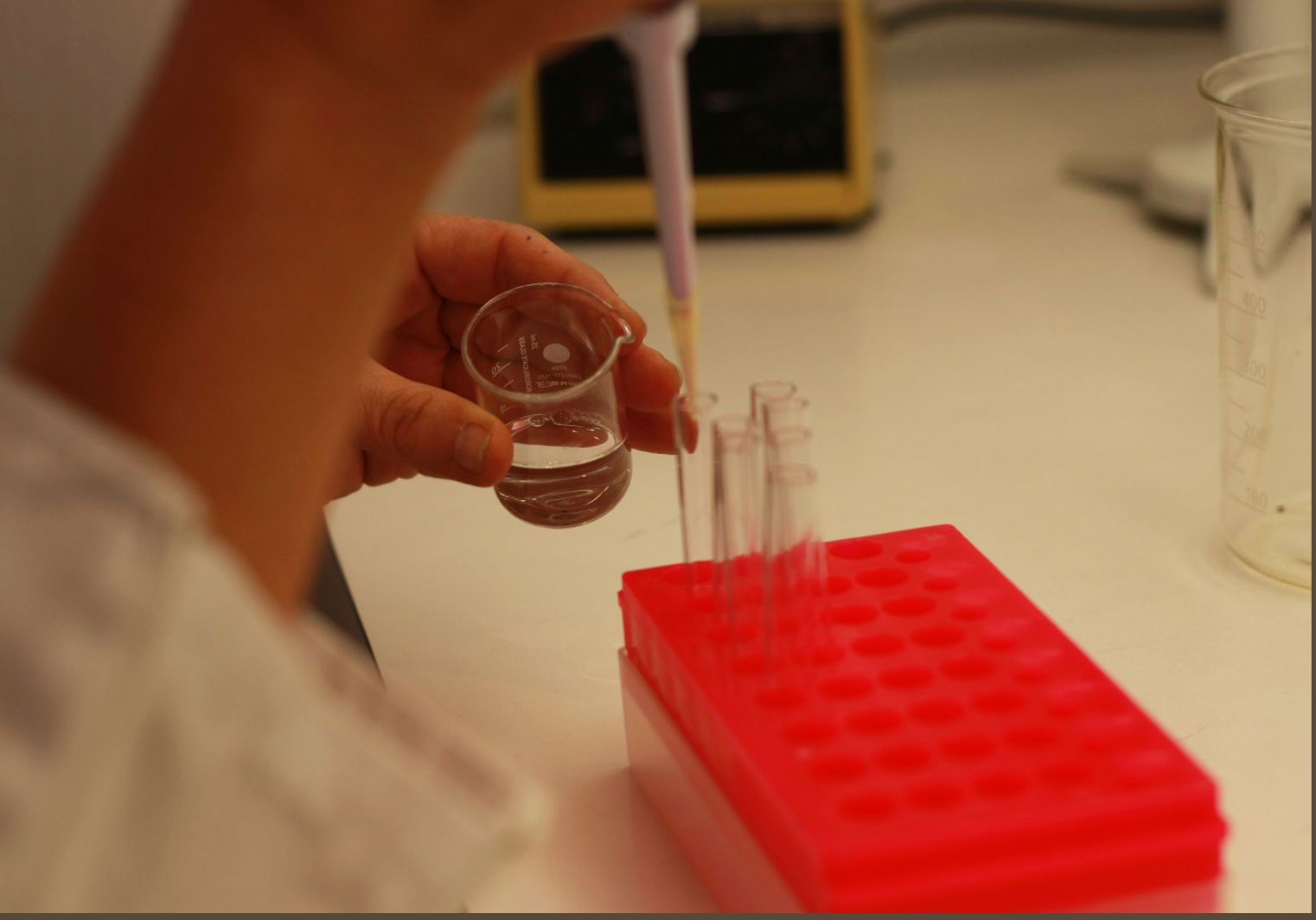

Physical and Chemical Characterization

The First Stage in Assessing the Biocompatibility of Medical Device Materials

Physical and Chemical Characterization of Medical Device Materials

From programmable pacemakers and laser surgical devices to inactive medical devices such as intraocular lenses, resorbable bone screws or intravascular catheters, today's state-of-the-art medical devices are a vital tool in the diagnosis and treatment of diseases and illnesses. Despite their numerous benefits, however, all medical devices present some degree of risk to a patient, even when used appropriately. For this reason, a risk assessment of any medical device must include an evaluation of the inherent safety of a device and its components.

