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Test preclinici, valutazione biologica e conformità alle norme armonizzate

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Agenda

- Regulatory context and ISO 10993-1:2025
- Risk management principles
- Testing
- Using harmonized Standards

Biological Evaluation – Regulatory requirements

MDR

EU MDR 2017/745

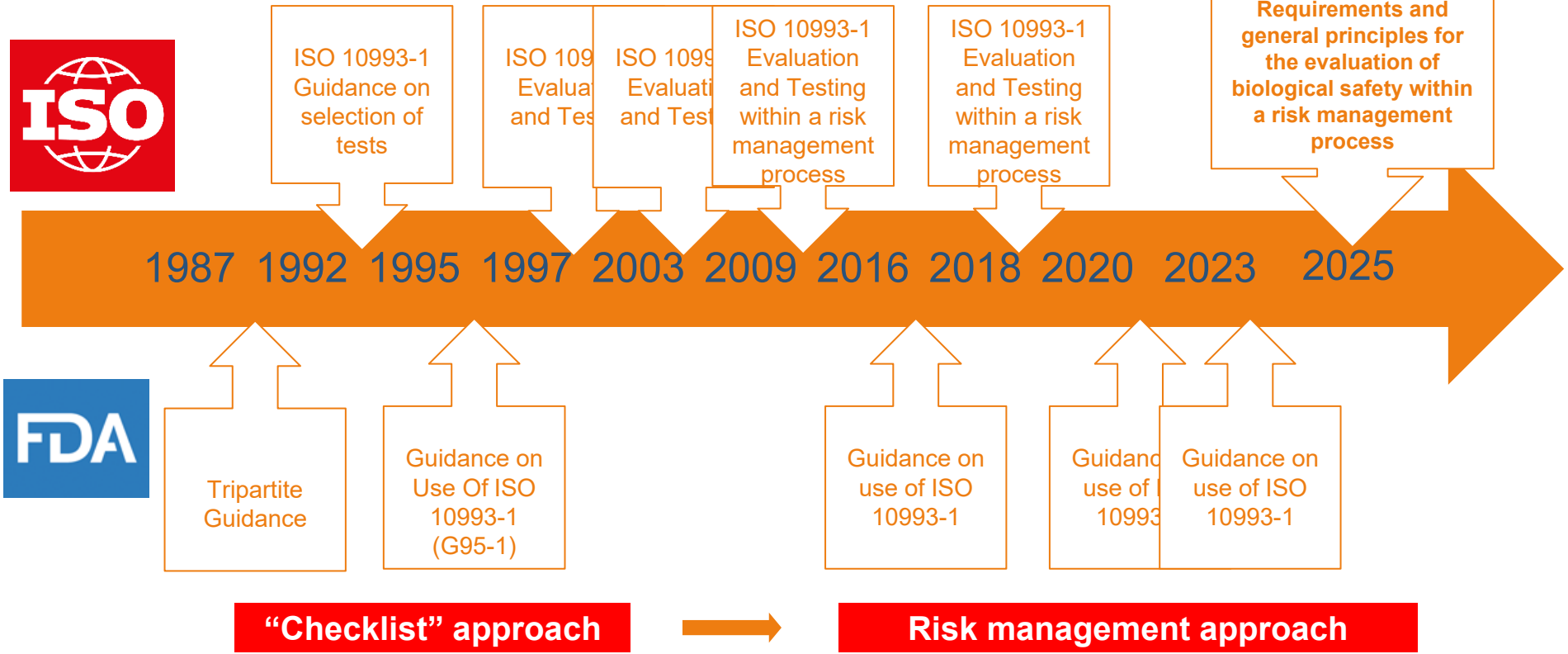
GSPR

MDR, Annex I
GSPR 10.1, 10.2, 10.3, 10.4 and 10.6

MDR Technical Documentation

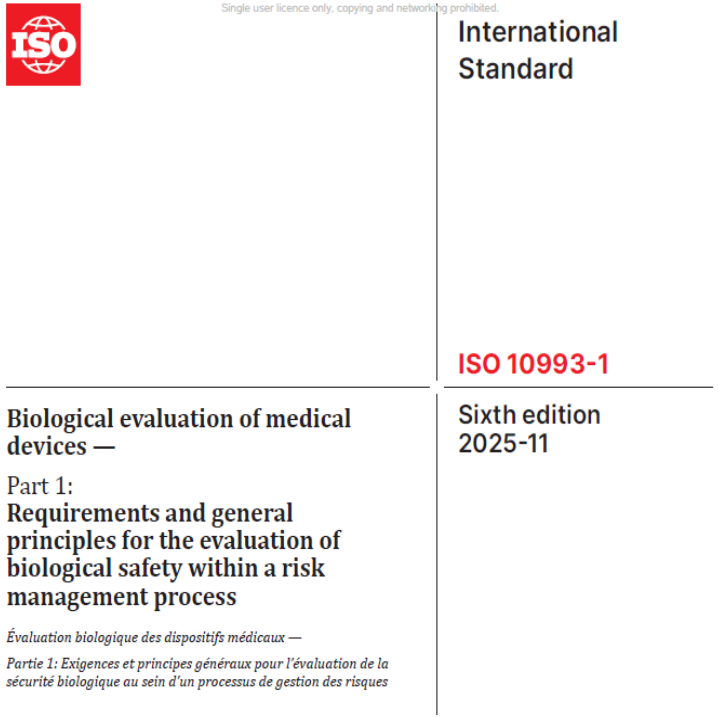
MDR, Article 8,
Harmonized standards and SOTA,
e.g. EN ISO 10993 series

Biological Evaluation – Regulatory requirements



ISO 10993-1:2025 – Redefining the rules of the game

- The standard has been completely reorganized, and the title was changed to align with the risk management framework described in ISO 14971.
