Changes in new revision of ISO 10993-1 and how this will impact your biological evaluation

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Rose-Marie Jenvert, PhD
Sr. Biocompatibility & Toxicology Manager, Veranex

ISO 10993-1:2025

ISO 10993-1 outlines how to assess the biological safety of medical devices through a risk-based approach. It helps manufacturers determine what testing or data is needed based on how a device contacts the body.

Was published in November 2025.



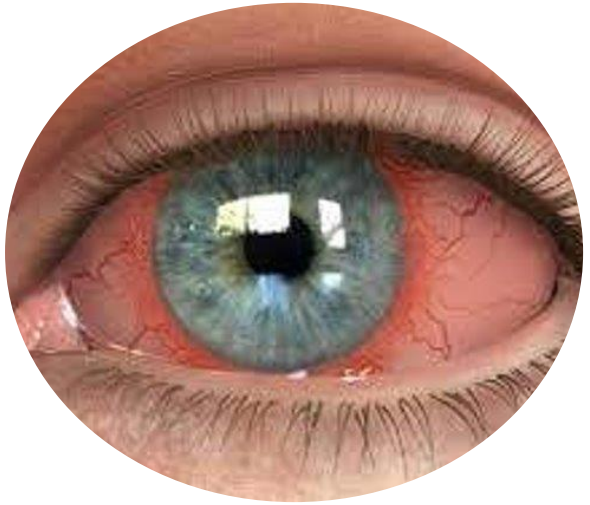
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Biocompatibility definition

ISO 10993-1:2018 AND ISO 10993-1:2025

“Ability of a medical device or material to perform with an appropriate host response in
a specific application”

Material is biologically compatible by not eliciting a local or systemic response from a living system or tissue



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ISO 10993-1:2025

Key changes:

- The document has been completely re-organized
- The title has been aligned with the risk management framework described in ISO 14971
- Risk management adopted
- Device categorization reorganized
- The identification of biological effects (previously referred to as biological end points) has been modified
- Guidance added for calculation of exposure duration
- Reasonably foreseeable misuse needs to be considered
- Bioaccumulation added as new concept
- Biological equivalence added also in this part
- Assessment of Life Cycle

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Risk Management Framework adopted

