OVERVIEW OF THE TOXICOLOGICAL RISK ASSESSMENT OF MEDICAL DEVICES

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The Regulation (EU) 2017/745 on medical devices aims to ensure a robust regulatory framework capable of maintaining a high level of quality and safety for products. Among the aspects highlighted in the Regulation are biocompatibility and the chemical and physical characterization of materials.
These elements are also found in Annex I of the Regulation, which pertains to the general safety and performance requirements. This annex is crucial because, to demonstrate that a device complies with the Regulation, it is necessary to verify that all requirements have been met, and clear justification for the inapplicable ones is required.

Compliance of Medical Devices

The series of ISO 10993 standards is not mandatory but is the recognized preferential method for assessing the biocompatibility of a medical device. By applying the principles outlined in the harmonized part of the ISO 10993 series, the medical device gains a presumption of conformity to the general safety requirements in terms of biocompatibility. This series is also accepted at international level; however, many countries, such as the United States, impose additional requirements or interpret this standard differently. The ISO 10993 standard addresses the assessment of the biological response to medical devices, providing general guidelines rather than specific details for each type of device. It is important to emphasize that, for the purpose of demonstrating the compliance of medical devices, the applicable regulation is represented by the Regulation and must be adhered to.

Biological Evaluation

Manufacturers of medical devices must ensure the safety of their devices and minimize potential risks, including biological risks. The assessment of the biological safety of medical devices is conducted to determine the potential toxicity resulting from the contact of the device's materials with the body. These materials must not produce local or systemic adverse effects, be carcinogenic, or toxic to reproduction. Therefore, the selection of materials and substances used in a medical device becomes crucial, especially from a toxicological perspective.
A biological evaluation must be conducted exclusively in line with a risk management process, in accordance with ISO 14971:2019, Annex I, and as indicated in Figure 1 (from ISO 10993-1).

This risk management process involves identifying biological

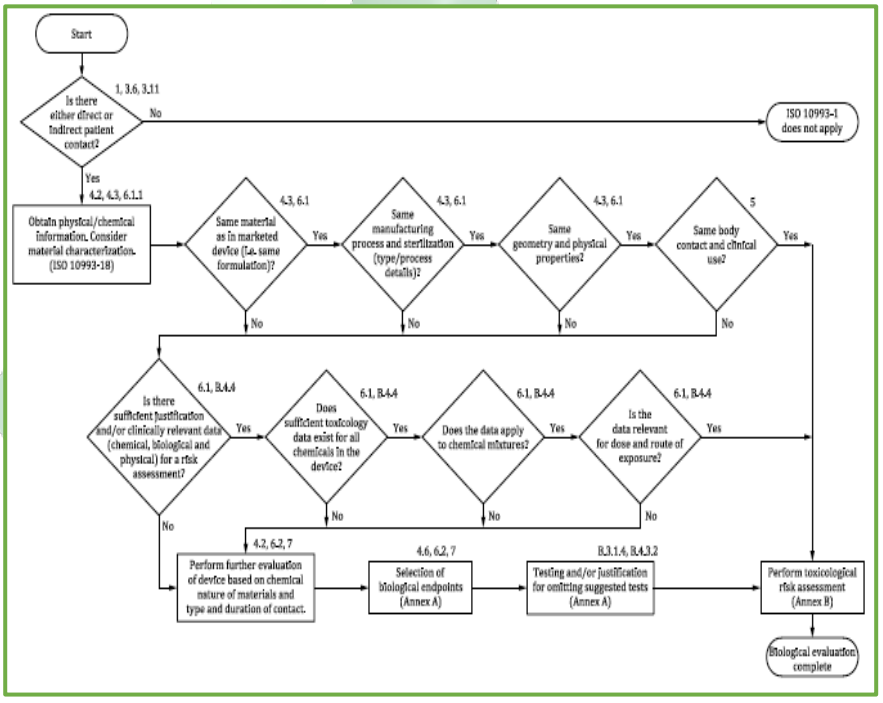


Figure 1 — Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process (from ISO 10993-1)

hazards, estimating associated biological risks, and determining their acceptability.

Risk management is understood as an iterative and continuous process that spans the entire lifecycle of a device, requiring constant and systematic updates.

The biological evaluation will commence with the categorization of medical devices based on the nature and duration of contact.

The evaluation of existing information enables a gap analysis to facilitate the selection of appropriate tests. The rigor required in the biological assessment is primarily determined by the nature, extent, frequency, and duration of exposure, as well as the identified hazards associated with the medical device or material.

Tests may not be necessary when sufficient information is already available to perform a risk assessment of the material and/or medical device.

