ISO 10993 – BIOCOMPATIBILITY A RISK BASED APPROACH

When biocompatibility is considered

- **New devices**: if medical device materials come into direct or indirect contact with the human body; or
- **Modified devices**: if changes are to any direct or indirect contacting components, or could affect another component that has tissue contact.

EXAMPLE – Modified Device:

New internal component added (no body contact). Heat applied to join to another component w/ body contact. Heat could change chemistry, so biocompatibility should be evaluated.

ISO 10993: A FAMILY OF NORMS

The **ISO 10993** set entails a series of standards for evaluating the biocompatibility of medical devices

- **Scope**: all medical devices
- **Aim**: planning appropriate testing to ensure safety of the materials and of the device
- **18 standards in the 10993 series**

LIST OF STANDARDS

- ISO 10993-1:2018 Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process
- ISO 10993-2:2006 Biological evaluation of medical devices Part 2: Animal welfare requirements
- ISO 10993-3:2014 Biological evaluation of medical devices Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- ISO 10993-4:2017 Biological evaluation of medical devices Part 4: Selection of tests for interactions with blood
- ISO 10993-5:2009 Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity
- ISO 10993-6:2016 Biological evaluation of medical devices Part 6: Tests for local effects after implantation
- ISO 10993-7:2008 Biological evaluation of medical devices Part 7: Ethylene oxide sterilization residuals

LIST OF STANDARDS

- ISO 10993-8:2001 Biological evaluation of medical devices Part 8: Selection of reference materials (withdrawn)
- ISO 10993-9:2010 Biological evaluation of medical devices Part 9: Framework for identification and quantification of potential degradation products
- ISO 10993-10:2013 Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization
- ISO 10993-11:2018 Biological evaluation of medical devices Part 11: Tests for systemic toxicity
- ISO 10993-12:2012 Biological evaluation of medical devices Part 12: Sample preparation and reference materials (available in English only)
- ISO 10993-13:2010 Biological evaluation of medical devices Part 13: Identification and quantification of degradation products from polymeric medical devices
- ISO 10993-14:2009 Biological evaluation of medical devices Part 14: Identification and quantification of degradation products from ceramics

LIST OF STANDARDS

- ISO 10993-15:2009 Biological evaluation of medical devices Part 15: Identification and quantification of degradation products from metals and alloys
- ISO 10993-16:2018 Biological evaluation of medical devices Part 16: Toxicokinetic study design for degradation products and leachables
- ISO 10993-17:2009 Biological evaluation of medical devices Part 17: Establishment of allowable limits for leachable substances
- ISO 10993-18:2009 Biological evaluation of medical devices Part 18: Chemical characterization of materials

ISO 10993: STRUCTURE

- A series of norms on planning
  - Part 1: Evaluation and testing within a risk management process: a main norm for
    - Identification
    - Planning
    - Reporting
  - Part 12: Sample preparation and reference materials: a general norm on GLP

ISO 10993: STRUCTURE

- A series of norms on standard biocompatibility testing:

  - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
  - Part 4: Selection of tests for interactions with blood
  - Part 5: Tests for in vitro cytotoxicity
  - Part 6: Tests for local effects after implantation
  - Part 10: Tests for irritation and skin sensitization – Part 11: Tests for systemic toxicity
  - Part 20: Principles and methods for immunotoxicology testing of medical devices (Technical Specification)

ISO 10993: STRUCTURE

- A series of norms on leachables:
  - Part 7: Ethylene oxide sterilization residuals
  - Part 16: Toxicokinetic study design for degradation products and leachables
  - Part 17: Establishment of allowable limits for leachable substances

ISO 10993: STRUCTURE

- A series of norms on degradation products:
  - Part 9: Framework for identification and quantification of potential degradation products
  - Part 13: Identification and quantification of degradation products from polymeric medical devices
  - Part 14: Identification and quantification of degradation products from ceramics
  - Part 15: Identification and quantification of degradation products from metals and alloys

ISO 10993-1 FOR RISK MANAGEMENT

- Guidance for the biological evaluation within a risk management process, as part of the design of each device.
  - protection of humans from potential biological risks arising from the use of medical devices.
  - concerning the biological evaluation of medical devices.

