eurofins | Medical Device Testing

Biological Evaluation of Medical Devices as an Essential Part of the Risk Management Process: Updates and Challenges of ISO 10993-1:2018

by Alice Cambiaghi, Eurofins Medical Device Testing

Abstract

Despite the numerous benefits of medical devices, all present some degree of risk even when used appropriately. For this reason, risk assessments of medical devices must include a Biological Safety Evaluation Plan. Such an evaluation plan is described in the ISO 10993 series of standards for both Europe and the United States.

According to the ISO 10993 standards, the biological risk has to be estimated within the scope of risk management in order for the medical device to be considered biocompatible. The responsibility for evaluating the biocompatibility of a final device lies with the manufacturer who should refer to these standards at the earliest phase of the product life cycle in order to plan a strategic and targeted approach to fulfill regulatory requirements.

In August 2018, a new version of ISO 10993-1 was published, which highlighted the importance of gaining deeper knowledge of the device. In the new version of the standard, not all biological effects should be assessed by biological testing. Some tests can now be waived if there is a sound rationale to support the decision. However, such a decision can only be derived from a full understanding of the device, its constituents, and its manufacturing process.

Eurofins Medical Device Testing can support manufacturers through this process, issuing a proper Biological Safety Evaluation Plan where all information already available is gathered and evaluated. This plan can guide manufacturers in finding a suitable approach for the proper testing strategy, which will help avoid additional time and expense. The Biological Safety Evaluation Plan, together with the final overall biological evaluation (i.e. the Biological Evaluation Report), can help the manufacturer fully understand the device and its biocompatibility. Moreover, these documents are useful for U.S. FDA submission and/or CE marking, since they are becoming more frequently used by regulatory authorities.

This new smart approach to biological evaluation is presented in this whitepaper, together with a brief description of relevant ISO 10993 standards.

Introduction

Despite all of the beneficial effects of medical devices, they must satisfy general safety and performance requirements[1] since contact with the human body can generate risks. In fact, when the materials composing the medical device are well known, their combination in the final medical device and the manufacturing, sterilization, and post-manufacturing processes can, in some way, modify their characteristics and generate concerns in terms of biocompatibility.

Manufacturers must demonstrate that medical devices are safe, but how can they succeed in this task? There is no standard pathway to follow. Manufacturers have to show scientific proof of safety, which can lead to a smooth review process with regulatory authorities that is time-saving and cost-effective.

Before clinical evaluation, pre-clinical analysis must be performed on medical devices to evaluate the interaction with the patient on the basis of the device's nature, duration of the contact, and part of the body involved, as specified in ISO 10993-1.[2]

The primary aim of ISO 10993 series is protection from potential biological risks arising from the use of medical devices. Indeed the referenced standards are not intended to provide a rigid set of test methods, including pass/fail criteria, but they should be considered as a guidance for the application of the risk management process to medical devices. Therefore, the ISO 10993 series provides an essential tool for the evaluation of potential biological risks of a medical device. They consist of a series of

Medical Device categorization by			Endpoints of biological evaluation														
Nature of Body contact		Contact Duration															
Category	Contact	A - limited (< 24h) B - prolonged (>24 h to 30 d) C - long term (>30 d)	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
Surface device	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 surfaces	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 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 [J]			
		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/ 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		
	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 – Brand New table A1 of ISO 10993-1:2018

X - prerequisite information needed for a risk assessment.

E - endpoints to be evaluated in the risk assessment (either through the use of existing data, additional endpoint-specific testing, or a rationale for why assessment of the endpoint does not require an additional data set). If a medical device is manufactured from novel materials, not previously used in medical device applications, and no toxicology data exists in the literature, additional endpoints beyond those marked "E" in this table should be considered. For particular medical devices, it may be appropriate to include additional or fewer endpoints than indicated.

J - for all medical devices used in extracorporeal circuits.

standards, which suggest ways to perform biological evaluations, describe biological effects that should be considered, and offer tests that could be performed. In particular, these biocompatibility tests are used to determine potential harmful effects of a medical device with direct or indirect contact with the human body, through *in vitro* and/or *in vivo* methods.