A particular safety concern associated with the use of medical devices is the risk presented by simple contact with the human body. Even when used as designed, medical devices and their constituent materials may have the potential to produce unintended local or systemic effects. Depending on the duration of contact, some materials may also be harmful or toxic to the body, or may have adverse developmental or reproductive effects. Further, processes such as manufacturing, packaging, shipping and routine sterilization may adversely affect a material's composition, rendering an otherwise safe device potentially harmful.

Biocompatibility testing represents a series of staged assessments to determine the potential harmful effects that can result from human contact with a medical device or component, and is an essential aspect of the overall product safety assessment required for global regulatory approval. The physical and chemical characterization of materials is the first stage of biocompatibility testing, and involves the analysis of substances that can potentially leach from a medical device during normal, anticipated use. When conducted in advance of other biocompatibility testing, material characterization testing may reduce overall testing time and speed regulatory approval.

This UL white paper discusses the physical and chemical characterization of medical device materials in the context of an overall biocompatibility assessment. Beginning with background information on biocompatibility issues associated with medical devices, the white paper reviews specific physical and chemical effects and the testing specified under ISO 10993-18 dealing with the chemical characterization of materials. The white paper then outlines a structured approach to the development of an effective material equivalency program to speed material selection, and concludes with a discussion of the benefits of maintaining such a program throughout a product's development and production cycle.

The Need for Biocompatibility Testing of Medical Devices

Modern medical devices are composed of a diverse range of materials and components, each with their own physical and chemical characteristics. Although these materials may pose minimal risk when incorporated in products intended for general use, their inclusion in medical devices that come in contact with the human body expands the scope of potential safety considerations. These considerations can include contamination from the device, the breakdown or decomposition of device materials, the migration of device materials to other parts of the body, and consequences from intended device degradation.

Even when materials incorporated into a medical device have been assessed for their biocompatibility, new biocompatibility risks can be introduced through manufacturing and post-production processes that can have an adverse effect on these materials. For example, contact with lubricants or other chemicals during the production process can compromise the chemical integrity of a material. Similarly, sterilization and packaging may adversely affect material composition. Leachable substances from the packaging materials, like residual solvents or ink from a package label, may interact with a biocompatible material.

In addition to direct risks to human safety, the physical and chemical characteristics of materials used in medical devices can indirectly interfere with device functionality. For instance, chemicals that leach from device materials can potentially alter the mechanical or electronic properties of the device itself. In these cases, a critical device such as a pacemaker might malfunction or cease to operate altogether, thereby placing a pacemaker recipient at significant risk. In other cases, vibration, shock or temperature variations encountered during shipment of a packaged device may damage a device.

Biocompatibility testing and evaluation looks at all of the potential adverse effects on a human body that may result from the materials used in a medical device. The complete range of testing conducted as part of a biocompatibility assessment is detailed in the standard ISO 10993-1:2009, Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing Within a Risk Management System. However, in determining which specific tests to conduct, special consideration is given to how a medical device will actually be used and the degree and duration of contact between the device and the patient.

Table 1 provides additional details on the criteria used to determine which potential biological effects must be considered when evaluating a given medical device. This framework outlines an assessment program for the final evaluation of the biocompatibility of a device under evaluation. However, a detailed risk analysis is required to identify the actual tests to be performed and any additional test required for the evaluation of other biological aspects. For example, tests for chronic toxicity, carcinogenicity, biodegradation, toxicokinetics, immunotoxicity, reproductive/developmental toxicity or other organ-specific toxicities should be considered in addition to those tests identified in Table 1, based on the intended use of the medical device.