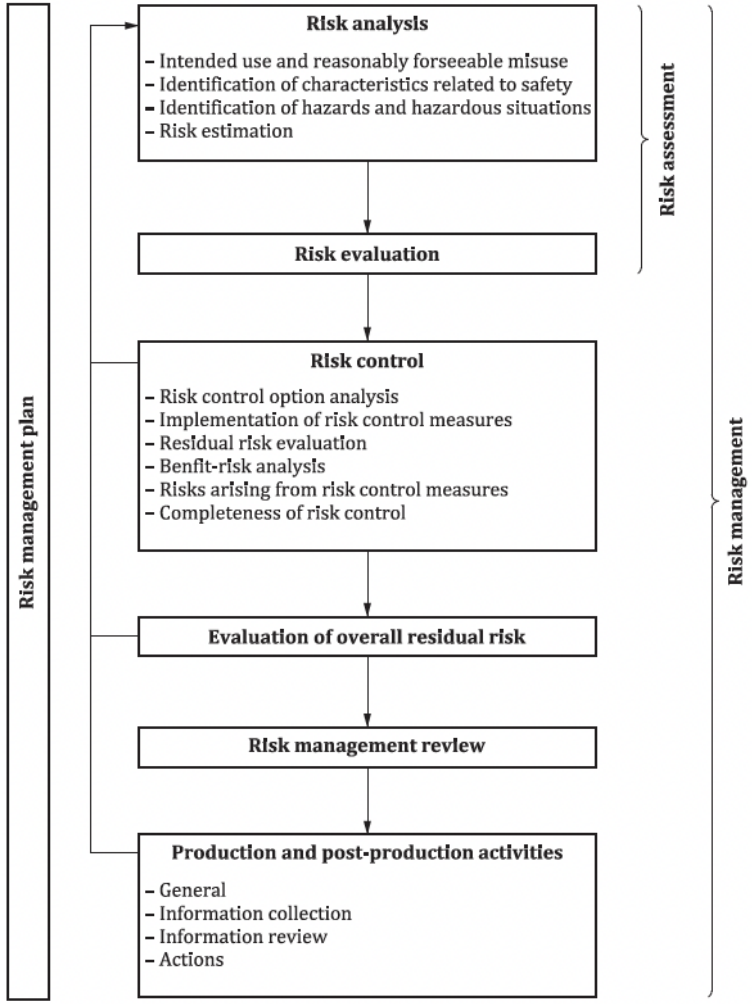
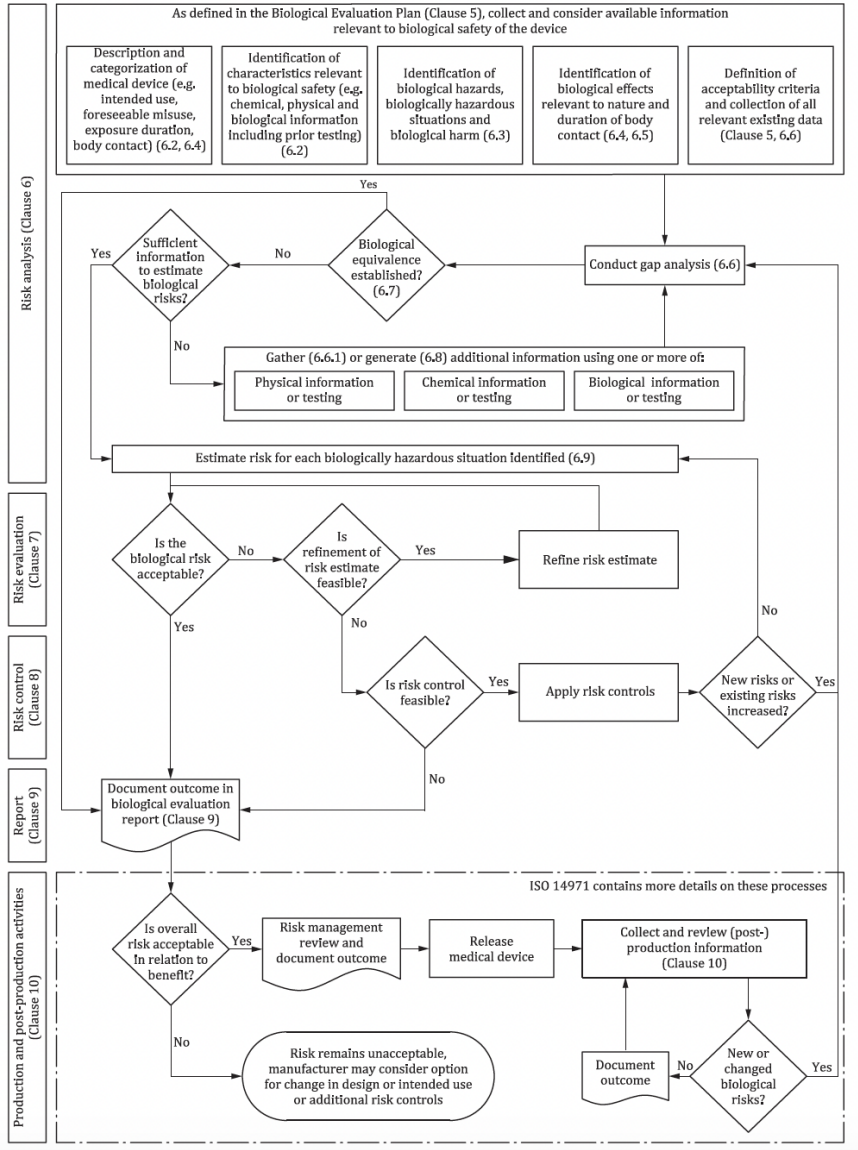


Figure 1 — ISO 14971 risk management framework



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Risk Management Process

- Biological evaluation plan
- Biological risk analysis
- Biological risk evaluation
- Biological risk control
- Biological evaluation report
- Production and post-production activities

Main clause structure reflects ISO 14971 process

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Device categorization

Nature of contact

Categorization – four groups:

- Intact skin
- Intact mucosal membranes
- Breached or compromised surfaces or internal tissues other than circulating blood
- Circulating blood

Non contacting being the 5th group

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Device categorization

Intact skin

Intact mucosal membrane

Breached or compromised surface

Circ. Blood

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	Acute systemic toxicity	Subacute toxicity	Subchronic toxicity	Chronic toxicity	Implantation effects	Haemocompatibility	Genotoxicity	Carcinogenicity	Reproductive/developmental toxicity	Degradation
Surface medical device	Intact skin	A	Xe	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		
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[l]			
		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		

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	Acute systemic toxicity	Subacute toxicity	Subchronic toxicity	Chronic toxicity	Implantation effects	Haemocompatibility	Genotoxicity	Carcinogenicity	Reproductive/developmental toxicity	Degradation
Implant medical device	Tissue/bone[i]	A	X	E	E	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		

Duration	Biological effect[a b c]							
	Cytotoxicity (6.5.2)	Sensitization (6.5.3)	Irritation (6.5.4)	Systemic toxicity (6.5.5)[d]	Local effects after tissue contact (6.5.6)	Genotoxicity (6.5.7)	Carcinogenicity (6.5.8)	Haemocompatibility (6.5.9)
A – limited (≤24 h)	E	E	E					
B – prolonged (24h to 30 d)	E	E	E					
C – long-term (>30 d)	E	E	E					

Duration	Biological effect[a b c]							
	Cytotoxicity (6.5.2)	Sensitization (6.5.3)	Irritation (6.5.4)	Systemic toxicity (6.5.5)[e]	Local effects after *tissue* contact (6.5.6)[d]	Genotoxicity (6.5.7)	Carcinogenicity (6.5.8)	Haemocompatibility (6.5.9)
A – limited (≤24 h)	E	E	E					
B – prolonged (24 h to 30 d)	E	E	E	E	E	E		
C – long-term (>30 d)	E	E	E	E	E	E	E	

Duration	Biological effect[a b c]							
	Cytotoxicity (6.5.2)	Sensitization (6.5.3)	Irritation (6.5.4)	Systemic toxicity (6.5.5)[e]	Local effects after tissue contact (6.5.6)[d]	Genotoxicity (6.5.7)	Carcinogenicity (6.5.8)	Haemocompatibility (6.5.9)
A – limited (≤24 h)	E	E	E	E				
B – prolonged (24 h to 30 d)	E	E	E	E	E	E		
C – long-term (>30 d)	E	E	E	E	E	E	E	

Duration	Biological effect[a b c]							
	Cytotoxicity (6.5.2)	Sensitization (6.5.3)	Irritation (6.5.4)	Systemic toxicity (6.5.5)[f]	Local effects after tissue contact (6.5.6)	Genotoxicity (6.5.7)	Carcinogenicity (6.5.8)	Haemocompatibility (6.5.9)
A – limited (≤24 h)	E	E	E	E		E[e]		E
B – prolonged (24 h to 30 d)	E	E	E	E	E[d]	E		E
C – long-term (>30 d)	E	E	E	E	E[d]	E	E	E

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Device Categorization

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	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[i]			
		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		

Table A.1 (continued)

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]
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		

Breached or compromised surface

Circ. Blood

External communicating and implants not referenced, categorized as either:

- Breached or compromised surfaces or internal tissues other than circulating blood OR
- Circulating blood

Duration	Biological effect[a b c]							
	Cytotoxicity (6.5.2)	Sensitization (6.5.3)	Irritation (6.5.4)	Systemic toxicity (6.5.5)[e]	Local effects after tissue contact (6.5.6)[d]	Genotoxicity (6.5.7)	Carcinogenicity (6.5.8)	Haemocompatibility (6.5.9)
A – limited (≤24 h)	E	E	E	E				
B – prolonged (24 h to 30 d)	E	E	E	E	E	E		
C – long-term (>30 d)	E	E	E	E	E	E	E	