ISO 10993-1 describes the framework for a biological evaluation and is considered the "gold standard" in terms of biological assessment in both Europe and the United States. The accompanying document, "Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process - Guidance for Industry and Food and Drug Administration Staff," should be considered as well.[3]

Recently, ISO 10993-1 has been revised, and its new version became available in August 2018. The most relevant differences with the superseded standard are listed below:

Table A1 of Annex A of ISO 10993-1:2018 (see Figure 1) includes a complete list of all the biological endpoints that should be evaluated in the risk assessment. Annex A, "Endpoints to be addressed in a biological risk assessment," was revised as normative, and Table A1 was changed to allow new columns for specific endpoints in line with FDA requirements (See Figure 1). Introduction of a new approach for the evaluation of transitory contacting devices for products made with coatings or lubricants, cumulative use should be considered.

Also the introduction of a new approach for evaluating surface-contacting devices used in sterile or non-sterile environments, including components that can come into contact with a user's gloved or ungloved hands, should be considered. If these types of components can be shown to be made from materials in common use for other consumer products with a similar nature of contact, no further biological evaluation is needed.

The addition of information for evaluating non-contacting devices, nanomaterials, absorbable materials and breathing gas pathways in healthcare applications is referenced in ISO 18562 series.

This matrix, which specifies the risks associated with a medical device to be addressed within a biological risk assessment, should now be considered as a framework for the selection of endpoints to consider instead of a checklist of required biocompatibility tests, as the "checklist approach" does not take into account some aspects of the medical device safety and it does not allow its full understanding.

Therefore, the biological evaluation of a medical device shall follow a more targeted strategy, and each biological effect listed in the table should be evaluated on its own.

Testing Approach

The approach to the biological evaluation has changed the assessment based upon the review of established scientific data and physico-chemical characterization, whereas *in vitro* and *in vivo* testing should be carried out only to fill gaps in our understanding.

It is important to understand that biological effects can be addressed in different ways besides biocompatibility testing. This explains why the assessment of an endpoint does not imply the performance of an additional set of tests. This is also in accordance with the 3Rs principle (Replacement, Reduction and Refinement) and ISO 10993-2, which requires that any pain, suffering, distress, or lasting harm to the animals used shall be minimized.[4]

So, which is the right testing strategy? As already mentioned, the new version of ISO 10993-1 emphasizes the importance of a chemical characterization preceding any biological testing. Physico-chemical and morphological properties of a device and of its constituents should also be considered if they have an impact on biocompatibility (see ISO/TS 10993-19.) Before performing any tests, especially *in vivo,* we need a better understanding of the medical device by analyzing its composite materials, manufacturing, sterilization and other post-manufacturing processes.

On the basis of this preliminary evaluation, the intrinsic properties of a medical device can be understood; so it will be possible to establish the endpoints requiring further investigations through biological testing. Chemical characterization and toxicological evaluation may provide information related to long-term systemic effects; therefore they may allow the waiver of some tests. Also, other effects, including cytotoxicity, irritation, and sensitization might not be adequately assessed using a chemical characterization or risk assessment approach; so it may be necessary to conduct suitable biological tests.

When testing is deemed necessary, it must be performed on the final device or representative samples and processed in the same manner, including sterilization, if needed.

A brief description of the biological tests, which could be performed on a medical device, are reported below.

Cytotoxicity tests, described in ISO 10993-5:2009, employ cell culture techniques to determine the lysis of cells (cell death), the inhibition of cell growth, colony formation, and other effects on cells caused by the medical device.[8] Cytotoxicity is considered a pilot project test since it is an important indicator for toxicity evaluation of medical devices. It is a simple and fast *in vitro* test with a high sensitivity[9]. Three types of cytotoxicity tests are listed in ISO 10993-5: extract, direct, and indirect contact tests. Both a qualitative and a quantitative (i.e. NRU or other equivalent techniques) evaluation should be carried out. Reduction of cell viability by more than 30% compared with the negative control is considered a cytotoxic effect. Cytotoxicity data should be evaluated in relation to other biocompatibility test results on the medical device and in relation to its intended use. In fact, cytotoxicity tests are primarily an indication of potential for *in vivo* toxicity. A device cannot be determined to be suitable or unsuitable for a given clinical application based solely on cytotoxicity data.[8]

Irritation is evaluated according to ISO 10993-10:2010[10]. Irritation tests can be used to estimate the irritation potential of medical devices, materials and/or their extracts, on appropriate sites for application, such as skin, eye and mucosal membranes, using a suitable model. The test(s) performed shall be appropriate for the route and duration of exposure or contact. Where the determination of irritation by dermal or mucosal tests is unsuitable, the intracutaneous reactivity test can be performed to assess the localized reaction of tissue to the tested device.