MEDICAL DEVICE CATEGORIZATION BY			BIOLOGICAL EFFECT*							
NATURE OF BODY CONTACT										
CATEGORY	CONTACT	CONTACT DURATION A - LIMITED (≤24 H) B - PROLONGED (> 24 H TO 30 D) C - PERMANENT (> 30 D)	CYTOTOXICITY	SENSITIZATION	IRRITATION OR INTRACUTANEOUS REACTIVITY	SYSTEMIC TOXICITY (ACUTE)	SUBCHRONIC TOXICITY (SUBACUTE TOXICITY)	GENOTOXICITY	IMPLANTATION	HAEMOCOMPATIBILITY
Surface device	Skin	A	X	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/ dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

Table 1: ISO 10993-1 Biocompatibility Testing Selection Criteria

* The Xs indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

Material Characterization Testing

Complete biocompatibility testing and evaluation of a medical device should always include the physical and chemical characterization of materials used in the device. Ideally, this material characterization will occur at the earliest possible stages in the research and development of a new medical device. Information derived from early analysis will support material selection decisions and, potentially influence the design of a device itself. In addition, initial material characterization efforts can identify suitable substitute materials in cases where material availability or pricing considerations require sourcing alternatives at any point during the production life of the device. Finally, material characterization analysis can preclude unnecessary animal testing in the later stages of a device's biocompatibility assessment.

Originally published in 2005, the standard ISO 10993-18, Biological Evaluation of Medical Devices—Part 18: Chemical Characterization of Materials, describes the physical and chemical analysis procedures that are an essential part of the material characterization process. Under the standard, chemical characterization testing is based on the nature of contact between a device and the human body, i.e., devices placed on the surface of the skin, external communicating devices or implantable devices, and the type of material used, i.e., polymeric material, metal or ceramic.

Due to the large variety of medical devices addressed by the standard, ISO 10993-18 does not provide a detailed characterization structure similar to that found in ISO 10993-1. According to ISO 10993-18, "the extent of chemical characterization required should reflect the nature and duration of the clinical exposure and shall be determined by the toxicological risk assessor based on the data necessary to evaluate the biological safety of the device."

To assist medical device manufacturers, mdt medical device testing GmbH (a UL company) has developed a matrix (see Table 2) that can be used to determine a suitable series of tests to create an appropriate characterization of newly developed materials. This matrix is similar to the matrix for the biological evaluation of medical devices found in ISO 10993-1. Note that this material characterization matrix is intended only as a guide, and that the actual characterizations tests to be performed must be based on a device's nature of body contact and its constituent materials.

Here is a brief summary of the various test procedures that are used as part of the material characterization process:

Physico-chemical tests — Physico-chemical tests generate nonspecific information regarding the amount of water-soluble (extraction with water) and solvent-soluble (extraction with isopropanol) substances in a given material. These tests can be conducted on all polymeric device materials, regardless of the nature of contact between the device and the human body. Physico-chemical tests can also be used to assess and compare materials from different production lots or from different manufacturers.

Fourier-transformed infrared spectroscopy (FT-IR) — This testing technique is used to identify organic substances in a given material, or to prepare a product "fingerprint." Like physico-chemical testing, FT-IR testing can be conducted on all polymeric device materials, regardless of the nature of body contact.

Analysis of organic substances — An analysis of organic substances can be conducted on all polymeric materials, regardless of the nature of contact between the device and a human body. Leachable and/or extractable organic substances are analyzed after extraction from a material, following procedures detailed in ISO 10993-12. Nonextractable organic substances can be identified and, if applicable, quantified after dissolving a material sample in a suitable solvent using any of the following analysis techniques:

- Gas chromatography equipped with a mass selective detector (GS/MS), used for separating volatile and semi-volatile organic substances
- High performance liquid chromatography equipped with a diode array detector (HPLC/DAD), used for separating non-volatile and thermally fragile organic substances

- FT-IR is used for the identification of leachables and/or extracted substances or substance groups. In cases where a mixture of multiple substances is extracted, a detailed identification using FT-IR is unlikely. Instead, GC/MS or HPLC techniques should be employed

Analysis of inorganic substances — An analysis of inorganic substances can be conducted on all materials and for all types of medical devices. The composition of metals and ceramic materials can be determined using an inductive coupled plasma (ICP) spectrometer. With this technique, it is also possible to identify even small amounts of inorganic substances, such as metal ions, that are present in polymers or their extracts. X-ray photoelectron spectroscopy (XPS) and Auger-electron spectroscopy (AES) are useful techniques for analyzing the surfaces of metal-coated materials.