Chemical Characterization

Chemical characterization is the first crucial step in the biological evaluation process, as highlighted by the current standard on biological evaluation, ISO 10993-1:2018. The extent of required chemical characterization depends on available toxicological, safety, preclinical, and clinical data, as well as the nature and duration of the body contact with the medical device.

ISO 10993-18 provides a flowchart describing the general chemical characterization process (see Figure 2). Chemical characterization is the process of identifying, characterizing, and understanding the constituents that may migrate from the medical device and be bioavailable to the patient. These chemical constituents are often referred to as Extractables (substances that potentially can migrate when the material is exposed to high stress) and Leachables (compounds that can potentially migrate from the device under normal conditions of use).

Following the studies on extractables and leachables, a toxicological risk assessment is conducted to evaluate safety for clinical use.

The material characterization, if conducted, should be carried out in accordance with ISO 10993-18. For extractables and leachables of devices with sufficient toxicological data related to the anticipated exposure (quantity, route, and frequency), additional tests are not required. Where there is the potential for degradation under conditions of production, sterilization, transportation, storage, and use of the medical device, the presence and nature of degradation products must be characterized in accordance with ISO 10993-9, ISO 10993-13, ISO 10993-14, and ISO 10993-15, as applicable. For materials or medical devices that may release wear particles, the potential release of nanoparticles must be considered as described in ISO/TR 10993-22.

Toxicological Risk Assessment

The standard that specifies the process and requirements for the toxicological risk assessment of components of medical devices is ISO 10993-17, the latest update of which was published on September 13, 2023, after many years since the last version.

The first difference compared to the previous version is evident from the title itself, "Toxicological risk assessment of medical device constituents," rather than "Establishment of allowable limits for leachable substances". This change

Figure 2 – General chemical characterization process (from ISO 10993-18)

highlights the shift from assessing the risk only for components potentially leachable from the device (leachables) to emphasizing the need for a toxicological risk assessment for constituents of the device itself.

Toxicological risk assessments are carried out in four main phases with the objective of scientifically identifying and estimating the real risks associated with a medical device, in accordance with ISO 14971 - Application of risk management to medical devices.

These main steps are:

- Hazard Identification
- Hazard Characterization
- Exposure Assessment
- Risk Characterization

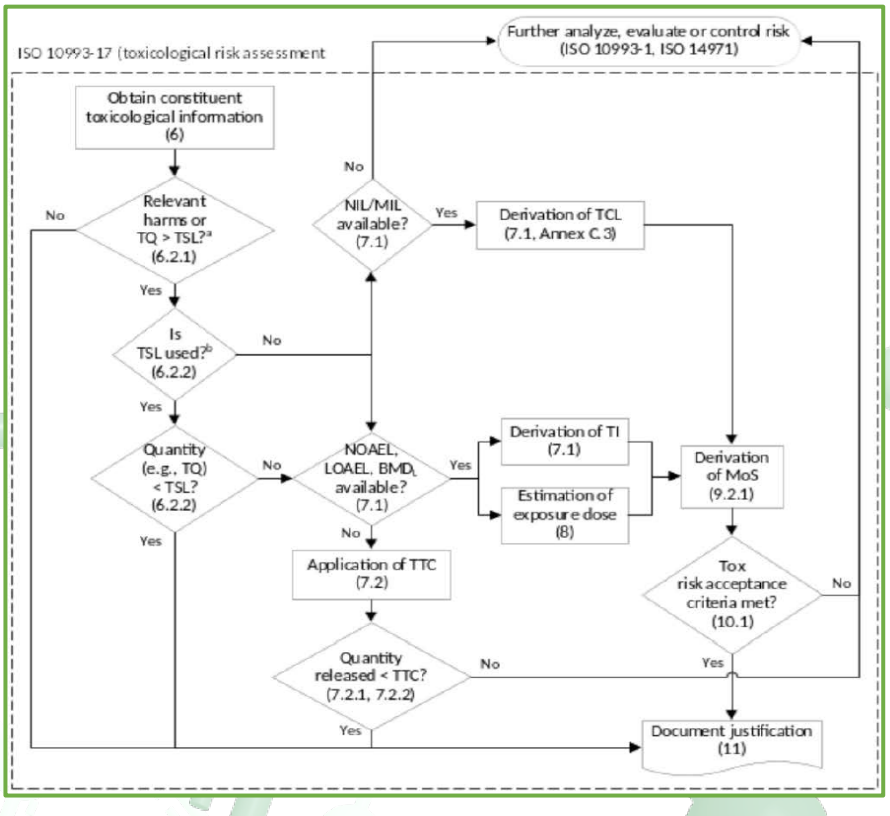
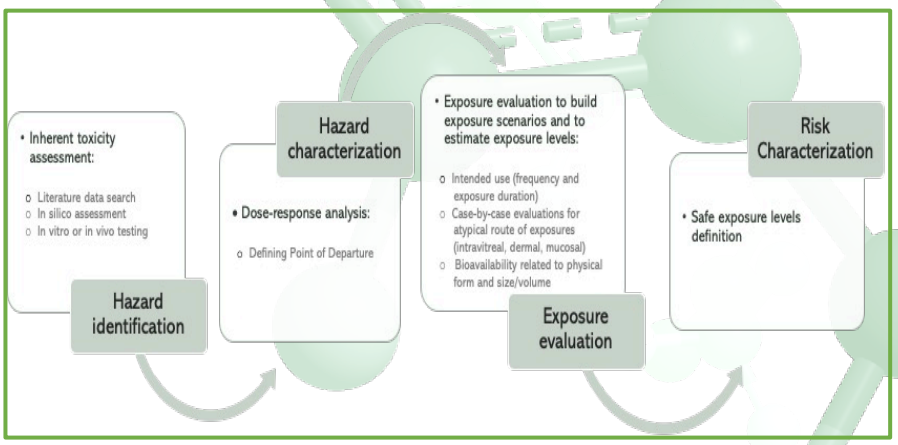


