



TECHNICAL NEWSLETTER

Biocompatibility of Plastics

Introduction

Plastics have many unique properties in terms of their manufacturability and production possibilities, and these are being increasingly 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 GDP growth for several years. This trend is predicted to continue into the future with the aging population, improvements in plastics technology (both materials and processing), and the development of increasingly innovative medical devices.

Despite this significant growth, one thing remains constant. The application of any material in a medical device must continue to meet stringent requirements:

- It must be biocompatible to the levels required for the specific use.
- It must comply with complex legislative and regulatory requirements.
- It must comply with environmental regulations.

Biocompatibility

Biocompatibility is a general term used to describe the suitability of a material for exposure to the body or bodily fluids. It is the ability of a material to perform with an appropriate response in a specific application and is very dependent on the particular application or circumstances.

A material will be considered biocompatible (in a specific application) if it allows the body to function without any complications such as allergic reactions or other adverse side effects.

Biocompatibility is not the same as sterility. Sterility is the treatment of a material to remove or destroy all living organisms (including bacterial or fungal spores), and does not concern itself with the actual biocompatibility of the material.

If a material is used that is not biocompatible there may be complications such as:

- Extended chronic inflammation at the contact point or where leachates interact with the body
- Generation of materials that are toxic to cells (cytotoxicity)
- Cell disruption



- Skin irritation
- Restenosis (narrowing of blood vessels after treatment)
- Thrombosis (formation of blood clots)
- Corrosion of an implant (if used)

Lack of biocompatibility can result in disruption of the normal healing processes and additional complications. Biocompatibility is vital for medical devices.

Testing and Assessment

Biocompatibility testing is essential for all materials that will be used in medical devices to minimize any potential hazards to the patient. This should consist of *in vitro* assessments (studies carried out in an artificial environment) and *in vivo* assessments (studies carried out in living organisms) that are relevant to the device application. Testing should also include a medical device safety evaluation to assess the risks of normal use and any possible misuse of the device.

No single test is sufficient to define biocompatibility and a variety of tests are necessary to determine biocompatibility, depending on the device and application.

ISO 10993/EN 30993: Biological Evaluation of Medical Devices

Medical devices sold in the EU must comply with the EU Medical Devices Directive 93/42/EEC. This specifies the safety assessment requirements to ensure that patients are not exposed to unnecessary risks. The Directive uses the safety assessments of ISO 10993/EN 30993 (Biological Evaluation of Medical Devices) as a method to define the testing required for devices that are directly or indirectly in contact with the body or bodily fluids. Compliance with the Directive is necessary to achieve CE marking of products for sale inside the EU.

Eighteen parts of ISO 10993 have been issued with more parts under development for future requirements (listed in Table 1 below).

Part 1 of the standard defines how to categorize the safety testing and the other parts define animal welfare requirements, sample preparation and the individual tests.

ISO 10993 Structure	
Part	Title
1	Evaluation and testing
2	Animal welfare requirements
3	Tests for genotoxicity, carcinogenicity 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, mechanical and morphological characterization (under development)
20	Principles and methods for immunotoxicology testing of medical devices (under development)

Table 1 - The structure and parts of ISO 10993: Biological evaluation of medical devices.

The first stage of ISO 10993 is material characterization. If the material and use are the same as a device that has been historically safe, then biological evaluation may not be required and unnecessary testing can be avoided. For new materials and uses ISO 10993 provides a methodology for choosing a biological evaluation test program.

The test program chosen depends on the ISO 10993 device category. This is based on the material used, the device category and the contact regime. In each category the length of contact is also important in setting the test program. Limited contact is regarded as less than 24 hours, prolonged contact is between 24 hours and 30 days, and permanent contact is greater than 30 days. The device categories and examples are given in Table 2 (below).

ISO 10993 Device Categories			
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 intrainestinal 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 communicating 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, subperiostealimplants, 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

Table 2 - The device categories and example products of ISO 10993: Biological evaluation of medical devices (from ISO 10993: Part 1).

Once the device category, contact regime, and contact timescale have been determined, ISO 10993 suggests the required biological testing for biocompatibility validation. ISO 10993 is not a formal checklist but a guide to the typical information requirements of approval authorities that can be used to design a testing program. The actual details of the specific tests required are too complex for this Newsletter and readers are referred to the relevant Parts of ISO 10993.

United States

There are some significant differences between practice in the USA and the ISO but the test methods used are very similar. Generally ISO test results are acceptable for applications in the USA.

United States Pharmacopoeia (USP)

The USP has largely been superseded by ISO 10993 but some manufacturers have used the USP in the past for testing medical devices. This was primarily the USP 88 Biological Reactivity Tests for *in vivo* testing to rate plastics in Classes I to VI. These tests measured the biological response of animals to the plastic by direct or indirect contact, or by injection of extracts from the material. The tests are:

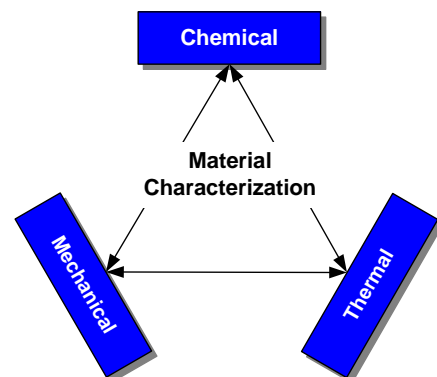
- Systemic Injection Test (intravenous and intraperitoneal)
- Intracutaneous Test
- Implantation Test

The tests are classification based (Classes I to VI) from the responses to various specified extracts, materials, and routes of administration. The systemic injection test and the intracutaneous test use extracts prepared at one of three standard temperature/time regimes: 50°C for 72 hours, 70°C for 24 hours or 121°C (250°F) for 1 hour.