ISO 10993-1 aims at:

- Full evaluation of the biological responses to each medical device, relevant to its safety in use
- Determination of the effects on tissues, mostly in a general way, not a specific device-type situation

ISO 10993-1:2018: Terms and definitions

- **Biocompatibility (3.1)**

is the ability of a medical device or material to perform with an appropriate host response in a specific application

- **Direct contact (3.6)**

Medical device (and/or component) that comes into physical contact with body tissue

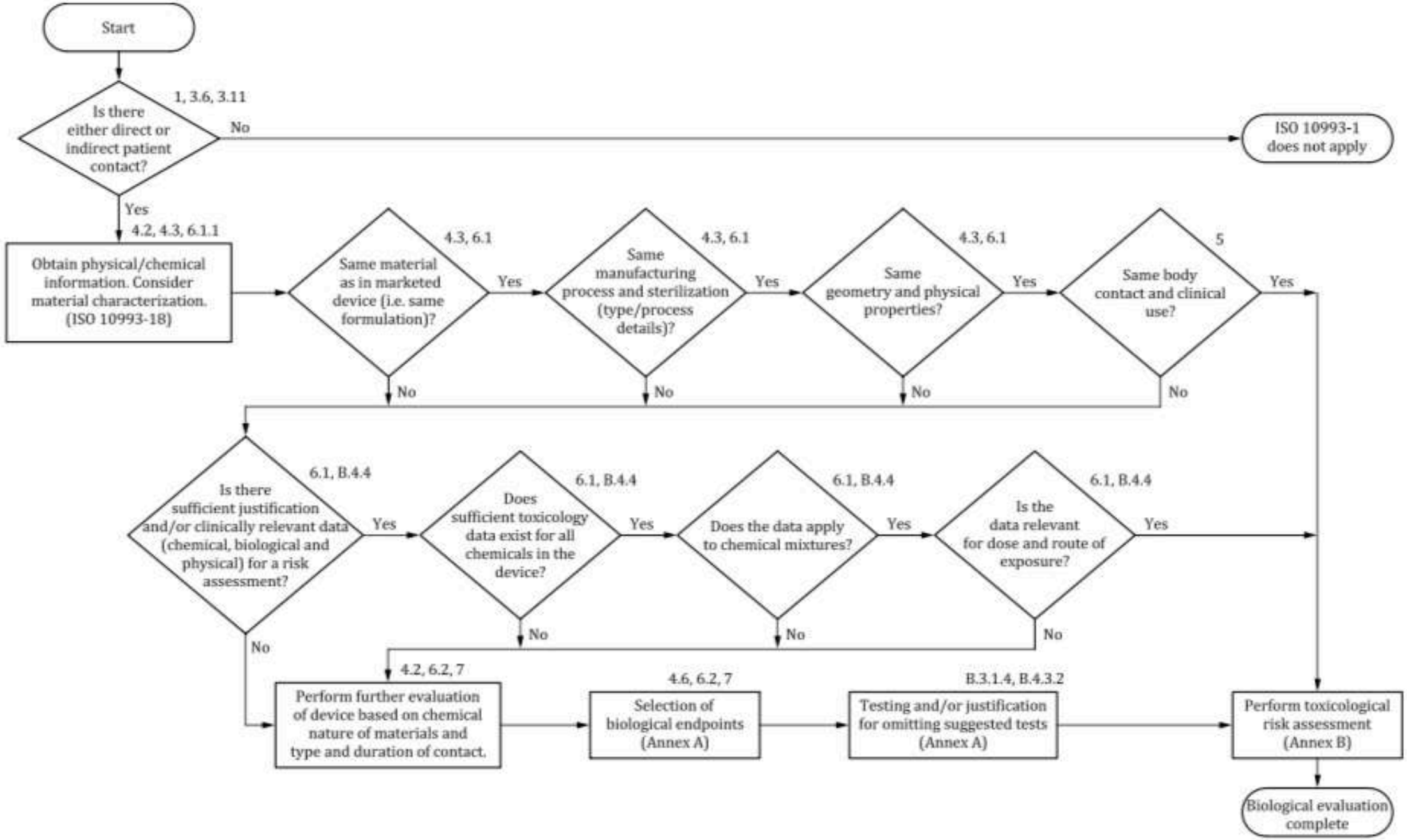
- **Indirect contact (3.11)**

Medical device or medical device component though which a fluid or gas passes, prior t the fluid or gas coming into physical contact with body tissue (in this case the medical device or medical device component itself does not physically contact body tissue).