Figure 3 – Critical toxicological risk assessment activities



The 2023 revision of ISO 10993-17 introduces new calculation methods and numerous clarifications, harmonizing toxicological assessments and providing more relevant and clinically applicable conclusions for the use of the device. The new ISO 10993-17 provides a more systematic approach to toxicological risk assessment. An overview of this method is shown in Figure 3.

The toxicological risk assessment is described comprehensively based on:

- Toxicological information on the components describing potential harm and the circumstances under which harm can occur;

- Determination of a tolerable contact level or tolerable intake (TI and TCL);

- Estimation of the exposure dose in the worst-case scenario (EEDmax);

- Derivation of a MoS, as appropriate. The new ISO provides risk acceptance criteria to assess the margin of safety for each component.

During the hazard identification process, all available toxicological data on the chemical constituents/raw materials must be collected using multiple sources, and values such as NOAEL (No Observed Adverse Effect Level),

LOAEL (Lowest Observed Adverse Effect Level), or BMD (benchmark dose) derived from a relevant toxicological study should be identified as the starting point (PoD).

There are several databases used for the search of toxicological information, including:

- *PubChem (https://pubchem.ncbi.nlm.nih.gov) database on toxicology, hazardous chemicals, environmental health, and toxic substances;*
- *PubMed (https://pubmed.ncbi.nlm.nih.gov/) comprising more than 33 million citations for biomedical literature from MEDLINE, life science journals, and online books.;*
- *OECD Existing Chemicals Database (https://hpvchemicals.oecd.org/UI/Search.aspx) containing all documents associated with the final published assessment (profiles, assessment reports and dossiers) for a given compound;*
- *ECHA (https://echa.europa.eu/it/home) providing information of substances registered under REACH (i.e. hazardous properties, classification and labelling and precautions for use).*
- *IARC (https://www.iarc.fr), specialized cancer agency of the World Health Organization, it contains a database with available information on known carcinogenic risks of substances.*
- *NTP- National Toxicology Program (https://ntp.niehs.nih.gov/) providing toxicity for more than 2800 substances for potential human health.*

The selection and search criteria must be documented and justified. The reliability and quality of data must be assessed and established. When toxicity information for the chemical substance is not available, the read-across approach may be utilized. The read-across is one of the most commonly used alternative approaches, relying on relevant information regarding structurally similar analog substances with adequate toxicity data.

Biological Testing

After a careful chemical characterization and toxicological risk assessment, the evaluation of endpoints (i.e., cytotoxicity, irritation, sensitization) is conducted to examine the biocompatibility of the device.

The biological evaluation of the medical device, aligned with the principles outlined in the reference standard for risk analysis (ISO 14971), recommends conducting testing activities only when the existing data and literature on the device are inadequate to address the specified endpoints in the standard. With regard to the endpoints to be considered in a biological risk assessment, ISO 10993-1 provides a framework for developing a biocompatibility assessment. This is not a checklist for testing, but tests should be selected based on the information and risk associated with the medical device. Table I (Table A.1 of Annex A of ISO 10993-1:2018) outlines the relevant endpoints for assessment and identifies the biological effects that should be evaluated based on the categorization of the medical device, body contact, and the duration of clinical exposure.

As specified in Annex A of ISO 10993-1:2018, for a particular medical device, there is the possibility that it may be appropriate to include additional or fewer endpoints than those indicated.