- Additional content has been added to provide more guidance and clarification of calculation of exposure duration.
- Additional content has been added to provide more guidance on characterization of the device and identification of biological hazards.
- The identification of biological effects (previously referred to as biological endpoints) has been modified.



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ISO 14971 principles in biological risk evaluation

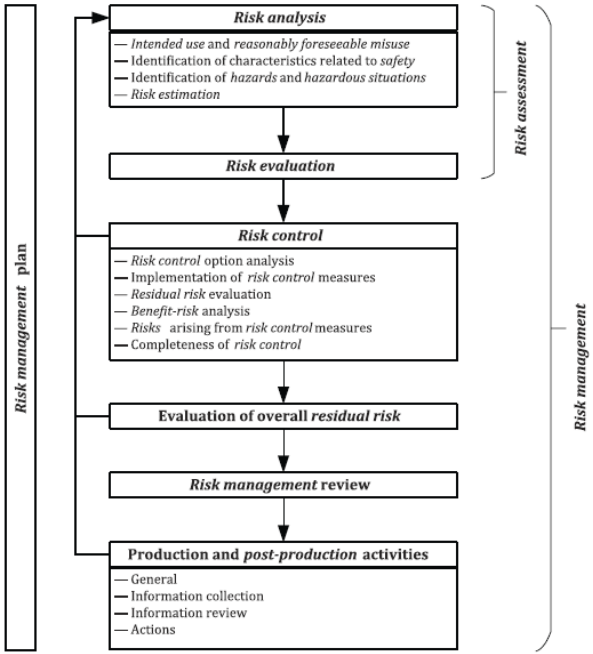
Biological Hazard
Potential source of biological harm (e.g., hazardous constituents or physical characteristics)

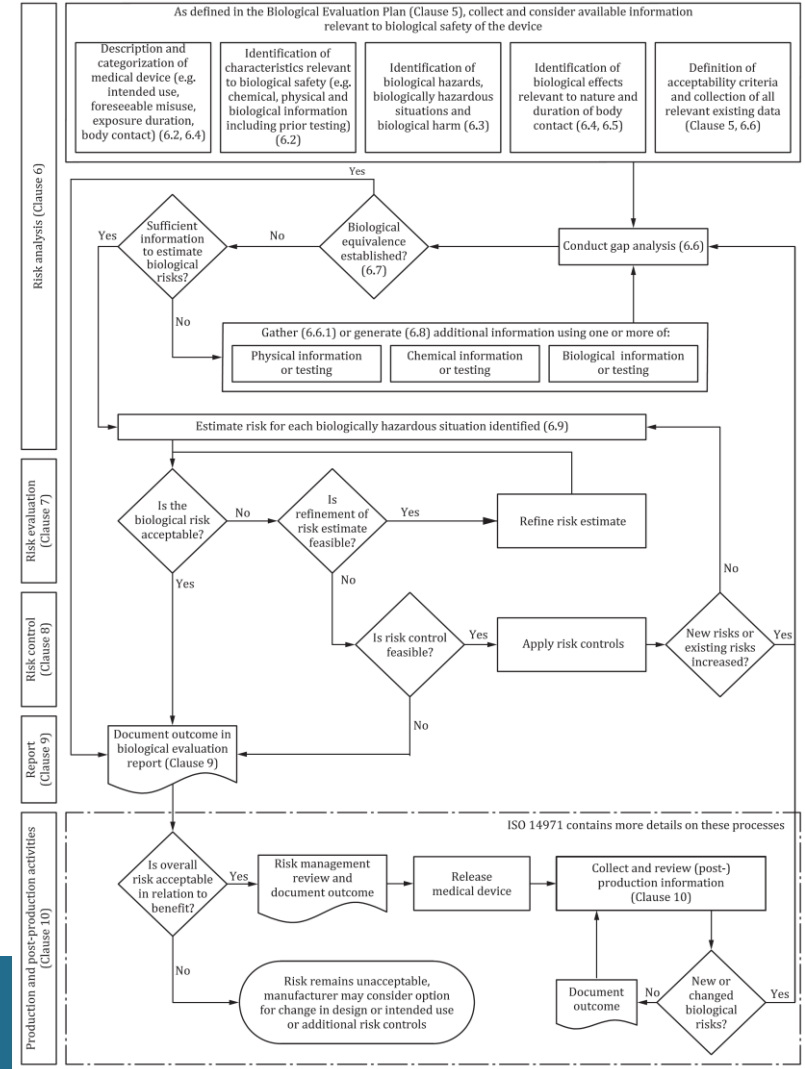
Biologically hazardous situation
Circumstances which result in exposure to one or more biological hazards (e.g. direct or indirect contact causes exposure to hazardous constituent)