Duration	Biological effect[a b c]							
	Cytotoxicity (6.5.2)	Sensitization (6.5.3)	Irritation (6.5.4)	Systemic toxicity (6.5.5)[f]	Local effects after tissue contact (6.5.6)	Genotoxicity (6.5.7)	Carcinogenicity (6.5.8)	Haemocompatibility (6.5.9)
A – limited (≤24 h)	E	E	E	E		E[e]		E
B – prolonged (24 h to 30 d)	E	E	E	E	E[d]	E		E
C – long-term (>30 d)	E	E	E	E	E[d]	E	E	E

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Determination of exposure duration

a) Limited exposure – a medical device that has a total exposure period of less than or equal to 24 h

b) Prolonged exposure – a medical device that has a total exposure period of more than 24 h but not more than 30 d

c) Long term exposure – a medical device that has a total exposure period of more than 30 d



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Determination of exposure duration

- Total exposure period: number of contact days from the first to the last use of a medical device
- Contact day: day in which a medical device or component thereof comes into contact with tissues including circulating blood, irrespective of the length of time of that contact within the day (Note: Daily contact, Intermittent contact, Bioaccumulation)
- Daily contact: When a medical device contacts the body every day for any portion of a day. For these medical devices, the total exposure period is the number of calendar days from the first to the last use of the medical device or a replacement of the same medical device on a single patient.
- Intermittent contact: Use of the device where there is a period of at least 24 hours between consecutive tissue contacts. The total exposure period is calculated by adding the number of contact days from the first to the last use of the medical device on a single patient. This is regardless of how long a single device is used for on a particular day.



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Determination of exposure duration

Total exposure period: number of contact days from the first to the last use of a medical device.

- If a material or medical device can be placed in more than one duration category, requirements applicable to the longest contact duration shall apply.
- For certain medical devices where constituents can remain after removal of the medical device, re-categorization following gap analysis to consider longer exposure can be needed.



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Exposure duration, Bioaccumulation

ISO 10993-1:2025 states:

“The potential for bioaccumulation of medical device constituents shall be considered for all duration categories. Where bioaccumulation is expected (e.g. a raw material contains perfluoro-heptanoic acid, a substance known to bioaccumulate in humans), the contact duration of the medical device shall be long-term unless otherwise justified.

During the subsequent biological evaluation of the medical device, where risk for bioaccumulation is identified, the contact duration of the medical device shall be long-term unless otherwise justified”

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Exposure duration, Bioaccumulation

Definition:

- Bioaccumulation occurs when an organism absorbs a substance faster than it can be lost or eliminated by catabolism and excretion.
- Bioaccumulation is the product of the absorption, distribution, and removal of a compound in an organism. For bioaccumulation to occur, all sources absorption rate is greater than the rate of chemical loss of organism tissues.

What does this mean in practice?

If you have knowledge about the presence of a bioaccumulating chemical then you need to evaluate your device for long term exposure which can include biological effects like systemic toxicity, genotoxicity, carcinogenicity and local tissue effects after tissue contact.

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Reasonably foreseeable misuse

ISO 14971:2019

*"The manufacturer shall also document reasonably foreseeable misuse… It is important that the manufacturer **tries to look into the future** to see the hazards due to potential uses of their medical device and also the reasonably foreseeable misuse."*

What **COULD** happen, a certain amount of prediction with or without evidence.

ISO 10993-1:2025

"Categorization of the medical device shall also consider the potential impact of reasonably foreseeable misuse in accordance with ISO 14971, ***where there is information available*** *(e.g. post-market surveillance data, clinical literature) to suggest that the device can be used outside of its intended use, **and this misuse is identified as being systematic**."*

What HAS happened, demonstrated foreseeable misuse with evidence.

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Reasonably foreseeable misuse

ISO 10993-1:2025

"Categorization of the medical device shall also consider the potential impact of reasonably foreseeable misuse in accordance with ISO 14971, ***where there is information available*** *(e.g. post-market surveillance data, clinical literature) to suggest that the device can be used outside of its intended use,* ***and this misuse is identified as being systematic****."*

- Post market surveilance
- Clinical studies
- Risk Management file
- Experience from similar devices
- Clinical litterature