Physical mechanical analysis — The mechanical analysis of materials is necessary to evaluate how they react under a variety of loading conditions. Hardness tests are performed with metals and polymeric materials to determine their resistance to scratching or indentation, and their rebound resilience. These investigations are also useful in identifying insufficient material properties or to compare different production lots. Specific gravity assessments can be used to characterize the identity, purity and concentration of materials.

Molecular weight distribution — When characterizing polymeric materials, gel permeation chromatography (GPC) can be used to determine the molecular weight distribution. A Ubbelohde viscometer can be used to determine solution viscosity.

Morphological characterization — Depending on the intended use of a medical device, the relative smoothness of a device surface can greatly affect its interaction with bodily fluids or contacting tissues. For implantable medical devices and some external communicating devices, scanning electron microscopy can be used to obtain important information regarding relative surface integrity. In addition, valuable information concerning the qualitative and semi-quantitative composition of a material surface can be obtained when using scanning electron microscopy in combination with energy dispersive X-ray (SEM-EDX).

Thermal Analysis — Thermal analysis is performed using a differential scanning calorimeter (DSC) and is used to identify critical thermal properties of a given material, such as polymer melting point and glass-transition temperature. A thermal analysis can also provide information regarding the thermal history and purity of a polymer. Thermal analysis is mainly suggested for implantable and external communication medical devices.

MEDICAL DEVICE CATEGORIZATION			MATERIAL CHARACTERIZATION TEST PROCEDURE																					
					ANALYSIS OF ORGANIC SUBSTANCES			ANALYSIS OF INORGANIC SUBSTANCES		PHYSICAL/MECHANICAL TESTS			MOLECULAR WEIGHT DISTRIBUTIONS		MORPHOLOGICAL	THERMAL ANALYSIS								
NATURE OF BODY CONTACT		A - POLYMERIC MATERIAL B - METAL C - CERAMIC	PHYSICOCHEMICAL TESTS	FT-IR	GC/MS	HPLC/DAD	FT-IR	ICP	XPS/AES	MECHANICAL TESTS	SPECIFIC GRAVITY	HARDNESS	GPC	VISCOSITY	SEM ORSEM-EDX	DSC								
Surface device	Skin	A	E	M	E[1]	E[2]	E[2]	E																
		B						E																
		C																						
	Mucosal membrane	A	E	M	E[1]	E[2]	E[2]	E																
		B						E																
		C						E																
	Breached or compromised surface	A	E	M	E[1]	E[2]	E[2]	E																
		B						E																
		C						E																
External communicating device	Blood path, indirect	A	E	M	E/M	E/M	E/M	E/M		M							M							
		B						E/M	M[2]	M														
		C						E/M		M														
	Tissue/bone/ dentin	A	E	M	E/M	E/M	E/M	E/M		M							M							
		B						E/M	M[2]	M														
		C						E/M		M														
	Circulating blood	A	E	M	E/M	E/M	E/M	E/M		M	M	M	M	M	M	M								
		B						E/M	M[2]	M						M								
		C						E/M		M						M								
Implant device	Tissue/bone	A	E	M	E/M	E/M	E/M	E/M		M	M	M	M	M	M	M								
		B						E/M	M[2]	M						M								
		C						E/M		M						M								
	Blood	A	E	M	E/M	E/M	E/M	E/M		M	M	M	M	M	M	M								
		B						E/M	M[2]	M						M								
		C						E/M		M						M								

Table 2: Proposed Analytical Procedures for Material Characterization (mdt Material Characterization Matrix)

E - Extractables, quantitative determination
E[1] - Extractables, qualitative and semiquantitative 'Fingerprint'
E[2] - Extractables, 'Fingerprint'
M - Material
M[2] - Material, only present as coating

When is Material Characterization Necessary?

As previously noted, the physical and chemical characterization of materials used in a medical device is an essential part of the overall biocompatibility assessment of that device. Material evaluation is a complex and time-consuming endeavor, and the evaluation process may result in the rejection of a number of seemingly suitable materials before identifying those that are appropriate to the device's intended use, and which present minimal risk to patients. By beginning material characterization efforts as early as possible in the design phase of a new medical device, product development teams can proceed with greater confidence that material incompatibilities will not derail progress in the later stages of product development.