Biological harm
Injury to humans from one or more adverse biological effects. Can be caused by biologically hazardous situations

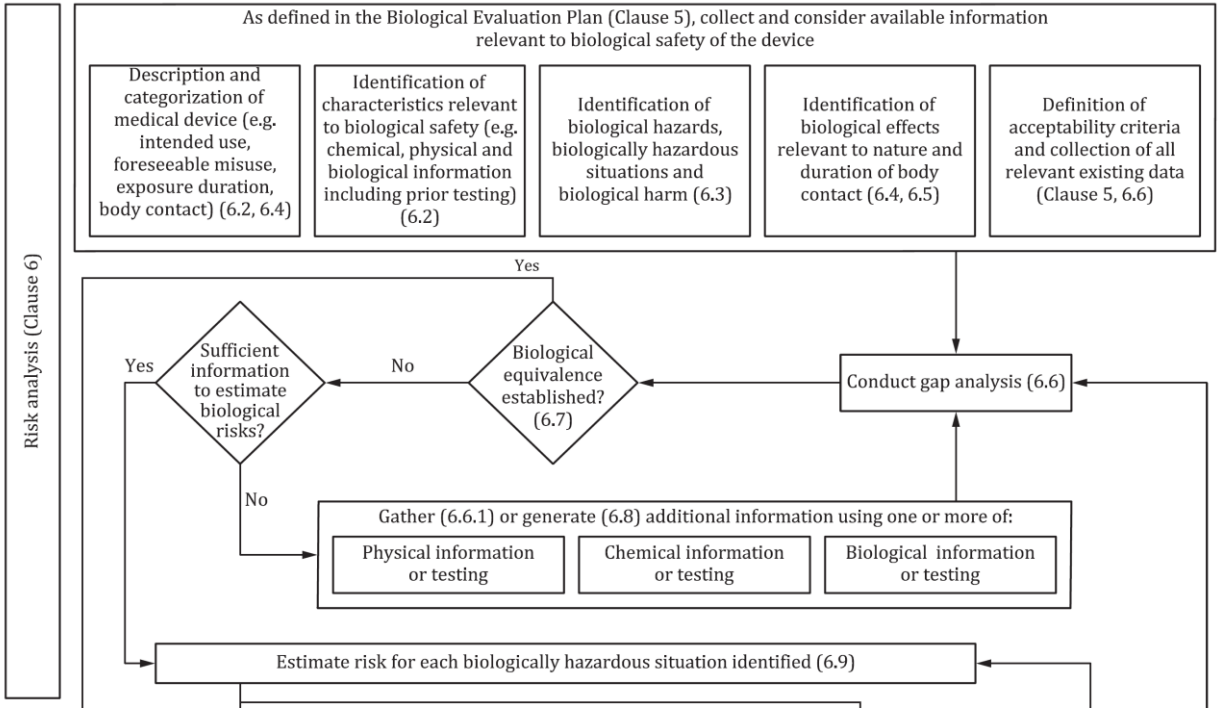
Biological risk
Combination of probability of occurrence and severity of adverse biological effect caused by biologically hazardous situation