ISO 10993-1 : CONTENTS

The risk based approach

- **Categorization of medical devices**
  - nature of body contact
  - duration of contact
- **Biological evaluation process**
  - Material and subproducts characterization
  - Biological evaluation tests
- **Interpretation of results**
- **Test planning (annex A and B)**
- **Literature review guidance (annex C)**


Start
1, 3.6, 3.11
Is there either direct or indirect patient contact?
No
ISO 10993-1 does not apply
Yes
4.2, 4.3, 6.1.1
Obtain physical/chemical information. Consider material characterization. (ISO 10993-18)
4.3, 6.1
Same material as in marketed device (i.e. same formulation)?
Yes
4.3, 6.1
Same manufacturing process and sterilization (type/process details)?
Yes
4.3, 6.1
Same geometry and physical properties?
Yes
5
Same body contact and clinical use?
Yes
No
No
No
No
6.1, B.4.4
Is there sufficient justification and/or clinically relevant data (chemical, biological and physical) for a risk assessment?
Yes
6.1, B.4.4
Does sufficient toxicology data exist for all chemicals in the device?
Yes
6.1, B.4.4
Does the data apply to chemical mixtures?
Yes
6.1, B.4.4
Is the data relevant for dose and route of exposure?
Yes
No
No
No
No
4.2, 6.2, 7
Perform further evaluation of device based on chemical nature of materials and type and duration of contact.
4.6, 6.2, 7
Selection of biological endpoints (Annex A)
B.3.1.4, B.4.3.2
Testing and/or justification for omitting suggested tests (Annex A)
Perform toxicological risk assessment (Annex B)
Biological evaluation complete

RISK BASED APPROACH

New biocompatibility testing may not be needed if:

- The device is made of materials that:
  - Have been well characterized chemically and physically in the published literature; and
  - Have a long history of safe use;
- Materials and manufacturing information is provided to demonstrate that no new biocompatibility concerns exist.

RISK BASED APPROACH

It may be possible to leverage previously conducted biocompatibility information if:

- The previously tested device has similar indications, type, and duration of contact;
- An explicit statement is provided regarding any differences in materials or manufacturing between the new and leveraged devices under consideration; and
- Information is provided to explain why differences aren't expected to impact biocompatibility

CATEGORIZATION BY NATURE OF BODY CONTACT

Non-contacting medical devices

These include medical devices (or components) that have neither direct nor indirect contact with the body and where biocompatibility information would not be necessary.

Diagnostic software, an in vitro diagnostic device and a blood-collection tube are examples of non-contact devices.

CATEGORIZATION BY NATURE OF BODY CONTACT

Surface-contacting medical devices

These include medical devices in contact with the following.

- **Skin**

  Medical devices that contact intact skin surfaces only.

  EXAMPLES Electrodes, external prostheses, fixation tapes, compression bandages and monitors of various types.

CATEGORIZATION BY NATURE OF BODY CONTACT

➢ Mucosal membranes

Medical devices that contact intact mucosal membranes.

EXAMPLES Contact lenses, urinary catheters, intravaginal and intra-intestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gastroscopes), endotracheal tubes, bronchoscopes, some dental prostheses and orthodontic devices.

➢ Breached or compromised surfaces

Medical devices that contact breached or otherwise compromised body surfaces.

EXAMPLES Dressings or healing devices and occlusive patches for ulcers, burns and granulation tissue.

CATEGORIZATION BY NATURE OF BODY CONTACT

Externally communicating medical devices

Externally communicating medical devices shall be categorized according to their contact with the following application sites.

- **Blood path, indirect**

  Medical devices or components that do not necessarily directly contact the blood path directly but serve as conduits to deliver fluids into the vascular system.

  EXAMPLES Solution administration sets, extension sets, transfer sets and blood administration sets.

CATEGORIZATION BY NATURE OF BODY CONTACT

➢Tissue/bone/dentin

Medical devices that contact tissue, bone or pulp/dentin systems.

EXAMPLES Laparoscopes, arthroscopes, draining systems, dental filling materials and skin staples.

Medical devices or components that do not necessarily directly contact tissue or bone but serve as conduits to delivery fluids to the tissue or bone.

EXAMPLES Tubing used for irrigation and medical device components that have fluid contact that can also contact the patient.

➢Circulating blood

Medical devices that contact circulating blood.

EXAMPLES Intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialysers, dialysis tubing and accessories, haemoadsorbents and immunoadsorbents.

CATEGORIZATION BY NATURE OF BODY CONTACT

Implant medical devices

Implant medical devices shall be categorized according to their contact with the following application sites.