The biological evaluation of the medical device suggests resorting to testing activities only if the available data and literature on the device's constituents are insufficient to cover the endpoints specified by ISO.

If existing data lead to the conclusion that the risks are acceptable, further tests to support biological safety are unnecessary. However, when

Medical device categorization by			Endpoints of biological evaluation															
Nature of body contact		Contact duration																
Category	Contact	A - limited (≤24 h) 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[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/developmental toxicity[d,e]	Degradation[f]
Surface medical device	Intact skin	A	X[g]	E[h]	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		
Externally 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[i]	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 medical device	Tissue/bone[i]	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		

[a] Refer to ISO 10993-11:2017, Annex F.

[b] Information obtained from comprehensive implantation assessments that include acute systemic toxicity, subacute toxicity, subchronic toxicity and/or chronic toxicity may be appropriate if sufficient animals and timepoints are included and assessed. It is not always necessary to perform separate studies for acute, subacute, subchronic, and chronic toxicity.

[c] Relevant implantation sites should be considered. For instance medical devices in contact with intact mucosal membranes should ideally be studied/ considered in contact with intact mucosal membranes.

[d] If the medical device can contain substances known to be carcinogenic, mutagenic and/or toxic to reproduction, this should be considered in the risk assessment.

[e] Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, medical devices with relevant target populations (e.g. pregnant women), and/or medical devices where there is the potential for local presence of device materials in the reproductive organs.

[f] Degradation information should be provided for any medical devices, medical device components or materials remaining within the patient, that have the potential for degradation.

[g] X means prerequisite information needed for a risk assessment.

[h] E means 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, there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated.

[i] Tissue includes tissue fluids and subcutaneous spaces. For gas pathway devices or components with only indirect tissue contact, see device specific standards for biocompatibility information relevant to these medical devices.

[j] For all medical devices used in extracorporeal circuits.

Table I. Endpoints to be addressed in a biological risk assessment (from ISO 10993-1:2018)

existing data are insufficient, obtaining additional information becomes necessary.
Therefore, ISO 10993-1 does not mandate medical device manufacturers to conduct all tests. However, it is crucial that, to avoid non-compliance with Notified Bodies or Authorities, all endpoints are covered with a robust scientific justification provided by competent toxicologists and experts capable of making informed decisions based on scientific data and knowledge of medical devices.
Furthermore, significant strides have been made in the effort to reduce the necessity of conducting animal tests to assess medical devices. Evaluating the risk-benefit ratio of medical devices is a crucial aspect of this endeavor; however, in many cases, the need to perform in vitro and in vivo biocompatibility studies on medical devices is inevitable.

Biological Evaluation Plan and Biological Evaluation Report (BEP - BER)

ISO 10993-1 introduces the Biological Evaluation Plan (BEP), which is a set of activities defining the biocompatibility profile of a device in relation to the biological risk it poses to the end user. This considers all available data and appropriate literature research. f the available information on the device, along with its supporting bibliography, is not sufficient on its own to cover the endpoints indicated by ISO, the BEP proposes an appropriate testing plan to minimize potential risks and ensure the safety of the end user. ISO 14971 requires that risk management activities be planned in advance. The drafting of a scientifically robust BEP necessitates experienced professionals with cross-disciplinary expertise and qualifications in both regulatory affairs and toxicology.
After conducting the tests, the next step is the preparation of the Biological Evaluation Report (BER). The BER integrates the considerations outlined in the BEP and formalizes the conclusions regarding the biocompatibility of the device based on the test results.
The process of biological risk assessment is not concluded with the development of the BEP and BER but continues throughout the entire lifecycle of the device through post-market surveillance activities. The risk assessment must be continually updated based on new information that becomes available through post-market monitoring. It is easy to understand that the technical documentation of a medical device, to be compliant with current regulations, must be well-organized and unambiguous to demonstrate the safety and performance of the medical device. The technical documentation of a medical device is a compilation of data that brings together experts from various fields. Therefore, it is essential to maintain transparent and open communication among all involved parties.

ToxHub comprises a specialized team dedicated to ensuring the safety and regulatory compliance of medical devices. Our toxicologists possess extensive experience in toxicological risk assessments for medical devices. They are available to provide technical consultancy to ensure the success in the development of your product and offer the required expertise in regulatory compliance.

References:

REGOLAMENTO (UE) 2017/745 – MDR.

ISO 14971:2019 – Medical Device, Application of risk management to medical devices. Annex I: Guidance on Risk Analysis Procedures for Biological Hazards.

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

ISO 10993-17:2023 – Biological evaluation of medical device – Part 17: Toxicological risk assessment of medical device constituents.

ISO 10993-18:2020 – Biological Evaluation of Medical Devices – Part 18: Chemical characterization of materials.