Although the current version issued in 2010 recognizes the need to follow scientific progress that already uses recognized methods as validated alternatives to *in vivo* tests, ISO 10993-10 currently only describes *in vivo* assays. Several studies have been published on the evaluation and validation of *in vitro* assays for the determination of irritating activity of chemicals as an alternative for *in vivo* irritation tests[11, 12]. A new international standard, ISO 10993-23, including *in vitro* skin irritation testing of medical devices, is in development as a replacement for the animal skin irritation studies currently indicated in ISO 10993-10[13, 14].

Sensitization is evaluated following ISO 10993-10:2010[10]. These tests can be used to estimate the potential for contact sensitization by medical devices, materials and/or their extracts, using an appropriate model. These tests are important because repeated exposure or contact to very small amounts of potential leachable substances can result in sensitization and allergic reactions.

There are currently three animal assays available for the determination of the sensitizing potential of a medical device.

These include two guinea pig assays and one murine assay. So far, the two most commonly used methods for testing for skin sensitization are the Guinea Pig Maximization Test (GPMT) and the closed-patch test (Buehler test). Of these, the maximization test is the most sensitive method, whereas the closed-patch test is suitable for topical products. The murine Local Lymph Node Assay (LLNA) was internationally accepted for testing single chemicals as a stand-alone alternative to the guinea pig assays, and is now the preferred assay for chemicals.

Systemic toxicity is evaluated according to ISO 10993-11:2017[15]. These described tests must be designed carefully to ensure that medical device components will have no systemic adverse effect[16]. An important change introduced in the last version of the standard is the addition of a new informative Annex describing concurrent parenteral administration of polar and nonpolar extracts for subchronic toxicity in rats. In fact, when a medical device is implanted or externally communicated, the patient is exposed to both polar and non-polar leachables during its clinical use. This test is designed to address this concurrent exposition with two-week treatments available to evaluate sub-chronic effects. Moreover, this also contributes to reduction in the number of animals requested for testing in line with the 3Rs principles.

Material-mediated pyrogenicity is now included among the biological effects to evaluate. Pyrogenicity information is used to help protect patients from the risk of a febrile reaction. There are two sources of pyrogens that should be considered: material mediated and enodotoxin mediated. Material-mediated pyrogens are caused by chemicals that can leach from a medical device during device use. Enodotoxin mediated pyrogens are due to the presence of bacteria. For detection of material-mediated pyrogenicity, the rabbit pyrogen test is currently recommended. Methods for performing the rabbit pyrogen test can be found in the United States Pharmacopoeia, the European Pharmacopoeia, and the Japanese Pharmacopoeia.

Genotoxicity, carcinogenicity, and reproductive toxicity effects are evaluated according to ISO 10993-3:2014[17] supplemented by ISO/TR 10993-33:2015[18]. Since no single test is capable of detecting all relevant genotoxic agents, the usual approach is to conduct a battery of *in vitro* tests, and under certain circumstances, also *in vivo* tests. These tests include a test for gene mutations in bacteria, and either an *in vitro* test with cytogenetic evaluation of chromosomal damage with mammalian cells, an *in vitro* mouse lymphoma TK assay, or an *in vitro* mammalian cell micronucleus test for chromosomal damage and aneugenicity. The carcinogenicity tests shall be performed in accordance with OECD 451 or OECD 453[19, 20]. For reproductive toxicity, testing may start with OECD 421 in order to provide initial information on possible effects on reproduction and/or development[21]. Positive results with these tests are useful for initial hazard assessment and contribute to decisions with respect to the necessity for and timing of additional tests. If additional tests are considered necessary, they shall be performed in accordance with OECD 414, OECD 415 or OECD 416, as appropriate[22-24].