- **Tissue/bone**
  - Medical devices principally contacting bone.
    - EXAMPLES Orthopaedic pins, plates, replacement joints, bone prostheses, bone cements and intraosseous devices.
  - Medical devices principally contacting tissue and tissue fluid.
    - EXAMPLES Pacemakers, drug supply devices, neuromuscular sensors and simulators, replacement tendons, breast implants, artificial larynxes, subperiosteal implants, ligation clips and intrauterine devices that do not achieve their primary function by chemical activity.

CATEGORIZATION BY NATURE OF BODY CONTACT

- **Blood**

  Medical devices principally contacting circulating blood in the cardiovascular system.

  EXAMPLES, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug-delivery catheters and ventricular assist devices.

CATEGORIZATION BY DURATION OF CONTACT

Medical devices shall be categorized according to the anticipated duration of contact as follows.

a) Limited exposure (A)

medical devices whose cumulative sum of single, multiple or repeated duration of contact is up to 24 h.

- Needles

b) Prolonged exposure (B)

medical devices whose cumulative sum of single, multiple or repeated contact time is likely to exceed 24 h but not exceed 30 d.

- Catheters

c) Long-term exposure (C)

medical devices whose cumulative sum of single, multiple or repeated contact time exceeds 30 d.

- Implants
- Repeated use devices

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		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		

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		Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[h,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		

[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.

ENDPOINTS TO BE ADDRESSED IN A BIOLOGICAL RISK ASSESSMENT

The following is a framework for the development of a biocompatibility evaluation and is not a checklist for testing. Where Table indicates that an endpoint is relevant for assessment, the existing data sets relevant to that endpoint should be evaluated to determine if any additional data sets are needed. For particular medical devices, there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated.

- X means prerequisite information needed for a risk assessment;
- 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 assessment)

Any variation should be justified in the biological risk assessment. If there are device specific standards that include specific recommendations regarding biocompatibility, these should be considered.

ENDPOINT CONSIDERATIONS

- If it is determined that some testing is needed, the guidance identifies:
  - General testing considerations for sample preparation;
  - Specific testing considerations for various biocompatibility endpoints (e.g., cytotoxicity); and
  - Why literature is often used to assess specific endpoints (e.g., carcinogenicity, reproductive and developmental toxicity)
- Test-specific issues included where deficiencies are frequently identified in premarket submissions.

EXERCISE

Please identify:

- Contact
- Contact Duration
- Endpoints of biological evaluation

For:

- *Neurovascular Embolization Device*
- *Neonatal Breathing Device*
- *Heart Monitor Implant Device*

CASE STUDY 1

Neurovascular Embolization Device

Categorization of the device:

- Implant
- Blood Contact
- Long term

Recommended Biological Endpoints:

- Full Suite: Cytotoxicity, Sensitization, Irritation, Acute Systemic Toxicity (w/ MMP), Subacute/Subchronic Toxicity, Genotoxicity, Implantation, Hemocompatibility, Chronic Toxicity, and Carcinogenicity

CASE STAUDY 2

Neonatal Breathing Device

Categorization of the device:
- External Communicating,
- Tissue (Lung)
- Long term

Recommended Biological Endpoints:
- Cytotoxicity, Sensitization, Irritation, Acute Systemic Toxicity (w/ MMP), Subacute/Subchronic Toxicity, Genotoxicity, and Implantation