From ISO 14971 to ISO 10993-1:2025





From ISO 14971 to ISO 10993-1:2025

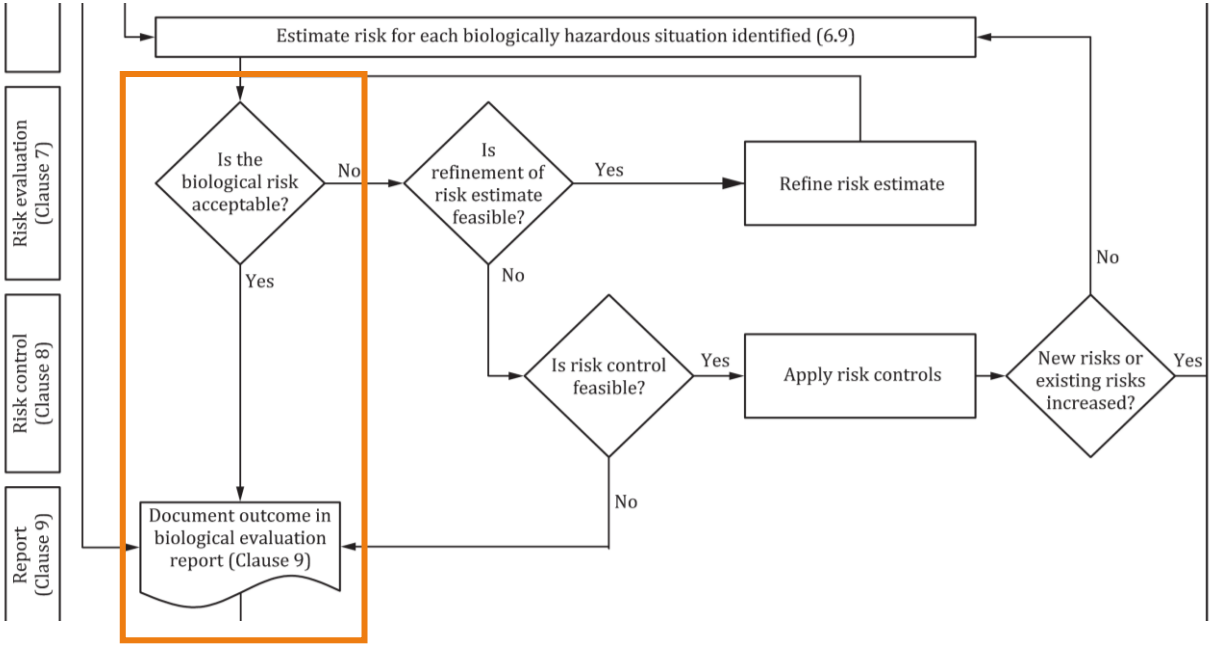


Gather available information relevant to biological safety of the device.

If the information is not sufficient, additional data shall be gathered or generated and the gap analysis repeated.

Biological risk(s) estimated using data gathered/ generated. Consider severity and probability of occurrence of harm.

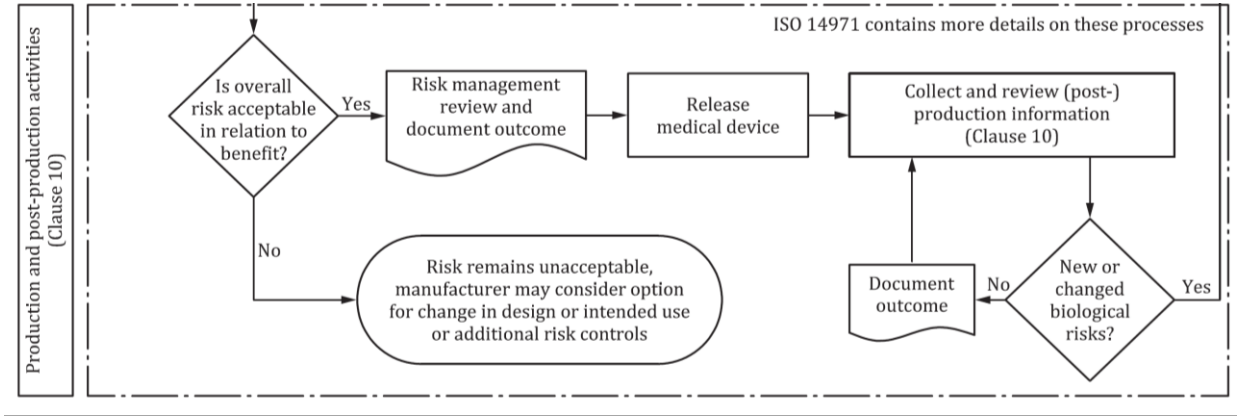
Biological risk evaluation



Compare the biological risk against defined criteria to determine the acceptability of biological risk

Biological safety is established when acceptability criteria are met!

Production and post-production activities



Biological evaluation conducted in a life cycle risk management framework

Biological evaluation shall be reviewed whenever changes to design, production process or emerging post-market information can impact biological safety

If there is a new or changed biological risk a gap analysis of the available information should be performed.

