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Biocompatibility Testing for Medical Devices: "The Big Three"

With the tremendous growth of the implantable device market and continuous emergence of new medical device technologies, the FDA has increased scrutiny of medical device biocompatibility. Additionally changes to ISO 10993 are being considered including a new ISO 10993-1, which may contain an expanded contact category and a modified table of Biocompatibility Evaluation Endpoints. The current ISO 10993-1 (2018) document includes an expanded table of Biocompatibility Evaluation Endpoints, which can be seen 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 duration and nature of patient contact.

Cytotoxicity testing (ISO 10993- 5) assesses the effects of leachables, which can be drawn out of the device, on living cells. This testing uses L929 mouse fibroblast cells, and results can be evaluated via quantitative methods (e.g., Neutral Red Uptake, MTT, XTT, and Colony Formation) or 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.

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 10993-23) determines if a medical device will immediately cause a reaction when it comes in contact with the patient. 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 may also need to be considered in accordance with ISO 10993 to fully evaluate the biological effects of your specific 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. 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, whether or not there are any properties of the device that might lead to a false positive, and how best to prepare a sample that most accurately represents the biological response to the final finished product. It may also reduce the need for animal testing, replacing some of these

tests with literature review and toxicological assessment. 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.

Medical Device categorization by			Endpoints of biological evaluation															
Nature of Body contact		Contact Duration	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material Mediated pyrogenicity	Acute systemic toxicity	Subacute toxicity	Subchronic toxicity	Chronic toxicity	Implantation effects	Hemocompatibility	Genotoxicity	Carcinogenicity	Reproductive/developmental toxicity	Degradation
Category	Contact	A - limited (< 24h) B - prolonged (>24 h to 30 d) C - long term (>30 d)															
Surface medical device	Intact Skin	A	X	E	E	E											
		B	X	E	E	E											
		C	X	E	E	E											
	Mucosal Membrane	A	X	E	E	E											
		B	X	E	E	E		E	E			E					
		C	X	E	E	E		E	E	E	E	E		E			
	Breached or compromised surface	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E	E		
External Communicating medical device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue/ bone/ dentin	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulating blood	A	X	E	E	E	E	E					E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
Implant device	Tissue/ Bone	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Blood	A	X	E	E	E	E	E				E	E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

Figure 1. Biocompatibility Evaluation Endpoints derived from ISO 10993-1 (2018)

References:

ISO 10993-1:2018, Biological Evaluation of Medical Devices — Part 1: Evaluation and testing within a risk management process.

US-FDA Guidance Use of International Standard ISO 10993 -1, "Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing within a Risk Management Process" of 8 September 2023.

ISO 10993-5:2009, Biological Evaluation of Medical Devices — Part 5: Tests for in vitro cytotoxicity.

ISO 10993-10:2021, Biological Evaluation of Medical Devices — Part 10: Tests for skin sensitization.

ISO 10993-23:2021, Biological Evaluation of Medical Devices — Part 23: Tests for irritation.

ISO 10993-3:2014, Biological Evaluation of Medical Devices — Part 3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity.

ISO 10993-6:2016, Biological Evaluation of Medical Devices — Part 6: Tests for local effects after implantation.

ISO 10993-11:2017, Biological Evaluation of Medical Devices — Part 11: Tests for systemic toxicity.

ISO 10993-4:2017, Biological Evaluation of Medical Devices — Part 4: Selection of tests for interactions with blood.