Implantation is evaluated according to ISO 10993-6:2016[25]. The tests described assesses local effects on living tissues due to the implantation of a device both at macroscopic and microscopic levels. They are not intended to determine the performance of the test sample in terms of mechanical or functional loading. The test sample is implanted into a site of an animal species suitable for the evaluation of the biological safety of the material. The local effects are microscopically evaluated by a comparison of the tissue response caused by the test sample with one caused by control materials used in medical devices with established clinical acceptability and biocompatibility characteristics. The objective of the test is to characterize the history and evolution of the tissue response after implantation of a device/biomaterial, including an evaluation of its final integration or absorption/degradation. The test period shall be chosen on the basis of the likely clinical exposure time or will be continued until or beyond reaching

biological response. This evaluation should be done according to a scoring system ranging from minimal or no reaction, slight reaction, moderate reaction, and severe reaction.

Even if ISO 10993-6 does not discuss systemic toxicity, carcinogenicity, teratogenicity, or mutagenicity, the long-term implantation studies intended for evaluation of local biological effects might provide insight into some of these properties. Systemic toxicity studies conducted by implantation might satisfy the requirements of this part of ISO 10993. Therefore, when conducting combined studies for evaluating local effects and systemic effects, the requirements of both standards should be fulfilled.

ISO 10993-4:2017 considers the evaluation of hemocompatibility for any medical device that has contact with circulating blood, directly or indirectly[26]. This standard identifies two test categories for hemocompatibility (hemolysis and thrombosis) and provides a structured test-selection system based on the intended use of the device. Although it does not describe test methods or evaluation criteria, it cites various applicable standards, such as ASTM F756, ASTM F1984[27, 28].

Indications on sample preparation for biological testing are reported in ISO 10993-12[29]. If extracts of the devices are prepared, the solvents and conditions of extraction used should be appropriate to the nature and use of the final product, as well as to the predictability (such as test purpose, rationale, sensitivity, specificity, etc.) of the test method. Whenever possible, the extraction conditions selected should represent at a minimum, an exaggeration of use conditions. Requirements of U.S. FDA for extraction conditions differ from ISO requirements. For chemical characterization, the use of three extraction solvents instead of two is deemed appropriate. Furthermore, for prolonged contact devices and for those categorized as permanent implants, extraction at 37°C may not be sufficient to obtain an extract that represents the chemicals extracted over the duration of device use. In these cases, extraction at 50°C for 72 hours is deemed appropriate.

The Biological Evaluation Plan

The new approach of ISO 10993-1 underlines the importance to thoroughly analyze a device in order to fully understand it before testing begins. Therefore, biological evaluation is now set in the context of broader risk management processes where the consideration of biological risks is only one aspect of the risk assessment of a medical device. The entire biological evaluation process should be planned in advance. And only after having identified the possible biocompatibility hazards and determined the risks that they might pose to the patient, can a biocompatibility safety evaluation plan be strategized.

A risk management plan should start with an evaluation of the physical and chemical characteristics of the device and an analysis of its intended use. Any history of clinical use or human exposure data and any existing toxicological and other biological safety data should be included. The approach suggested by Eurofins Medical Device Testing, consistent with current ISO 10993-1 requirements, consists of the review and evaluation of existing data from all sources, followed by the selection

and execution of additional tests only when necessary. If a potential hazard is identified, then further steps may involve referring to similar medical devices and manufacturing methods, accessing reliable information in the public domain, or performing tests to gather the data.

Even if all medical devices should be evaluated for biocompatibility, this evaluation does not automatically imply testing. In fact, depending on the final formulation, manufacturing, and application, it may result that no testing or no additional testing is needed. On the basis of this information and on the device categorization according to ISO 10993-1, the associated biological risk is identified, and a suitable strategy for biological safety evaluation plan is proposed. A biological safety evaluation plan is also useful to identify potential normative gaps and to face changes related to the device or to the production cycle. Once all the needed information has been collected and the required tests have been completed, a conclusive document that summarizes the biological evaluation performed on the device is drafted. This biological evaluation report provides an assessment of the overall safety evaluation of the device, including a description of the biocompatibility tests performed and, when necessary, solid rationales to justify any tests waived.