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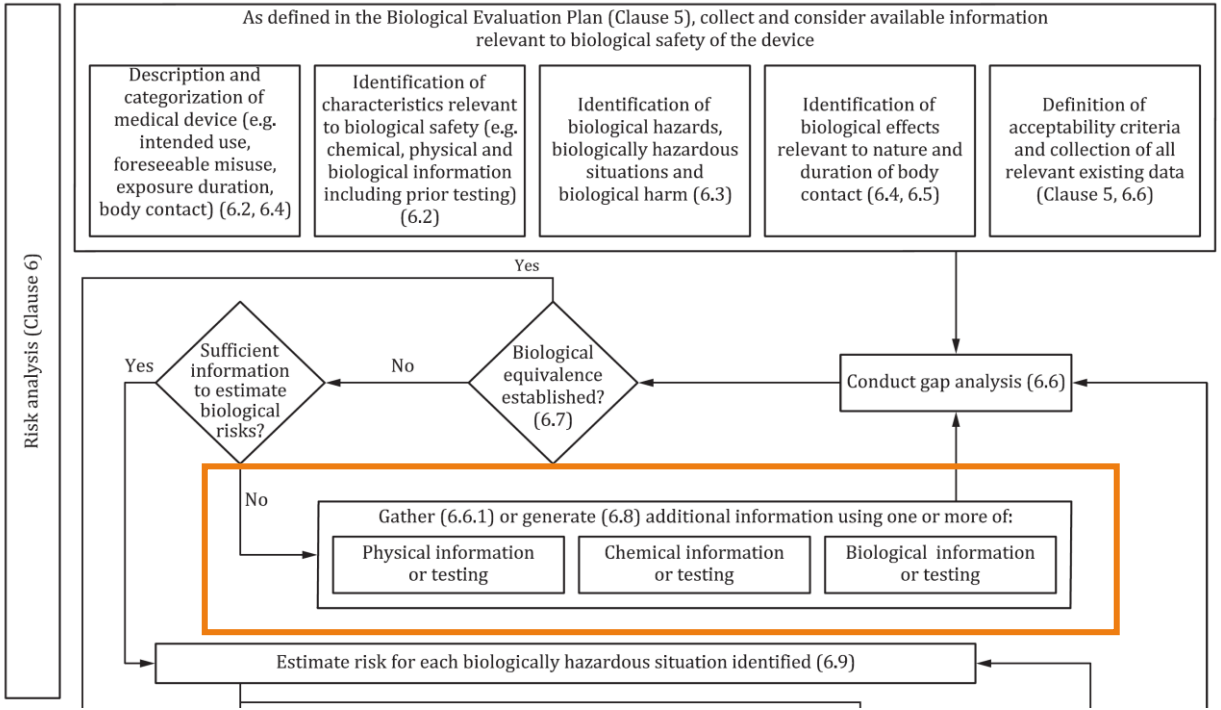

If the information is not sufficient, additional data shall be gathered or generated and the gap analysis repeated.

Before testing..

Why testing?

Why performing test X, Y, Z?

What information are we looking for?

Is the test method appropriate?

Planning is key!

What to test?

Identify test item

Worst case selection

Different components of the device to be tested separately?

How to test?

Sample preparation ISO 10993-12

Preparatory treatments?

Reprocessing procedures?

Testing

- Testing shall be performed on the final device, or representative samples from the final device or materials processed in the same manner as the final device (including sterilization, if needed).
- A representative sample can be a worst case taken from a medical device family. The choice of representative sample shall be justified and documented. For example, sample selection should account for process variation or changes that can occur during the medical device life cycle.
- For medical devices with multiple components that are tested separately due to different categorisations, interactions between the components shall be considered (e.g. simulated deployment prior to testing of an implanted component).
- If the medical device includes non-contacting components, the non-contacting components should not be included in the test article, unless justified.
- If the medical device includes both implanted and non-implanted components, and testing is carried out using an extract, the implanted components should not be combined in the same test article with the non-implanted components to prevent dilution of the implanted components, unless justified.

Testing

- The choice of test procedures shall consider:
  - type, duration, frequency and conditions of exposure to or contact with the medical device;
  - chemical and physical characteristics of the finished medical device;
  - toxicological activity of any known constituents in the formulation of the finished medical device;
  - the ratio of device surface area to recipient body size and mass;
  - animal welfare provisions;
  - that in vivo biological tests are not justifiable where valid information related to released constituents and degradation products (including particulates) have been addressed by other means and the constituents have a known and acceptable toxicity profile.