→

- Longer duration of exposure
- Different body contact
- Different population

Risk Management Framework adopted

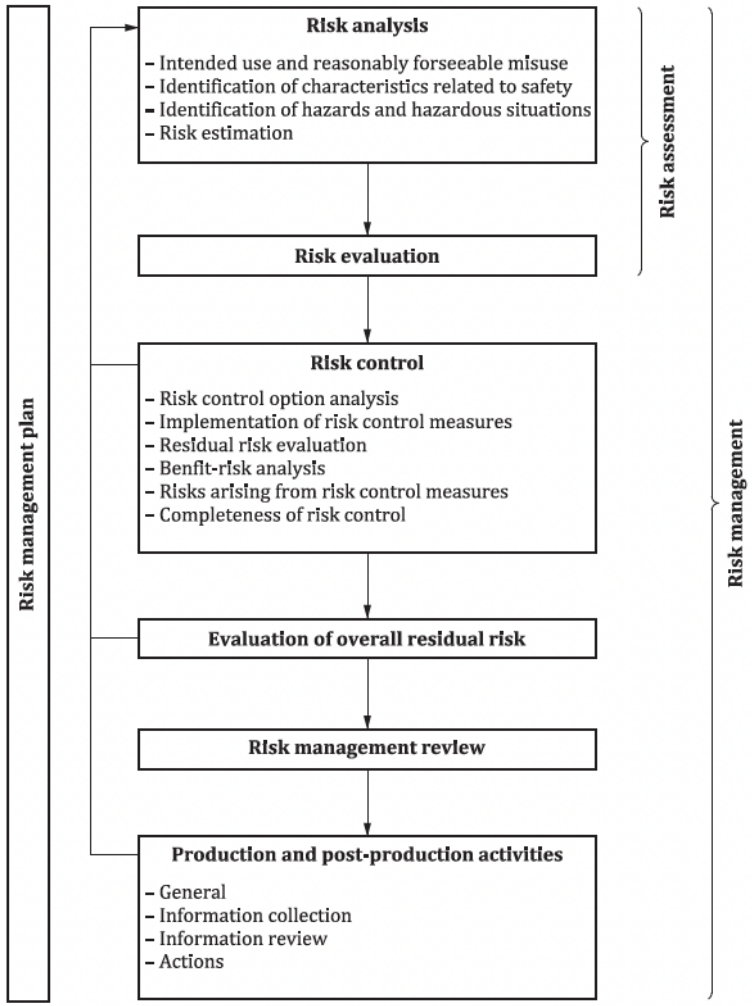
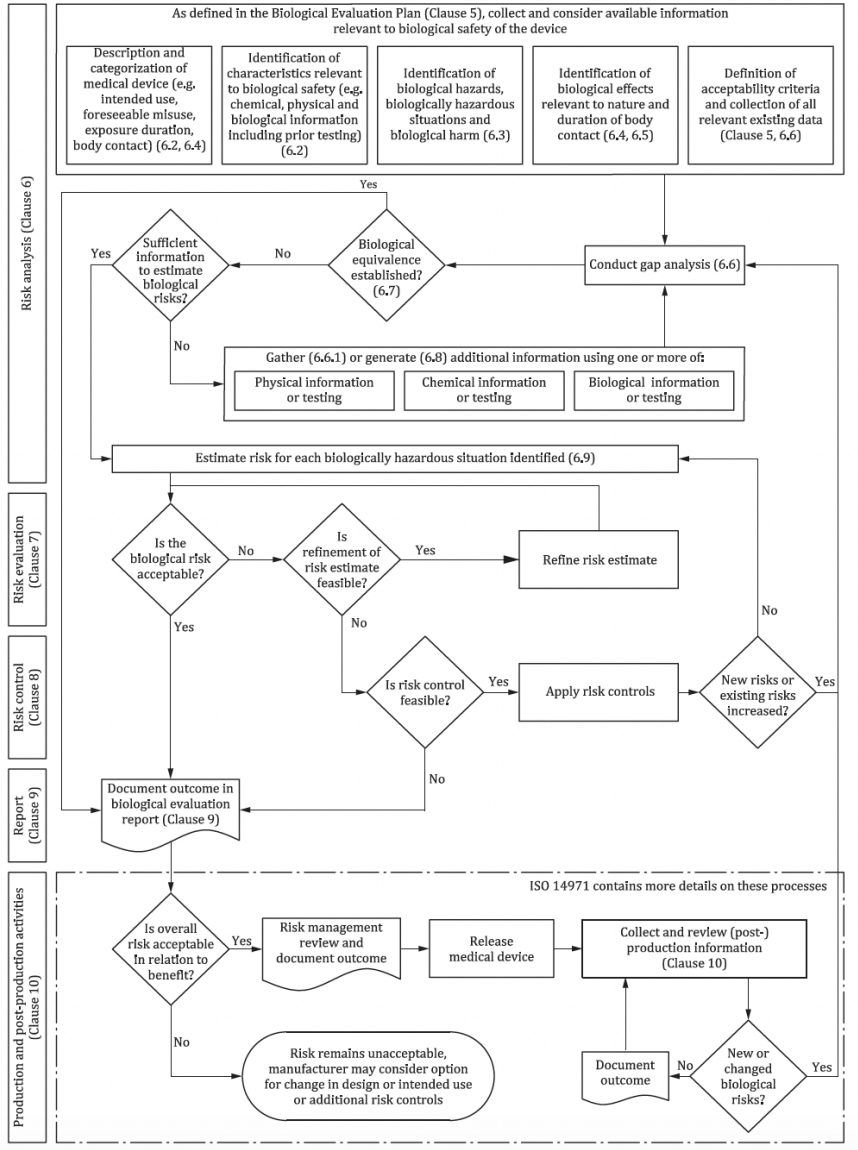