CASE STUDY 3

Heart Monitor Implant Device

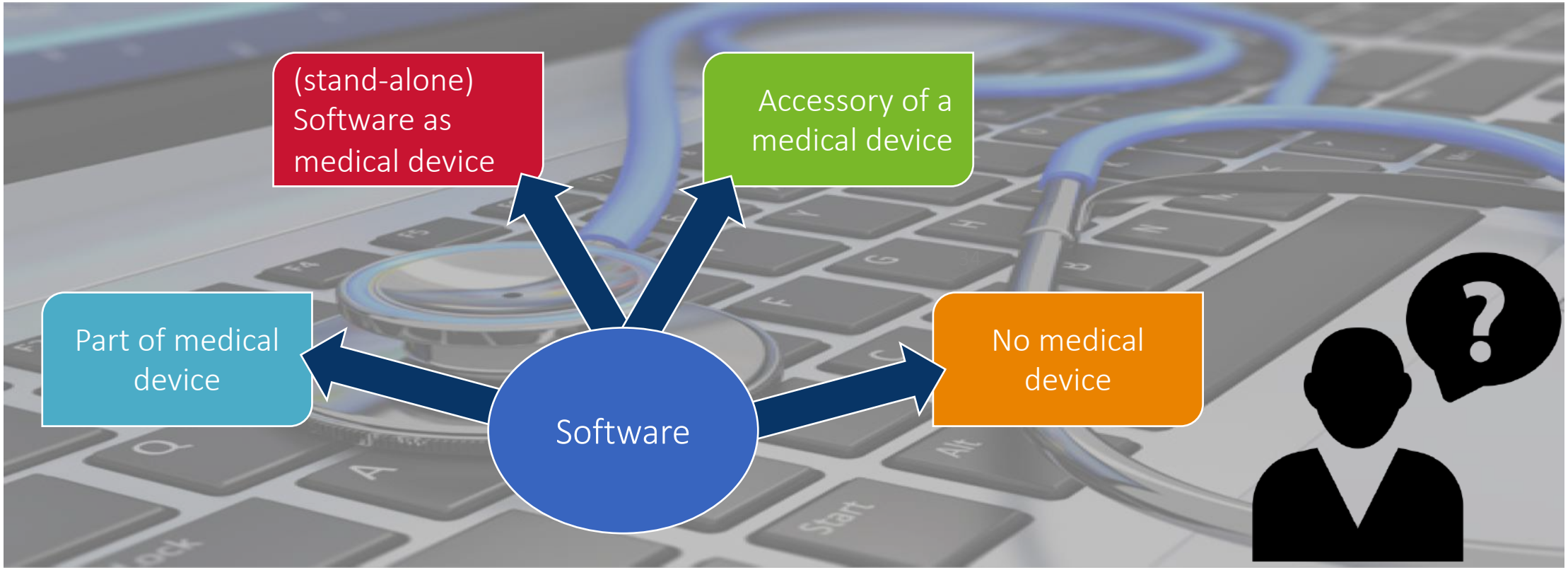
Categorization of the device:
- Implant
- Tissue (Heart & Pectoral Muscle)
- Long term

Recommended Biological Endpoints:
- Cytotoxicity, Sensitization, Irritation, Acute Systemic Toxicity (w/ MMP), Subacute/Subchronic Toxicity, Genotoxicity, Implantation, Chronic Toxicity, and Carcinogenicity

IEC 62304 – MEDICAL DEVICE SOFTWARE – SOFTWARE LIFE CYCLE PROCESSES

MEDICAL SOFTWARE

Software in medical product field are classified as:



Medical Software

Software in medical product field will be classified as

- Software as a part of a medical product
  - e.g. as embedded software of a medical device
- Software as medical product itself (standalone software)
- Software as accessories of a medical product
- Discrete software, that is not a medical product

Depending on this classification, manufacturers must pay attention to the different regulations.

TYPE OF SOFTWARE

- Embedded software
  - The software is a part of medical device, e.g. a patient monitor
- Software as Accessory
  - The software supports the use or medical function on the medical device, e.g. as service software
- Stand-alone software
  - The software is a medical device on its own, e.g. a medical app or decision support software
  - Stand alone software can directly control an apparatus (e.g. radiotherapy treatment), can provide immediate decision triggering information (e.g. blood glucose meters), or can provide support for healthcare professionals (e.g. ECG interpretation) MEDDEV 2.1/6 July 2016.

SOFTWARE AS MEDICAL DEVICE – STAND-ALONE

Stand alone software MUST HAVE a medical purpose to be qualified as medical devices

MDR 2017/745 (19)

BLOOD GLUCOSE METERS

RADIOTHERAPY TREATMENT

ECG INTERPRETATION

EXAMPLE FOR STAND-ALONE SOFTWARE AS MEDICAL DEVICE

Medical app, which:

- compares photos of patient's moles with a database of diagnosed melanomas using an algorithm, and
- based on this comparison, evaluates the photographed moles in detail and displays the probability for the moles to be a melanoma.

The data of this app play a role in the diagnosis of melanoma in humans. Presumably, the description of the intended purpose includes the terms "detect" or "diagnose". The algorithm interprets the data and may even change it, for example if the contrast is increased for better analysis.