Testing

- If extracts of the medical devices are prepared, the solvents and conditions of extraction used should be appropriate to the use of the finished medical device, including consideration for the potential loss of constituents during extraction. Extracts for biological testing shall be prepared in accordance with ISO 10993-12 and extracts for analytical chemistry testing shall be prepared in accordance with ISO 10993-18. Whenever possible, the extraction conditions should represent an exaggeration of use conditions.
- Positive and negative controls should be used where appropriate.
- Testing shall be carried out in accordance with appropriate laboratory quality assurance controls [e.g. ISO/IEC 17025, OECD Principals of Good Laboratory Practice (GLP)]. Where test methods not detailed in the ISO 10993 series are used in the biological evaluation, these tests shall be sensitive, precise and accurate.
- Where prior testing is considered during initial data gathering, evaluation of that testing shall be conducted and any differences relative to the applicable standards shall be justified and documented.

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EU harmonization system

The **essential requirements** are included in the **legal texts** (such as in Annex I MDR) concerning medical devices.

Technical specifications and requirements are **described in the standards**. Standards can be drafted on an international (ISO), regional (EN), or national level.

After a standard has been drafted and approved by a recognized standardization body on the international, regional, or national level, it must be harmonized before it can be used in the context of the New Approach Directives.

The harmonization is described in Regulation (EU) No 1025/2012 of the European Parliament and of the Council of 25 October 2012

EU harmonization system

Harmonization is achieved by approving a standard suitable to **provide a "presumption of conformity."**

Presumption of conformity means that if a product fulfills a harmonized standard's requirements, the Member States presume the product to be in conformity with the essential requirements.

The Commission publishes lists of harmonized standards providing a presumption of conformity with directives' or the Regulations' requirements in its Official Journal and on its website at http://www.ec.europa.eu/growth/single-market/european-standards/harmonised-standards/medical-devices/index_en.htm.

EU harmonization system

European standards (ENs) are based on Article 2(1)(c) of Regulation (EU) No 1025/2012 and are intended to provide safety and performance requirements for products placed on the European market.

It is a key instrument for the single EU market as each NSB within the SDO is obligated to adopt each EN as a national standard while withdrawing any existing national standards that conflicts with the new EN

ENs are **voluntary** and there is no legal obligation to follow them. However, standards become harmonized when they are published by CEN and CENELEC in response to a request by the European Commission (EC), also referred to as a mandate.

European and harmonized standards are denoted with “EN” at the beginning of the standard’s name and are published in the OJEU.

