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BIOCOMPATIBILITY OF PLASTICS

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INTRODUCTION

Plastics have many unique properties regarding their manufacturability and production potential. These properties are increasingly being utilized in the production of medical devices and medical packaging. The medical device industry is one of the fastest growing areas for plastics with growth rates exceeding gross domestic product growth for several years. This trend is predicted to continue into the future due to developments of increasingly innovative medical devices, improvements in plastics technology (both materials and processing), and an aging population. Despite this significant growth, one thing remains constant: The application of any material in a medical device must meet stringent safety requirements.

BIOCOMPATIBILITY

Biocompatibility is a general term used to describe the suitability of a material for exposure to the body or bodily fluids with an acceptable host response. Biocompatibility is dependent on the specific application and circumstance of the material in question: A material may be biocompatible in one particular usage but may not be in another. In general, a material may be considered biocompatible if it causes no harm to the host. This is distinct, however, from causing no side effects or other consequences. Frequently, material that is considered biocompatible once implanted in the body will result in varying degrees of inflammatory and immune responses. For a biocompatible material, these responses are not harmful and are part of body's normal responses.

Materials that are not biocompatible are those that do result in adverse (harmful) effects to the host. Non-biocompatible materials can disrupt normal healing processes and can have protracted and broad consequences. Indications that a material is not biocompatible include:

- Chronic inflammation at the area of contact
- Production of cytotoxic substances
- Cell disruption
- Skin irritation
- Restenosis (narrowing of blood vessels after stenting)
- Formation of blood clots (thrombosis)
- Corrosion of implanted material

Thus, biocompatibility is a fundamental hurdle that any potential implantable device or component must overcome.

TESTING AND ASSESSMENT

Testing and evaluation for biocompatibility vary widely based on the intended application of the device or component. One set of tests for a particular material may not be required for the material in a different application. Testing regimes are broad in scope and encompass *in vivo* and *in vitro* evaluations. Biocompatibility test protocols include those for cytotoxicity, hemocompatibility, genotoxicity, irritation, implantation, sensitization, and system toxicity. Additionally, biocompatibility protocols must account for potential misuse of the device or component.

ISO 10993: BIOLOGICAL EVALUATION OF MEDICAL DEVICES

The International Organization for Standardization (ISO) presents widely adopted medical device guidelines that are aimed with a keen focus towards risk management. Biocompatibility testing for these devices and device components is addressed by ISO standard 10993. (There are other country-specific guidelines that largely overlap with ISO 10993, however, but those programs shall not be discussed here). This set of documents entitled, Biological evaluation of medical devices, is issued currently in twenty parts and is regularly revised to reflect new findings (**Table 1**). Early consideration in biocompatibility testing is given to material characterization. If the material in question has a proven acceptably safe history of medical use, very often this phase of evaluation can be omitted. For new materials or new applications for previously used materials, ISO 10993 provides guidance on methodology and appropriate test program.

Table 1: Structure and parts of ISO 10993: Biological evaluation of medical devices	
Part	**Title**
1	Evaluation and testing
2	Animal welfare requirements
3	Tests for genotoxicity, carcinogeniticity and reproductive toxicity
4	Selection of tests for interaction with blood
5	Tests for cytotoxicity - in vitro methods
6	Tests for local effects after implantation
7	Ethylene oxide sterilization residuals
8	Clinical investigation of medical devices
9	Degradation of materials related to biological testing
10	Test for irritation and sensitization
11	Test for systemic toxicity
12	Sample preparation and reference materials
13	Identification and qualification of degradation products from polymers
14	Identification and qualification of degradation products from ceramics
15	Identification and qualification of degradation products from coated and uncoated metals and alloys
16	Toxicokinetic study design for degradation products
17	Glutaraldehyde and formaldehyde residues in industrially sterilized medical devices
18	Chemical characterization of materials
19	Physico-chemical, morphological and topographical characterization of materials
20	Principles and methods for immunotoxicology testing of medical devices