EXAMPLE FOR STAND-ALONE SOFTWARE AS MEDICAL DEVICE

Another example for a medical stand-alone software is a decision support system. It provides healthcare professionals with recommendations for diagnosing, predicting, monitoring and treating individual patients. This includes for example:

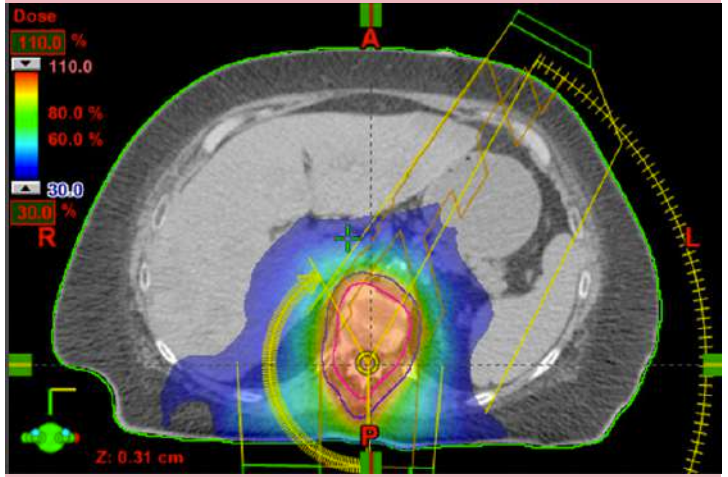
- radiotherapy planning systems for the dosage calculation of ionizing radiation in cancer therapy,
- drug planning systems to prevent resistance during chemotherapy or antibiotic treatment, and
- computer-assisted detection systems for imaging of cancer or coronary heart disease.

Stand-Alone Software – Classification

Stand-alone software shall also be deemed to be an ACTIVE device.

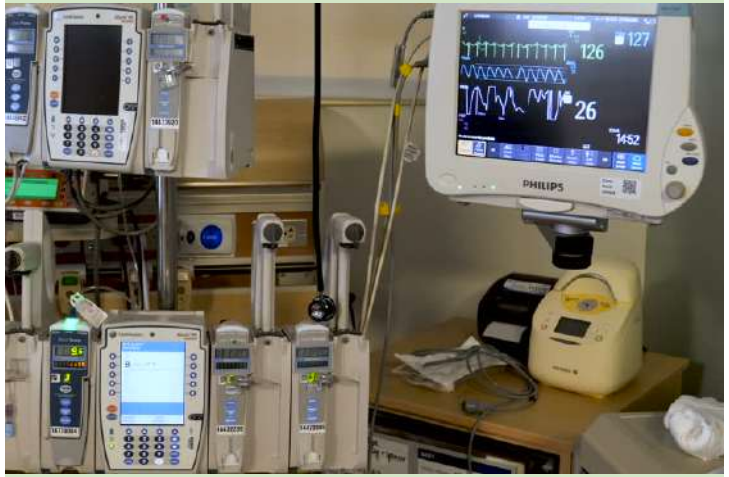
MDR 2017/745, Chapter I, Article 2 (4)