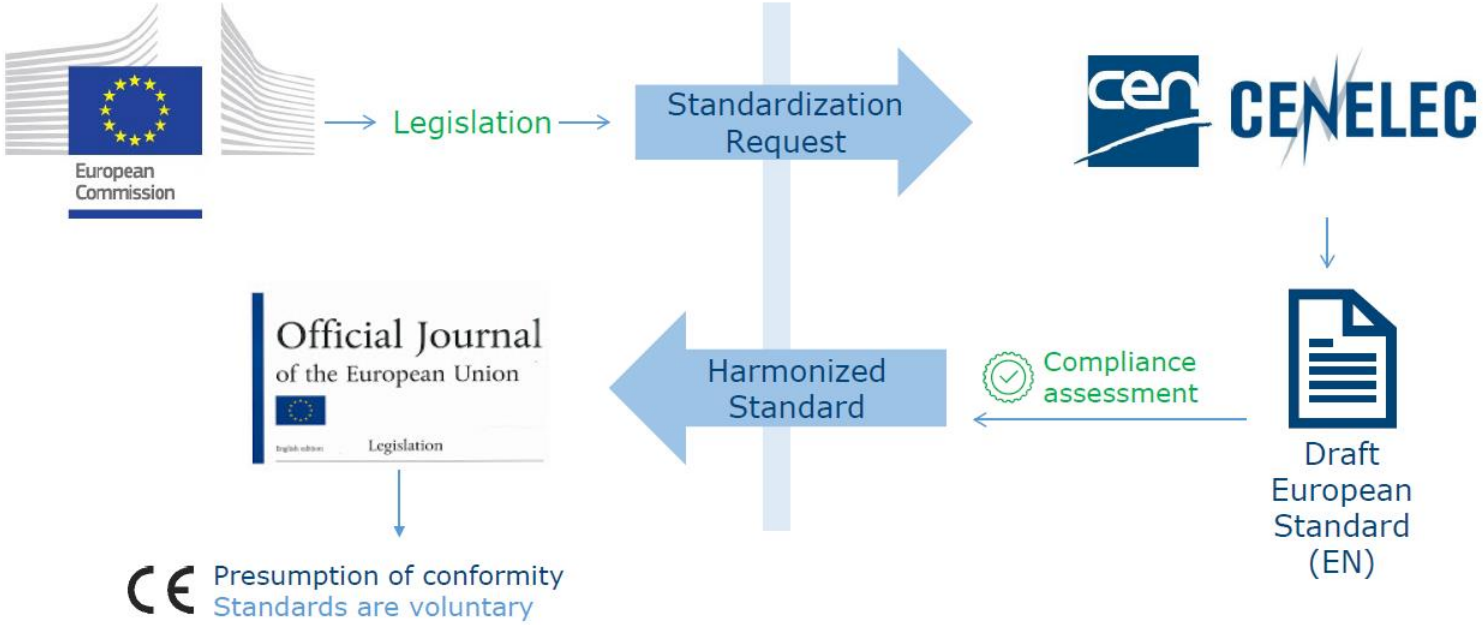
EU harmonization system

At a high level, the process of harmonization involves adopting international ISO or IEC standards and establishing a relationship between requirements of the EU legislation with the clauses in the standard.

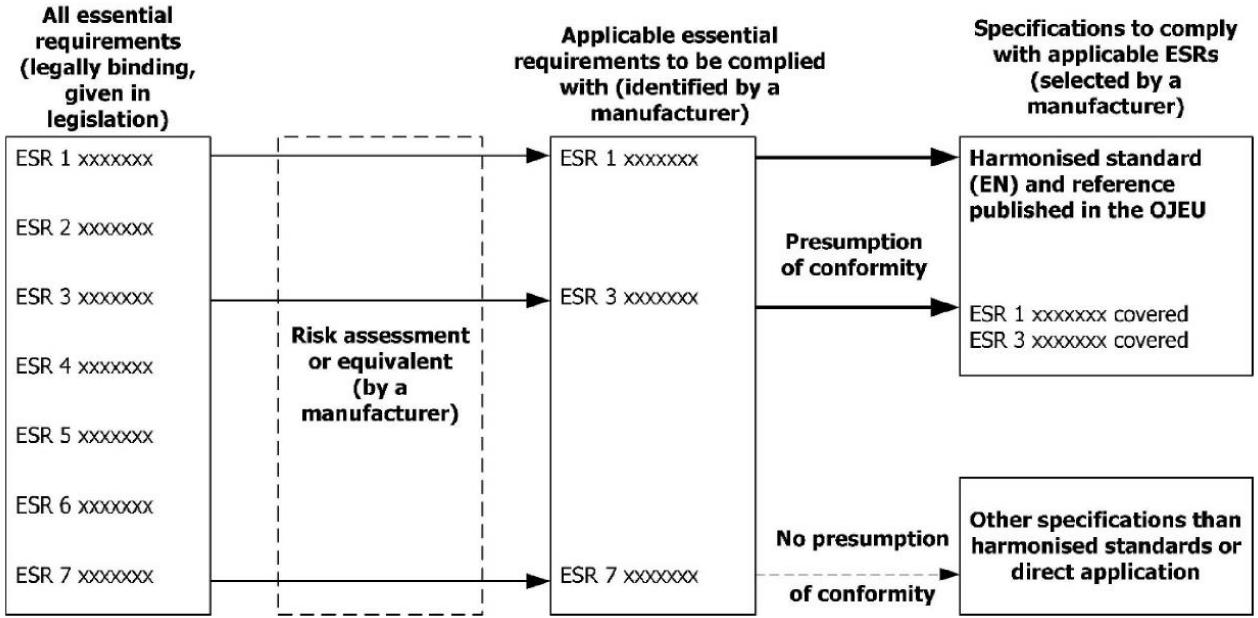
These relationships are described in the **informative "Z" annexes** which are added to the harmonized version of the standard.

Per Article 8 of the EU MDR or EU IVDR, harmonized standards are important as adherence with them provides presumption of conformity with legislative requirements, such as the General Safety and Performance Requirements (GSPR) and other requirements.

EU harmonization system



EU harmonization system



EU harmonization system - examples

Table ZC.1 — Correspondence between this European Standard and Annex I of Regulation (EU) 2017/745 [OJ L 117]

General Safety and Performance Requirements of Regulation (EU) 2017/745	Clause(s)/sub-clause(s) of this EN	Remarks/Notes
10.1 a), b), g) and h)	4, 5, 6, 7, 8 and Annex A, D and E	10.1 is only partly covered by EN ISO 10993-23, since the standard does not provide requirements on design and manufacture. However, this standard provides a means to assess potential irritancy induced by chemical and/or physical properties of substances used in the manufacture of medical devices. Other forms of toxicity and flammability (10.1 a) and b) are not covered.
10.2	4, 5, 6, 7, 8 and Annex A, D and E	10.2 is only partly covered by this standard, since the standard does not provide requirements on design, manufacture and packaging and does not oblige to minimize risk. However, this standard provides a means to assess irritancy to contaminants and residues in medical devices.
10.4.1 (First paragraph, first sentence)	4, 5, 6, 7, 8 and Annex A, D and E	10.4.1 is only partly covered by this standard, since the standard does not provide requirements on design and manufacture. However, this standard provides a means to assess irritancy to substances leaking from medical devices. This evaluation can be a preliminary step for risk minimization. Other forms of toxicity are not dealt with in this standard.