The selected test program depends on several factors based on the device category determined by ISO 10993. The material used, contact regime, and time duration of contact with the device help determine the test program (**Table 2**). Contact time is broken into three periods: short duration (< 24 hours), prolonged contact (24 hours to 30 days), and permanent contact (> 30 days). Contact regime describes how the device will come in contact with the body such as via blood, skin, bone, etc. These elements help provide a foundation for biological evaluation of medical devices. ISO 10993 is not a formal checklist but a guide to the typical information requirements for approval authorities. ISO 10993 is intended to assist manufacturers and engineers in designing an appropriate testing program for their device. Testing details are thus specific to each device and its application though there may be testing commonalities for multiple device types.

Table 2: Device categories and biological evaluation of medical devices for ISO (from ISO 10993: Part 1).			
Device category	**Contact regime**	**Contact Timescale**	**Example products**
Surface devices	Skin	Limited	Electrodes, external prostheses, fixation tapes, compression bandages, monitors of various types
		Prolonged	
		Permanent	
	Mucous membrane	Limited	Contact lenses, urinary catheters, intravaginal and intraintestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gastroscopes), endotracheal tubes, bronchoscopes, dental prostheses, orthodontic devices, IUDs
		Prolonged	
		Permanent	
	Breached or compromised surfaces	Limited	Ulcer, burn and granulation tissue dressings or healing devices, occlusive patches
		Prolonged	
		Permanent	
Externally communi-cating devices	Blood path indirect	Limited	Solution administration sets, extension sets, transfer sets, blood administration sets
		Prolonged	
		Permanent	
	Tissue / bone / dentin communicating	Limited	Laparoscopes, arthroscopes, draining systems, dental cements, dental filling materials, skin staples
		Prolonged	
		Permanent	
	Circulating blood	Limited	Intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialyzers, dialysis tubing and accessories, hemoadsorbents and immunoadsorbents
		Prolonged	
		Permanent	
Implant devices	Tissue / bone implant devices	Limited	Orthopedic pins, plates, replacement joints, bone prostheses, cements and intraosseous devices, pacemakers, drug supply devices, neuromuscular sensors and simulators, replacement tendons, breast implants, artificial larynxes, subperiosteal implants, ligation clips
		Prolonged	
		Permanent	
	Blood	Limited	Pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug delivery catheters, ventricular assist devices
		Prolonged	
		Permanent	
Time Span Key:	Limited: < 24 hours	Prolonged: 24 hrs - 30 d	Permanent: > 30 days

OTHER REGULATIONS

In conjunction with ISO 10993, in the United States the Food and Drug Administration (FDA) regulates medical devices. FDA guidelines largely agree with ISO 10993 regulations. (ISO test results are generally acceptable for applications in the United States). European Union device manufacturers under the authority of the European Commission are governed by Regulations (EU) 2017/745-6 for general medical devices and *in vitro* diagnostic medical devices. Collectively, these organizations address nearly all conceivable medical device testing concerns. Readers are encouraged to refer to individual parts of ISO 10993, the FDA, or EU Medical Device Directives for further information on specific testing.

UNITED STATES PHARMACOPOEIA (USP)

In some areas, the USP has been superseded by ISO 10993 for medical device evaluation. Some manufacturers, however, continue to use USP standards. One such example is USP 88 Biological Reactivity Tests for *in vivo* testing. This protocol is used to rate and categorize plastics into Classes I to VI. These tests measure the biological response of animals to plastics by direct or indirect contact and by injection of extracts from the material. The tests include systemic injection (intravenous and intraperitoneal), intracutaneous, and implantation. These tests are directly related to the intended use of the plastic component.