Figure 1 — ISO 14971 risk management framework



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Risk management, definitions

- Biological risk analysis = systematic use of available information to identify biological hazards and to estimate biological risks
- Biological risk assessment = overall process comprising a biological risk analysis and a biological risk evaluation
- Biological risk evaluation = process of comparing the biological risk of a medical device or material against defined criteria to determine the acceptability of the biological risk. Note, Biological risk evaluation is a subset of the overall biological evaluation
- Risk estimation = process used to assign values to the probability of occurrence. ISO 14971 defines the risk estimate as a measure of the severity of the harm and the probability of its occurrence
- Biological hazard = potential source of biological harm. Can arise from the presence of constituents which are in or on the medical device, or from physical characteristics of the medical device
- Biological hazardous situation = circumstances which result in exposure to one or more biological hazards i.e. can lead to a biological harm
- Biological harm = injury to humans from one or more adverse biological effects associated with a medical device or material
- Biological safety = freedom from unacceptable biological risk in the context of the intended use or reasonably foreseeable misuse

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Biological risk

Definition in ISO 10993-1:2025

combination of the probability of occurrence of biological harm and the severity of that harm”

Biological safety is, therefore, the freedom from unacceptable biological risk in the context of the intended use or reasonably foreseeable misuse



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Biological evaluation within a Risk Management process

- Biological hazards can arise from the presence of constituents which are in or on the medical device, or from physical characteristics of the medical device
- A biologically hazardous situation arises when direct contact or indirect contact with a medical device causes exposure to a hazardous constituent or physical characteristic
- The biologically hazardous situation can lead to a biological harm
- The biological risk is the combination of the probability of occurrence and severity of the adverse biological effect resulting from exposure to the hazardous constituent or physical characteristic



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Biological Risk analysis

- Identification of characteristics
- Device categorization
- Reasonably foreseeable misuse
- Identification of biological hazards, hazardous situation and potential biological harms
- Identification of relevant biological effects



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Biological Risk Estimation

Biological risk estimate =

Severity of harm x Probability of occurrence of harm

Explain your approach



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Risk Estimation

Severity of harm

Examples from ISO/TR 24971:2020

3-5 qualitative severity levels

Common terms	Possible description
Significant	Death or loss of function or structure
Moderate	Reversible or minor injury
Negligible	No injury or slight injury

Common terms	Possible description
Catastrophic / Fatal	Results in death
Critical	Results in permanent impairment or irreversible injury
Serious / Major	Results in injury or impairment requiring medical or surgical intervention
Minor	Results in temporary injury or impairment not requiring medical or surgical intervention
Negligible	Results in inconvenience or temporary discomfort