EN ISO 10993-23:2021

General Safety and Performance Requirements of Regulation (EU) 2017/745	Clause(s)/subclause(s) of this EN	Remarks/Notes
10.1 a), b), d), e), and h)	5, 6, 7, 8, 9, 10 and Annex A, Annex B, Annex C and Annex E	*EN ISO 10993-17 addresses the choice of materials as regards toxicity, but 10.1 is only partly covered. Flammability and mechanical or physical (e.g., surface) properties are not covered. This standard provides requirements for a toxicological risk assessment process for constituents present in or on, or released from, a medical device.* *This risk assessment process involves the identification of substances that have the capacity to interact with biological tissues, cells or body fluids and the assessment of the nature and likelihood of any associated harm to health arising as a result of the intended use of the medical device. While such an assessment can confirm the absence of appreciable toxicological risk, it does not necessarily demonstrate the ability of a medical device or material to perform with an appropriate host response in a specific application.* *The toxicological risk assessment is based on the composition of the finished medical device, which is dependent, in part, on the processing materials used and the impact of processes on the materials of manufacture.* *Where appropriate and necessary for the risk assessment, quantitative structure-activity relationships or mathematical models can be used as part of the process specified.* *The standard provides requirements for a process for specifying a level of exposure to a constituent of a medical device that is without appreciable harm to health and for confirming that a medical device meets the specification so defined.*
10.2	5, 6, 7, 8, 9, 10 and Annex A, Annex B, Annex C and Annex E	
10.4.1	5, 6, 7, 8, 9, 10 and Annex A, Annex B, Annex C and Annex E	

EN ISO 10993-17:2023

General Safety and Performance Requirements of Regulation (EU) 2017/745	Clause(s) / sub-clause(s) of this EN	Remarks / Notes
10.1 a), b) and h)	5 and 6	This standard provides requirements and recommendations for the chemical characterization of medical devices as part of a risk management process, including a qualitative characterization of the chemicals and materials used, a quantitative characterization of the amounts of chemicals and materials used and an evaluation of chemical release (leachable and extractable profile) in both the design and manufacturing processes. This chemical characterization can be used to define or confirm chemical specifications [10.1 h)] and evaluate the risk of toxicity [10.1 a) and b)] and biocompatibility [10.1 b)]. Flammability [10.1 a)] is not covered. For 10.1 b), ADME (absorption, distribution, metabolism, and excretion) is not covered. . For 10.1 h), physical specifications are not covered.
10.2	5 and 6	This standard provides requirements and recommendations for the chemical characterization of medical devices as part of a risk management process, including an evaluation of the release of contaminants and residues (composition, leachable and extractable profile) in both the design and manufacturing processes. Packaging is not covered. Aspects of contaminants and residues during transport and storage are not covered.
10.4.1 (First paragraph, first sentence)	5 and 6	This standard provides requirements and recommendations for the chemical characterization of medical devices as part of a risk management process, including an evaluation of chemical substances that may be released from the medical device (composition, leachable and extractable profile) in both the design and manufacturing processes. Particles and wear debris are not covered.

EN ISO 10993-18:2020+A1 2023

General Safety and Performance Requirements of Regulation (EU) 2017/745	Clause(s)/sub-clause(s) of this EN	Remarks/Notes
10.2 (first sentence only)	4, 5, 6, 7, 8, 9, 10 and 11	*10.2 is only partly covered by this standard, since the standard does not provide requirements on design and manufacture and does not oblige to minimize risk.* *However, this standard provides a means of preparing samples to assess conformity with this part of this general health and safety requirement in conjunction with other relevant parts of ISO 10993 for the design and manufacture of medical devices. Packaging is not covered.* *Risks from residues to person involved in the transport or storage of medical devices are not covered.*
10.4.1 (First paragraph only)	4, 5, 6, 7, 8, 9, 10 and 11	*10.4.1 is only partly covered by this standard, since the standard does not provide requirements on design and manufacture and does not oblige to minimize risk.* *However, this standard provides a means of preparing samples of medical devices to assess conformity with this part of this general health and safety requirement in conjunction with other relevant parts of ISO 10993.* *Other forms of toxicity are not dealt with in this standard.*

EN ISO 10993-12:2021

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Take home message

Biocompatibility as source of preclinical data

Biological Evaluation within a Risk Management process

Testing only when necessary

Use of Harmonized Standard to grant presumption of conformity

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Thank you

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