USP 88 also specifies routes of administration of the device or extract being tested. The systemic injection test and the intracutaneous test use extracts prepared at one of three standard temperature and time regimes: 50 °C (122 °F) for 72 hours, 70 °C (158 °F) for 24 hours, or 121 °C (250 °F) for 1 hour. Different media (including polyethylene glycol, ethanol, saline, or cottonseed oil) are also part of USP 88 testing to facilitate extraction. These screening tests characterize the biocompatibility of plastics and define them as USP Class I to VI.

MATERIAL CHARACTERIZATION

Well-defined material characterization is a fundamental requirement in biocompatibility assessment. This evaluation consists of chemical, mechanical, and thermal characterization elements (**Fig. 1**). Material characterization is of particular importance for plastics because nominally similar grades of plastics can vary significantly in their material and chemical attributes. Plasticizers, stabilizers, and fillers added to plastics during manufacturing can affect their biocompatibility. Leaching studies must be performed on plastics with additives such as these to ensure that leachates from the plastics are non-toxic. The amount and type of additive will also affect the biocompatibility of the final plastic product.

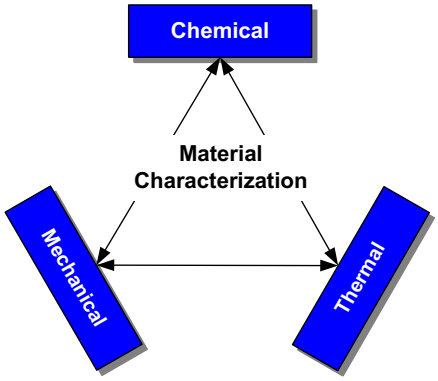

Figure 1: Elements of material characterization: mechanical, thermal, and chemical.

CHEMICAL TESTING

Chemical testing for material characterization uses a variety of techniques to reveal important chemical facets of the material. These tests may include, but are not limited to, infrared (IR) analysis, extraction analysis, chromatography, and trace metal analysis. IR provides detailed qualitative and semi-qualitative information on the types of material(s) present. Extraction analysis gives information of potential leachates. Gas or liquid chromatography characterizes additives, residual polymer monomers, and degradation products that remain from manufacturing. Lastly, trace metal analysis can be used to reveal the presence of lead, tin, barium, bismuth, or other metals which may have been added during processing of the plastics. These tests inform potential users of how devices and products will behave within the body chemically and how that behavior may affect patients.

MECHANICAL TESTING

Implantable devices have mechanical performance requirements dictated by their intended function (application). The performance of the device is limited, however, by the physical properties of the device materials and components. Mechanical testing is therefore necessary to determine properties such as elasticity, toughness, tensile strength, stress-strain curves, and many others for the finished device. Mechanical failure indeed is every much a concern as biocompatibility failure for medical devices. While not a direct determinant of biocompatibility, mechanical evaluation allows

design engineers and manufacturers to choose a plastic which will perform best for the intended use.

THERMAL TESTING

Thermal testing is performed to assess a plastic's response to heating. Techniques such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) are two common test methods used for biocompatibility thermal testing. TGA measures the test material's change in weight as it is heated. DSC compares the temperatures of a reference material and an unknown (test) sample as they are heated. Tests such as these (and others) can be used to gather critical information about the plastic being investigated such as purity, phase structure, thermal history, melting point (T_m), and glass transition temperature (T_g). These tests help manufacturers and engineers evaluate a plastic (or other material) specifically and its viability as a medical device or component.

STERILIZATION

Another especially important consideration for biocompatibility and material characterization is the effect of sterilization procedures on the device. Medical devices and components necessarily will be in contact with the body, thus sterilization will be required. Single use products, for example, need only be able to endure a single sterilization event. On the other hand, some products will be used multiple times and must be able to withstand repeated sterilization cycles. Multi-use products may also require exposure to more than one type of sterilization protocol or procedure during its usage lifetime. Biocompatible materials and products must survive sterilization without loss of critical properties and without significant deleterious effects. Sterilization, thus, should be considered at the earliest stages of material characterization.