Conclusion

Within the framework of the risk management process, which precedes the release on the market, every finished medical device needs to undergo a complete biological safety evaluation plan assessment, according to the ISO 10993 series. This process begins with the categorization of the medical device according to type and duration of body contact in order to plan a suitable testing strategy.

As underlined in the new version of ISO 10993-1, a biological safety evaluation plan should start with the physical and/or chemical characterization of the device. After all this information has been collected, further investigations can be planned accordingly.

Eurofins Medical Device Testing can support you in this process by reviewing scientific literature and other available data, suggesting an appropriate testing strategy, including rationales for the selection or waiving tests and providing an assessment and an interpretation of the biocompatibility data generated from the tests.

References:

1. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.

2. ISO 10993-1:2018, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.

3. 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 16 June 2016.

4. ISO 10993-2:2006, Biological evaluation of medical devices - Part 2: Animal welfare requirements.

5. ISO 10993-18:2005, Biological evaluation of medical devices - Part 18: Chemical Characterization of materials.

6. ISO 10993-17:2002, Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances.

7. ISO/TS 10993-19:2006, Biological evaluation of medical devices - Part 19: Physico-chemical, morphological and topographical characterization of materials.

8. ISO 10993-5:2009, Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity.

9. Li, W., J. Zhou, and Y. Xu, Study of the in vitro cytotoxicity testing of medical devices. Biomedical Reports, 2015. 3(5): p. 617-620.

10 ISO 10993-10:2010, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization.

11. Basketter, D., A. Poole, and I. Kimber, Behaviour of chemical respiratory allergens in novel predictive methods for skin sensitisation. Regulatory Toxicology and Pharmacology, 2017. 86: p. 101-106.

12. Kolle, S.N., B. van Ravenzwaay, and R. Landsiedel, Regulatory accepted but out of domain: In vitro skin irritation tests for agrochemical formulations. Regulatory Toxicology and Pharmacology, 2017. 89: p. 125-130.

13. Alépée, N., et al., A catch-up validation study on reconstructed human epidermis (SkinEthic™ RHE) for full replacement of the Draize skin irritation test. Toxicology in Vitro, 2010. 24(1): p. 257-266.

14. Casas, J.W., et al., In vitro human skin irritation test for evaluation of medical device extracts. Toxicology in Vitro, 2013. 27(8): p. 2175-2183.

15. ISO 10993-11:2017, Biological evaluation of medical devices - Part 11: Tests for systemic toxicity.

16. Wallin, R.F., A practical guide to ISO 10993-11: Designing Subchronic and Chronic Systemic Toxicity Tests. Medical Device & Diagnostic Industry Magazine, 1998.

17. ISO 10993-3:2014, Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.

18. ISO/TR 10993-33:2015, Biological evaluation of medical devices - Part 33: Guidance on tests to evaluate genotoxicity - Supplement to ISO 10993-3.

19. OECD Guidelines for the Testing of Chemicals, Section 4, No 451 "Carcinogenicity Studies".

20. OECD Guidelines for the Testing of Chemicals, Section 4, No 453, "Combined Chronic Toxicity/Carcinogenicity Studies".

21. OECD Guidelines for the Testing of Chemicals, Section 4, No 421, "Reproduction/Developmental Toxicity Screening Test".

22. OECD Guidelines for the Testing of Chemicals, Section 4, No 414, "Prenatal Developmental Toxicity Study".

23. OECD Guidelines for the Testing of Chemicals, Section 4, No 415, "One-Generation Reproduction Toxicity Study".

24. OECD Guidelines for the Testing of Chemicals, Section 4, No 416, "Two-Generation Reproduction Toxicity".

25. ISO 10993-6:2016, Biological evaluation of medical devices - Part 6: Tests for local effects after implantation.

26. ISO 10993-4:2017, Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood.

27. ASTM F756-17 - Standard Practice for Assessment of Hemolytic Properties of Materials.

28. ASTM F1984 - 99(2018) - Standard Practice for Testing for Whole Complement Activation in Serum by Solid Materials.

29. ISO 10993-12:2012, Biological evaluation of medical devices - Part 12: Sample preparation and reference materials.