Typically, a complete biocompatibility assessment of a medical device is performed using a prototype manufactured at a pilot plant. After this assessment has been completed, the scale of production is increased. Then, material characterization is performed on a final production device, with results compared with those generated from the testing of a prototype. Finally, a manufacturer must document that, beside the functionality of a device, its biocompatibility has not been negatively affected during storage until the end of its anticipated shelf life. Once again, material characterization is the best method for this assessment.

But material characterization efforts do not end once a medical device has been introduced to the marketplace. Products are often modified after their initial introduction to incorporate additional features or to address performance issues identified through actual use. In these cases, even minor changes in design or functionality can have a significant impact on a device's biocompatibility profile, and render prior material characterization analyses obsolete.

Even in those instances where a device itself is not modified, material characterization and biocompatibility can be impacted by changes in the raw materials used or in modifications to the manufacturing process. Such changes can occur when availability or pricing considerations result in the purchase of ostensibly similar material from multiple sources, or from undetected modifications in the processing of raw materials themselves. In addition, device manufacturers may modify their own internal production processes, with such changes potentially impacting the physical and chemical properties of selected materials.

For these reasons, material characterization efforts must extend beyond the initial product development process and serve as a key element of a device manufacturer's ongoing product management effort. By following this approach, manufacturers can have increased confidence that materials will not comprise a device's biocompatibility during its production and use life. Taking these steps can also reduce the incidence of product failures in the field and product recalls, events that can have significant financial consequences and which can adversely impact a manufacturer's reputation.

The Role of Material Characterization Testing in a Material Equivalency Program

Beyond maintaining continuous material characterization efforts, manufacturers should also consider the implementation of a material equivalency program as a part of their overall change control process. Such a program establishes a formal procedure for evaluating device materials when changes or substitutions occur, and can speed the clearance of new materials when additional material characterization testing is warranted.

At a minimum, an effective material equivalency program includes the following aspects:

- A system that identifies all possible material and production changes for a given medical device
- For any change identified, a procedure to assess whether the change is likely to have an impact on the physical or chemical characterization of the material
- In cases where material characterization is impacted by the change, a determination whether the impact requires material biocompatibility retesting
- When retesting is required, a streamlined material characterization assessment that can efficiently and effectively determine material equivalency

In addition to these essential aspects, a well-designed material equivalency program can be expanded to assess other aspects of a device's biocompatibility or safety profile, such as the potential effects from material aging. A material equivalency program can also be used as a basis for measuring and evaluating alternative methods of manufacturer, providing valuable data that can help increase production efficiency and profitability.

Conclusion

Biocompatibility is an important aspect of the overall safety profile of medical devices. A thorough biocompatibility evaluation looks at all of the potential effects on a human body that can result from contact with a device. However, assessing biocompatibility is a complex and lengthy process, and missteps can lead to delays in the product development cycle, resulting in delayed market introduction and the potential for lost revenue.

Testing the physical and chemical characteristics of materials used in medical devices is a key component of the biocompatibility assessment process. When conducted during the earliest stages of a product development cycle, material characteristic testing can help to identify suitable materials that support the biocompatibility goals of a given medical device. Material characterization testing that takes place after a device has been introduced into the marketplace can also help to reduce the impact of material changes that can affect biocompatibility. For this reason, material characterization efforts should be integrated into a formal material equivalency program to protect users of medical devices, and to safeguard against product failures in the field and their potential for costly product recalls that can damage a manufacturer's reputation for safe products.

UL offers medical device manufacturers and health sciences companies testing and evaluation services that address the requirements of the ISO 10993 series of biocompatibility standards as well as testing to the material characterization requirements of ISO 10993-18. UL can also conduct biocompatibility testing of medical devices consistent with the U.S. Pharmacopoeia (USP) standards accepted by the U.S. Food and Drug Administration, the standards accepted by Japan's Ministry of Health, Labor and Welfare (MHLW), as well as the standards needed for CE registration in Europe. UL's medical device biocompatibility testing capability allows manufacturers to work with a single testing laboratory to satisfy regulatory requirements for most of the world's medical device regulators.

For further information about UL's biocompatibility and material characterization testing capabilities for medical devices, contact Mr. Jan Peeters, director of testing services, mdt medical device testing GmbH, a UL Company located in Ochsenhausen, Germany, at info@mdt-gmbh.com, or UL at Medical.Inquiry@UL.com.