BIOCOMPATIBLE PLASTICS

Pure plastics are relatively chemically unreactive. Thus, they are very amenable to uses that require contact with the body. However, compounds and variants of the naïve version of these plastics may not be compatible as a biomaterial. Similarly, not all plastics may be suitable for certain demanding biomedical applications. Some plastics, such as PTFE and PEEK, have especially good chemical resistance and have become medical industry favorites. Other plastics have broad spectrum beneficial biocompatible properties that make them useful for a variety of less critical applications (**Table 3**). Complementing traditional plastics, new plastic products are continually in development, and many are beginning to substitute for established ones.

Table 3: Selected plastics and their common biomedical applications.

Plastic family	Typical applications
Polycarbonate (PC)	Dialysis filter cartridges, highly transparent glass containers, tubing and intravenous (IV) connectors, component for blood oxygenators, trocars
Polyetheretherketone (PEEK)	Prostheses, dental products, rigid tubing, replacements for metal implants
Polyethersulfone (PES)	Membranes: hemodialysis, gas separation, others; tubing, catheters, implantable drug infusion device
Polyethylene (PE, of various types)	Implantable products, sutures, surgical cables, orthopedic, and artificial tendons, catheter inner lining
Polypropylene (PP)	Suture material, meshes, laboratory containers and tubes, drug delivery systems
Polysulfone (PS)	Implantable ports, dialyzers, surgical instruments, device housings
Polytetrafluoroethylene (PTFE)	Vascular grafts, suture material, catheter base liners, prostheses
Polyurethane (PU)	Artificial hearts, wound dressings, catheter tubing, surgical drains
Polyvinylchloride (PVC)	Blood bags, feeding tubes, catheters / cannulae, inflatable splints
Polyetherimide (PEI)	Machinable parts for reusable medical devices, IV sets, medical and dental instruments, pharmaceutical containers

FLUOROPOLYMERS AND BIOCOMPATIBILITY

Fluoropolymers have among the best biocompatibility of all plastics. As such, they are have become thoroughly embedded in the medical sector with a multitude of applications and products. These generally alkene-based plastics have many key properties beneficial towards biomedical applications such as: lubricity, ability to be sterilized, little to no chemical reactivity within the body, broad temperature tolerance, and above all – biocompatibility. Class VI USP approved fluoropolymers include

ETFE, FEP, PFA, PTFE, and PVDF, to name but a few representatives from this group. Because of these attributes, fluoropolymers often represent a good starting point when choosing a plastic as a component or device that will be used within the body.

SUMMARY

Biocompatibility is a broad expression describing a material's fitness for use within the body. Implantable devices nearly always cause inflammatory or immune responses. For a biocompatible material, these responses do not rise to the level of being harmful. Testing for biocompatibility of materials is mainly centered on guidelines put forth by ISO 10993, the FDA (United States), Regulations (EU) 2017/745-6 (European Union), and the USP. The USP classification system for plastics groups them into Classes I – VI defined by compliance testing and approval criteria. Fluoropolymer plastics, for example, fall under USP Class VI.

For material evaluation specifically, testing includes chemical, mechanical, and thermal analyses. An additional and crucial step in biocompatibility assessment is the effect of sterilization on the material. Many plastic device components must tolerate repeated sterilizations. As a group, fluoropolymers have many attractive qualities for biocompatibility including near-inertness for chemical reactivity in the body, high lubricity, and broad temperature tolerance. Despite these properties and the multiple banks of testing necessary to attest to biocompatibility, absolute conclusive judgment regarding safety is not realistic. Biocompatibility instead is characterization based on current knowledge and the best judgment of accepted experts.

ABOUT ZEUS

Zeus is the world's leader polymer extrusion technologies. For over 50 years, Zeus has been serving the medical, aerospace, energy exploration, automotive, and fiber optics industries. Headquartered in Orangeburg, South Carolina, Zeus employs approximately 1,250 people worldwide and operates multiple facilities in North America and internationally. You can find us at www.zeusinc.com.

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