Material Characterization

Any assessment of biocompatibility requires good material characterization to ensure that the biocompatibility assessment is dealing with a well-defined material. Without adequate material characterization, the biocompatibility testing cannot be related to a specific material and is therefore of little use. Material characterization should be used to the extent that it is possible to positively identify the material being used.

This is of particular importance with plastics where nominally similar grades may contain varying amounts and types of plasticizers, stabilizers and fillers. These additives are critical in biocompatibility, and not only the



The elements of material characterization



type but the amount of additives must be positively identified. This information is critical in leaching studies where leachates can be toxic or lead to biocompatibility concerns.

One particular aspect of material characterization is the effect of sterilization on the plastic. Medical devices may be sterilized once (for single-use products) or subjected to multiple sterilizations (for multiple use products). Material characterization should consider sterilization, and the effect thereof, at an early stage to ensure that the complete product can be sterilized as required with no loss of properties or other deleterious effects.

Chemical testing

Chemical testing for material characterization can use a variety of techniques such as:

- Infrared analysis - This can be used to provide detailed qualitative (and semi-quantitative) information on the material present.
- Extraction analysis - This provides information on potential leachates by a variety of agents.
- Chromatography - Gas or liquid chromatography can be used to characterize additives, residual monomers and even degradation products from manufacturing.
- Trace metal analysis - This can be used to identify the presence and amount of trace metals such as lead, tin, barium, etc. which are added as part of the compounding of the plastic.

Mechanical testing

Mechanical testing such as a stress-strain test will identify the basic mechanical properties of the plastic. While not directly concerned with biocompatibility this information enables manufacturers to ensure that the chosen plastic will adequately perform in the application. Mechanical failure in a medical device can be as much of a concern as a biocompatibility failure.

Thermal testing

Thermal techniques such as Differential Scanning Calorimetry (DSC) and Thermal Graphic Analysis (TGA) can also be used as part of material characterization to identify thermal characteristics such as the melting point (T_m), the glass transition temperature (T_g) and other thermal properties.

Biocompatible Plastics

There is a large range of biocompatible base plastics that can be used for the manufacture of medical devices but this does not mean that all the possible compounds and variants of these plastics are biocompatible. Equally, not all plastics are suitable for the most demanding



categories and assessment for each individual application is required. Typical plastics and applications are given in Table 3.

Plastic family	Typical applications
Polyvinylchloride (PVC)	PVC is the largest volume medical plastic and can be biocompatible in both the plasticized and unplasticized grades. Large volumes are used for blood tubing, on peristaltic pumps (particularly Tygon® tubing) and as blood bags.
Polytetrafluoroethylene (PTFE)	Tubing (single and multi-lumen), endoscopes, cannulas, catheter linings, synthetic blood vessels (arterial grafts), patches for soft tissue regeneration, surgical sutures, reconstructive and cosmetic facial surgery
Polyethersulfone (PES)	Tubing (single and multi-lumen), catheters
Polyethylene (PE, of various types)	PE-UHMW is used for implantable products, surgical cables and orthopedic sutures, artificial tendons. PE-LD & HD for tubing
Polyurethane (PU)	Breathable wound dressing films
Ultem® (Polyetherimide, PEI)	Sterilizable and reusable applications, surgical skin staplers
Polycarbonate (PC)	Medical instruments and containers with glass transparency, check valves and tubing connectors
Polyetheretherketone (PEEK)	Dentistry products, rigid tubing
Polysulfone (PS)	Surgical and medical devices, clamps, artificial heart components, heart valves
Polypropylene (PP)	Heart valve structures

This list is only a small part of the possible applications of plastics in medical devices. Many plastics have good biocompatibility and the range of applications is rapidly increasing. New products are constantly being developed and traditional materials are being substituted by plastics.

Fluoropolymers and biocompatibility

The fluoropolymers, as a group of materials, have excellent biocompatibility and are used in medical applications in a wide variety of ways, such as:

- Single-lumen Tubing
- Special profiles
- Heat shrink tubing



- Monofilament
- Multi-lumen tubing
- Radio-opaque tubing

Biocompatibility with the fluoropolymers is not generally a concern. Many of the materials are approved to USP Class VI, such as PTFE, FEP, PFA, ETFE, and ePTFE.

Summary

Biocompatibility of plastics is a complex area because of the variety of plastics, the additive systems that are available, and the variety of exposure regimes to which they may be subjected. No possible range of assessment procedures for biocompatibility will ever be able to provide a conclusive judgment of safety - the best that can be achieved is a reasonable assessment based on the current knowledge. The use of plastics in medical device applications, especially the fluoropolymers, will continue to increase, providing more cost-effective solutions to the ever-growing demands of modern medical technology.

How Zeus Can Help

With a technical inside and outside sales force backed up with engineering and polymer experts, Zeus is prepared to assist in material selection and can provide product samples for evaluation. A dedicated R&D department staffed with PHD Polymer chemists and backed with the support of a world-class analytical lab allows Zeus an unparalleled position in polymer development and customization.

Since 1966 Zeus has been built upon the core technology of precision extrusion of high temperature plastics. Today, with a broad portfolio of engineered resins and secondary operations, Zeus can provide turnkey solutions for development and high-volume supply requirements.

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