Biological Safety Evaluation of Medical Devices

Regulatory background, safety strategy

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Regulatory background - General safety requirements

Annex I of Regulation (EU) 2017/745 on Medical Devices (MDR)

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§1: "*Devices […] shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art.*"

§8: *"All known and foreseeable risks, and any undesirable side-effects, shall be minimized and be acceptable when weighed against the evaluated benefits to the patient and/or user arising from the achieved performance of the device during normal conditions of use."*

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Regulatory background - General safety requirements

Annex II of Regulation (EU) 2017/745 on Medical Devices (MDR) - Technical documentation

4. General safety and performance requirements

The documentation shall contain information for the **demonstration of conformity with the general safety and performance requirements** set out in Annex I that are applicable to the device taking into account its intended purpose, and **shall include a justification, validation and verification of the solutions adopted to meet those requirements.** The demonstration of conformity shall include :

(a) […]

(b) the **method or methods used to demonstrate conformity** with each applicable general safety and performance requirement;

(c) the **harmonised standards**, CS or other solutions applied; and

(d) the **precise identity of the controlled documents offering evidence of conformity with each harmonised standard**, CS or other method applied to demonstrate conformity with the general safety and performance requirements. […]

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Regulatory background - ISO 10993 series

Evaluate potential biological risks arising from the use of medical devices

Risk analysis and risk characterization for toxicological hazard is based on the following standards:

ISO 10993-1:2018 => Describes the general principles of the biological evaluation of materials and medical devices

ISO 10993-18:2020 => Provides information for the quali/quantitative characterization of materials and medical devices

ISO 10993-17:2002 => Gives guidance for the determination of the allowable limits for substances

Regulatory background - ISO 10993-1:2018

Evaluation and testing within a risk management process

Section 4.1

"The biological evaluation of any medical device intended for use in humans shall form part of a structured biological evaluation plan within a risk management process in accordance with ISO 14971:2019. This risk management process involves identification of biological hazards, estimation of the associated biological risks, and determination of their acceptability."

Expert assessors shall determine and document in an accurate, clear and transparent way:

- ✓ The **strategy and planned content** for the biological evaluation of the medical device;
- ✓ The criteria for determining the **acceptability of the material for the intended purpose**, in line with the risk management plan;
- ✓ The adequacy of the **material characterization**;
- ✓ The rationale for **selection and/or waiving of tests**;
- ✓ The **interpretation of existing data** and **testing results** ;
- ✓ The need for **any additional data** to complete the biological evaluation;
- ✓ **Overall biological safety conclusions** for the medical device.

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Safety strategy

Use of Biological Evaluation Plan (BEP), chemical characterization testing, biocompatibility testing and toxicological risk assessment (TRA) are all necessary components of the successful mitigation of biological risks.

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Safety strategy - Step #1 - BSEP - Initial risk assessment

- ✓ Summarizes and characterizes the medical device (nature & body contact duration)
- ✓ Assesses the materials of construction
- ✓ Reviews the manufacturing processes
- ✓ Identifies the biological endpoints of concern
- ✓ Evaluates any existing research data available
- ✓ Recommends and supports a strategy (plan) to address areas of remaining biological risk, which may include both chemical and biological testing.

"BSEP defines the evaluation of the unknown so that a sufficient amount of information can be evaluated and risk can clearly be understood and characterized."

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Safety strategy - Step #2 - Testing & Toxicological Risk Assessment (TRA)

Testing selection - ISO 10993-1:2018

Table A.1 — Endpoints to be addressed in a biological risk assessment

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		

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Safety strategy - Step #2 - Testing & Toxicological risk assessment (TRA)

- ✓ **Material characterization**

  Broad and general process of collecting existing information about a **material's chemistry, structure and other properties**, and if appropriate, new data, to facilitate the evaluation of these properties.

  Description of medical device chemical constituents and consideration of material characterization including chemical characterization (see ISO 10993-18) **shall precede any biological testing**.

- ✓ **Chemical characterization (ISO 10993-18) - E&L analysis**

  Gathering of data through testing for VOCs, SVOCs, NVOCs and inorganic elements

  Chemical characterization should then be followed by consideration of the toxicology of the known material components.

- ✓ **Toxicological Risk Assessment (ISO 10993-17)**

  Evaluate the potential health risks associated with exposure to leachable impurities, contaminants, or other residues in a medical device (calculation of Tolerable Intake (TI) and Exposure (TE) and Margins of Safety (MoS))

  If all detected levels are less than toxicity thresholds, several biological tests can be omitted.

- ✓ **Biological testing**

  In vivo testing only being carried out to fill gaps.

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Safety strategy - Step #3 - BSER - Summary report

Overall evaluation with specific consideration to:

- ✓ The type of patient contact and intended clinical use;
- ✓ Potential hazards associated with the materials of construction;
- ✓ History of clinical use of the materials of construction;
- ✓ Manufacturing process information;
- ✓ Results of biocompatibility and chemical characterization testing performed;
- ✓ Clinical history of the device;
- ✓ Final conclusion regarding biocompatibility.

*Based on the testing results and information summarized, the MEDICAL DEVICE is **biocompatible** and meets the requirements of ISO 10993-1:2018*

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