Radiotherapy Planning System



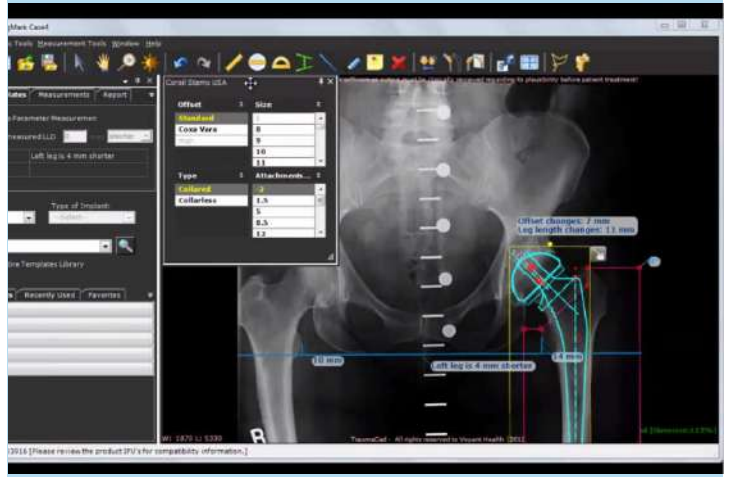
Class III

Software for Intensive care monitoring



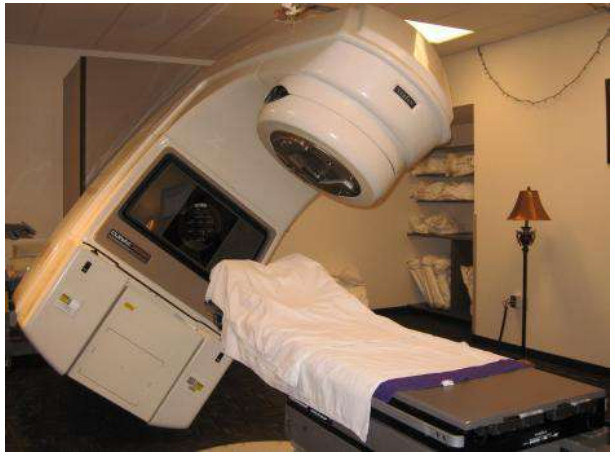
Class IIb

Orthopaedic planning software



Class I

WHY TEST? IN SOFTWARE GENERALLY…



Therac-25 Radiation Therapy Machine
Death of 3 patients due to massive overdose of radiation

Toyota Prius
100K+ vehicle recalls

Ariane 5 Flight 501
Loss of $370M spacecraft

IEC 62304 – SOFTWARE SAFETY CLASSIFICATIONS

"The MANUFACTURER shall assign to each SOFTWARE SYSTEM a software safety class (A, B, or C) according to the possible effects on the patient, operator, or other people resulting from a HAZARD to which the SOFTWARE SYSTEM can contribute.""

IEC 62304

IEC 62304 applies to he development and maintenance of medical device software when:

- The software is itself a medical device.
- Or the software is an embedded or integral part of the final medical device.

This standard covers safe design and maintenance of software. It provides processes, activities, and tasks to ensure safety.

There are nine parts of the safety standard:

- **Part 1:** Scope.
- **Part 2:** Normative references.
- **Part 3:** Terms and definitions.
- **Part 4:** General requirements.
- **Part 5:** Software development process.
- **Part 6:** Software maintenance process.
- **Part 7:** Software risk management process.
- **Part 8:** Software configuration management process.
- **Part 9:** Software problem resolution process

SAFETY CLASSIFICATION ACCORDING TO IEC 62304

The three classes are defined in the standard as follows:

- **Class A -** No injury or damage to health is possible.

The software system cannot contribute to a hazardous situation, or the software system can contribute to a hazardous situation which does not result in unacceptable risk after consideration of risk control measures external to the software system.

- **Class B -** Injury is possible, but not serious

The software system can contribute to a hazardous situation which results in unacceptable risk after consideration of risk control measures external to the software system, but the resulting possible harm is non-serious injury.

- **Class C -** Death or serious injury is possible

The software system can contribute to a hazardous situation which results in unacceptable risk after consideration of risk control measures external to the software system, and the resulting possible harm is death or serious injury.

