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Biocompatibility Testing for Medical Devices: "The Big Three"

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With the tremendous growth of the implantable device market and continuous emergence of new medical device technologies, the FDA has established a renewed concern regarding medical device biocompatibility. In June 2016, the FDA released an updated Industry Guidance for the Use of International Standard ISO 10993. Among the updates in this document is an expanded table of Biocompatibility Evaluation Endpoints, which can be seen in Figure 1. Previous versions of the guidance only listed the ISO 10993-1 recommended endpoints based on the type of medical device, the type of patient contact, and the duration of patient contact (denoted by X's in Figure 1). However, an updated version of this guidance now includes additional FDA recommended endpoints to consider (denoted by O's in Figure 1). Hence, it is important to have an understanding of medical device biocompatibility testing as outlined in ISO 10993, and which tests need to be considered for a given device.

In terms of biocompatibility, one will often hear reference to "The Big Three." This refers to cytotoxicity, sensitization, and irritation testing. Testing these three biological effects are required on most medical devices regardless of category, patient contact, and duration of use. Cytotoxicity testing (ISO 10993-5) is currently the only *in vitro* test of the big three and assesses the effects of leachables, which can be drawn out of the device, on living cells. This testing uses L929 mouse fibroblast cells (or one of several other cell lines endorsed by ISO experts) and results can be evaluated via quantitative methods (e.g., Neutral Red Uptake, MTT, XTT, and Colony Formation) and qualitative methods (e.g. Qualitative morphological grading of cytotoxicity of extracts). Analysts can record the presence of granules, signs of apoptosis or cell death, and cell proliferation or growth when evaluating cytotoxicity.

Sensitization testing (ISO 10993-10) is an *in vivo* test that evaluates the ability of leachables to cause Type IV Hypersensivity (i.e., delayed hypersensitivity). The tests are designed to determine if a patient will develop a reaction with repeated exposure to a medical device. Type IV Hypersensitivity is a cell-based immune reaction that results in edema and erythema, or swelling and redness respectively.

Figure 1

Medical device categorization by			Biological effect													
Nature of Body Contact		Contact Duration														
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity	Degradation	
Surface device	Intact skin	A	X	X	X											
		B	X	X	X											
		C	X	X	X											
	Mucosal membrane	A	X	X	X											
		B	X	X	X	O	O	O		O						
		C	X	X	X	O	O	X	X	O		O				
	Breached or compromised surface	A	X	X	X	O	O									
		B	X	X	X	O	O	O		O						
		C	X	X	X	O	O	X	X	O		O	O			
External communicating device	Blood path, indirect	A	X	X	X	X	O				X					
		B	X	X	X	X	O	O			X					
		C	X	X	O	X	O	X	X	O	X	O	O			
	Tissue/bone/ dentin	A	X	X	X	O	O									
		B	X	X	X	X	O	X	X	X						
		C	X	X	X	X	O	X	X	X		O	O			
	Circulating blood	A	X	X	X	X	O		O		X					
		B	X	X	X	X	O	X	X	X	X					
		C	X	X	X	X	O	X	X	X	X	O	O			
Implant device	Tissue/bone	A	X	X	X	O	O									
		B	X	X	X	X	O	X	X	X						
		C	X	X	X	X	O	X	X	X		O	O			
	Blood	A	X	X	X	X	O		O	X	X					
		B	X	X	X	X	O	X	X	X	X					
		C	X	X	X	X	O	X	X	X	X	O	O			

The gold standard for sensitization testing is the Magnusson & Kligman (M&K) Assay. The M&K Assay works by inducing and then re-exposing a medical device or device extract to determine if repeated exposures result in redness and swelling. The results of the M&K Assay are graded qualitatively using the Magnusson and Kligman Scale where a zero indicates no visible reaction and a three indicates intense redness and/or swelling.

Irritation testing (ISO 10993-10) is similar to sensitization; however, irritation testing evaluates the ability of a medical device to cause an immediate reaction. An irritant is a material which produces an inflammatory response as a result of a direct damaging effect to the skin (or other tissue). In severe cases, an irritant can even cause vesiculation and/or necrosis. Irritation testing is performed much like the M&K Assay with the exception that there is no induction step. To evaluate irritation, the medical device, or device extract, is directly applied and the level of redness and swelling observed. Similar to the M&K scale, the irritation response is qualitatively graded using a Primary Irritation Index that indicates the severity of the reaction from negligible to severe.

While "The Big Three" biocompatibility tests are the most widely performed, there are several other tests that also need to be considered in accordance with ISO 10993 to fully evaluate the biological effects of medical devices. For example, systemic toxicity (ISO 10993-11), implantation (ISO 10993-6), genotoxicity (ISO 10993-3) and hemocompatibility (ISO 10993-4) are all biological effects that need to be considered depending on the intended use of a medical device.

Simple *in vitro* tests such as cytotoxicity are relatively inexpensive in comparison to the much more time and resource consuming *in vivo* tests such as sensitization, irritation, systemic toxicity and implantation. However, in order to save costs, time, and potential issues with an FDA submission, it is important to gain a basic understanding of these tests. This basic background knowledge will help engineers understand the importance of these tests, why they have to be performed, the potential dangers of each test, and the impact a medical device may have on the test. With a basic understanding of biocompatibility testing for medical devices, companies will be equipped with the knowledge that is necessary to sufficiently present information to the FDA and get their device submissions approved.

Eurofins Medical Device Testing is a global leader for biocompatibility testing of medical devices. Our toxicologists have expertise in a wide range of products and manufacturing processes to help assess the risks of a new device design or process change and develop an appropriate testing program for assessing the safety of your products. Our experts are industry leaders in medical device biocompatibility and are actively engaged in the effort to reduce unnecessary animal testing. With more than 30 years of experience, Eurofins Medical Device Testing will provide you with the technical advice to ensure the success of your product development and the necessary regulatory compliance expertise to support your international regulatory submissions. Our GMP/GLP/ISO 17025 testing facilities ensure rapid turnaround times with the highest level of service. Our philosophy is to be more than a testing laboratory; we strive to be your global testing partner.

References:

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