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Risk Estimation

Probability of occurrence

Probability levels can be qualitative as in the example below from ISO/TR 24971:2020 or semi-quantitative

Common terms	Possible description
High	Likely to happen, often, frequently, always Likely to happen several times during the lifetime of the *medical device*
Medium	Can happen, but not frequently Likely to occur a few times during the lifetime of the *medical device*
Low	Unlikely to happen, rare, remote Not likely to occur during the lifetime of the *medical device*

Probability of a situation to occur and lead to harm



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Risk Estimation

Risk matrix

The severity level is combined with the probability in a risk matrix, example from ISO/TR 24971:2020

		Qualitative *severity* levels		
		Negligible	**Moderate**	**Significant**
Qualitative probability levels	**High**	R_1	R_2	
	Medium		R_4	R_5, R_6
	Low		R_3	

Criteria for acceptability of the risk needs to be defined



Biological Risk Evaluation

Evaluate the identified and estimated biological risk against acceptability criteria set in BEP.

If acceptability criteria is not met, then risk control shall be applied.



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Biological Risk Control

If needed implement biological risk control measures as:

- Protective measures
- Add information for safety and if appropriate training of users
- Replacement of material

If the risk remains,

- Is the overall residual risk acceptable?
- Do we have any significant residual biological risks that needs to be communicated to the user?



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Assessment of Life Cycle

Life cycle: All stages of the device's existence during which the device fulfils its intended clinical function

- Design: The selection of materials should be fitness for purpose with regard to characteristics and properties of the material, which include chemical, toxicological, physical, electrical, morphological and mechanical properties
- Use: cumulative stresses across all phases: design, use (e.g. implant degradation over time within the body), reprocessing, Assess biological risks from material degradation, wear, and substance release over time.
- Reprocessing: Reprocessing evaluation of biological safety shall take into consideration the number of processing cycles based on the expected use life of the device.
- Transportation and storage: The potential for change in the characteristics of the medical device during transport, storage or use (e.g. where there is anticipated degradation or potential for physical failures causing exposure to previously unevaluated materials or constituents) shall be considered.
- Post-market data shall be reviewed and updated as required by post-market information or where new or changed biological risks are identified.

Biological evaluation is a continues process and does not end with market approval

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Assessment of Life Cycle

Example; Implantable medical devices

- Implantable medical devices – Key points
- Lifetime evaluation - Must address material degradation inside the body for both resorbable and permanent implants
- Relevant standards - ISO 10993-9 and related parts (-13, -14, -15) guide modeling of long-term biological responses (e.g., corrosion, particle release, systemic effects from leachables)
- Life cycle factors - Material properties, storage conditions, and manufacturing strongly influence degradation profile
- Manufacturer responsibility - Clearly define device lifetime to ensure comprehensive risk assessment and risk control



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Changes in ISO 10993-1:2025 that might trigger an update

- Material assessments – e.g. Bioaccumulation
- Contact category: limited – prolonged?
- Reasonably foreseeable misuse
- Lifecycle management

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Biological evalution performed using previous version

- No mandate to re-test marketed devices with acceptable safety profiles
- Changes in design or additional biological effects to consider – history of safe use (including relevant information about biological effects to consider) – No further biological evaluation needed
- Changes in production and post-production (e.g. identified previous unidentified biological hazards, change in specification, processing, source of any material in indirect or direct contact) – Review of the Biological evaluation is needed

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Biological evalution performed using previous version

- No grace period was communicated
- FDA, partially recognized. Transition period until 1 July 2029
- Japan, ISO 10993-1:2018 will valid until publication of their own standard.

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New guidance documents development

WG1 is currently progressing six projects aimed at further strengthening and clarifying the standard:

- Project 1: Risk Estimation ISO/CD TS 26177
- Project 2: Bioaccumulation for short-term contacting devices – ISO/NP TS 26420
- Project 3: Lifecycle of devices (including reprocessed devices) – ISO/PWI TS 26399
- Project 4: Biological Equivalence – ISO/PWI 26376
- Project 5: Reasonably foreseeable misuse – ISO/CD TS 26397
- Project 6: Principles of research for biocompatibility



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