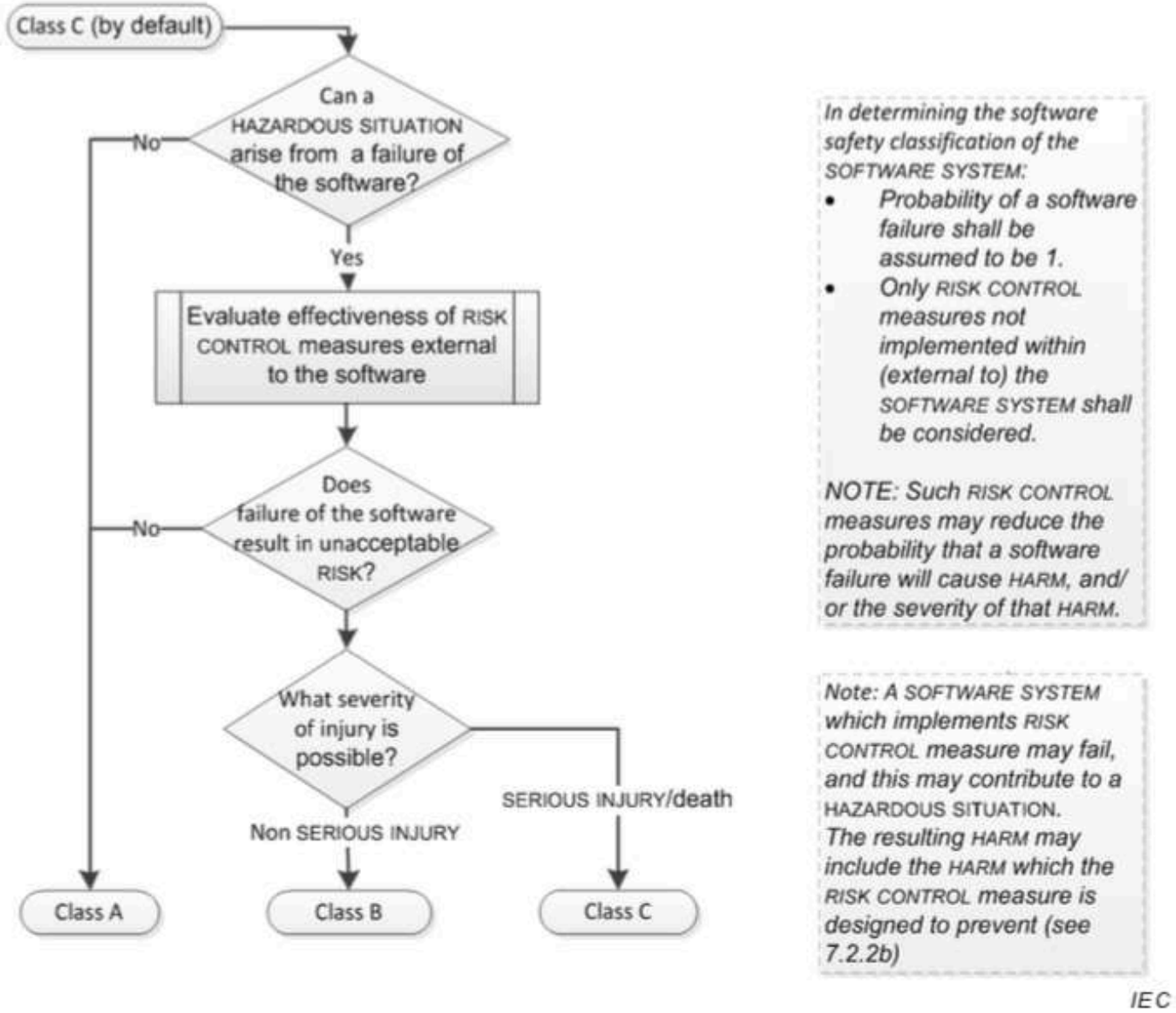


Figure 3 – Assigning software safety classification

SAFETY CLASS FOR SOFTWARE

Three safety class for software:

CLASS A NO INJURY OR DAMAGE TO HEALTH IS POSSIBLE	CLASS B NON-SERIUS INJURY IS POSSIBLE	CLASS C DEATH OR SERIUS INJURY IS POSSIBLE
If the thermometer gives a wrong value, then the nurse is going to touch the forehead of the patient, or redo the measurement with another thermometer to confirm the fever. No damage is possible.	If the thermometer gives a wrong value, then the nurse may give a wrong treatment to the patient. However there is no chance that this may endanger the patient.	If the thermometer gives a wrong value, then the nurse is going to give a medicine to treat the fever. The wrong medicine may endanger the patient, and eventually cause death.
NO DESIGN DOCUMENTATION, POOR TESTING	DESIGN DOCUMENTATION AND TESTING	DEEP DESIGN DOCUMENTATION AND DEEP TESTING

IEC 62304 SAFETY CLASSIFICATION EFFECTS

Software Documentation	Class A	Class B	Class C
Software development plan	Must contain contents to sections 5.1 IEC 62304:2006. The plan's content list increases as the class increases, but a plan is required for all classes.		
Software requirements specification	Software requirements specification conforming to 5.2 IEC 62304:2006. The content list for the software requirements specification increases as the class increases, but a document is required for all classes.		
Software architecture	Not required.	Software architecture to 5.3 IEC 62304:2006. Refined to software unit level for Class C.	
Software detailed design	Not required.		Document detailed design for software units. (5.4).
Software unit implementation	All units are implemented, documented and source controlled (5.5.1).		
Software unit verification	Not required.	Define process, tests and acceptance criteria (5.5.2, 5.5.3). Carry out verification (5.5.5)	Define additional tests and acceptance criteria (5.5.2, 5.5.3, 5.5.4). Carry out verification (5.5.5).
Software integration and integration testing	Not required.	Integration testing to 5.6 IEC 62304:2006.	
Software system testing	Not required.	System testing to 5.7 IEC 62304:2006.	
Software release	Document the version of the software product that is being released (5.8.4).	List of remaining software anomalies, annotated with an explanation of the impact on safety or effectiveness, including operator usage and human factors.	

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IN SUPREMÆ DIGNITATIS
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