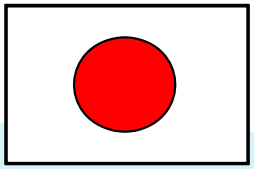
1. History and Points of Revision of JIS T0993-1 (Text)

2. Points of Revision of JIS T0993-1 (Annexes A and B)

3. Impact of the revisions including the revisions to the Japanese guidance (2020)

Biological Safety Testing Guidance

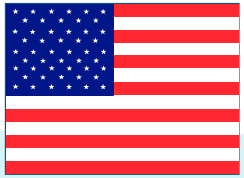
No. 1



Amendment of Basic Principles of Biological Safety Evaluation Required for Application for Approval to Market Medical Devices

MHLW Notification by Director, MDED, Yakuseikishin-hatsu 0106 No.1, January 6, 2020

FDA



Use of International Standard ISO-10993-1, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing within a risk management process" Guidance for Industry and Food and Drug Administration Staff

FDA Guidance, 2020 (updated)

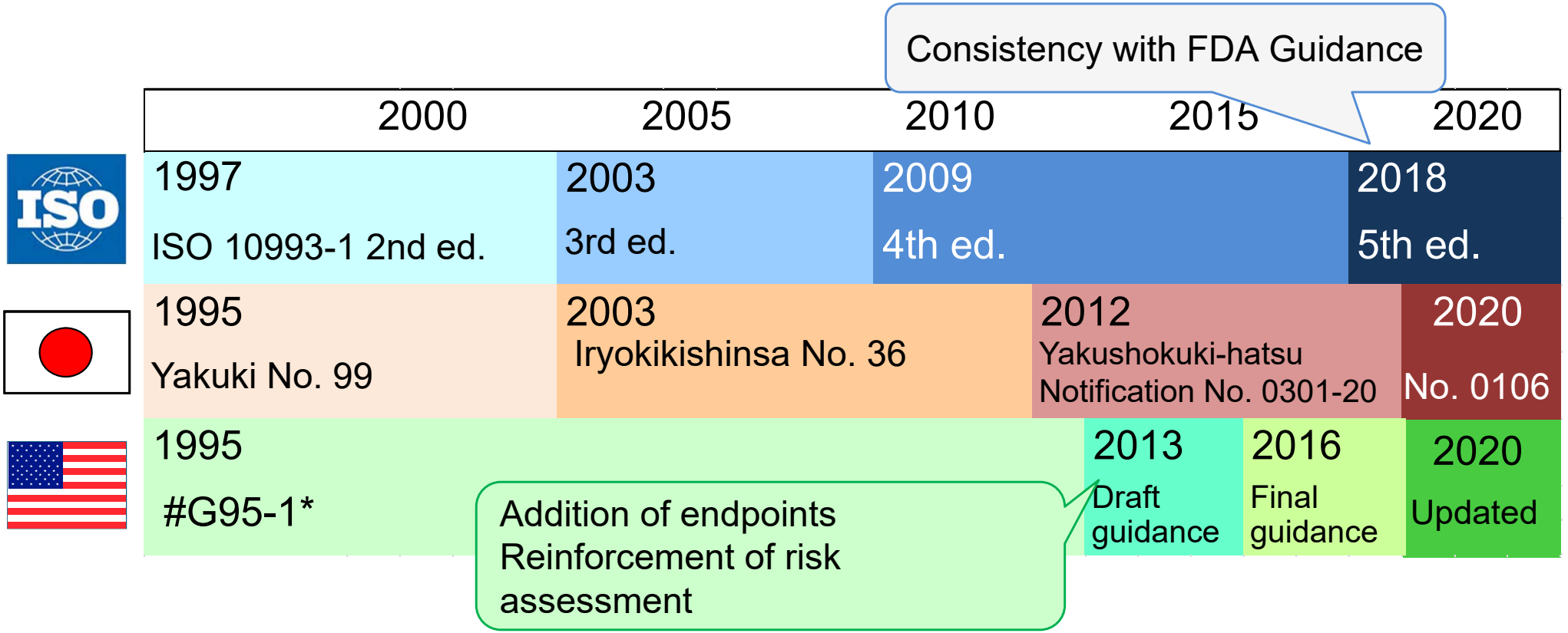
ISO

Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process

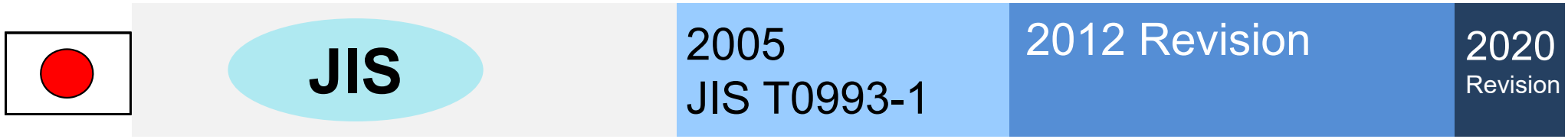
ISO 10993-1, August, 2018

JIS ! 2020

History of revision of guidance and JIS standards



*Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing' (Replaces #G87-1 #8294) (blue book memorandum #G95-1)



It has been revised corresponding to the revision of ISO 10993-1.

Major revisions in JIS T0993-1

a) Scope
For protective equipment such as surgical gloves, healthcare professionals are added.
Biological hazards caused by aging and damage are also covered.

b) Terms and definitions
"Toxicological threshold"
"Transitory contact"

c) General principles applying to biological evaluation of medical devices
Addition of physical and chemical information, particularly comparison of physical characteristics such as surface properties, and change of Annexes A and B

d) Overall biological evaluation of medical devices
Evaluation of packaging materials

e) Evaluation of nanomaterials ISO/TR10993-22

f) Endpoints to be addressed in the biological risk assessment (Annex A)

g) Guidance on the conduct of biological evaluation in the risk management process (Annex B)

TABLE OF CONTENTS

Introduction

Purpose: To protect humans from potential biological risks arising from the use of the medical devices.

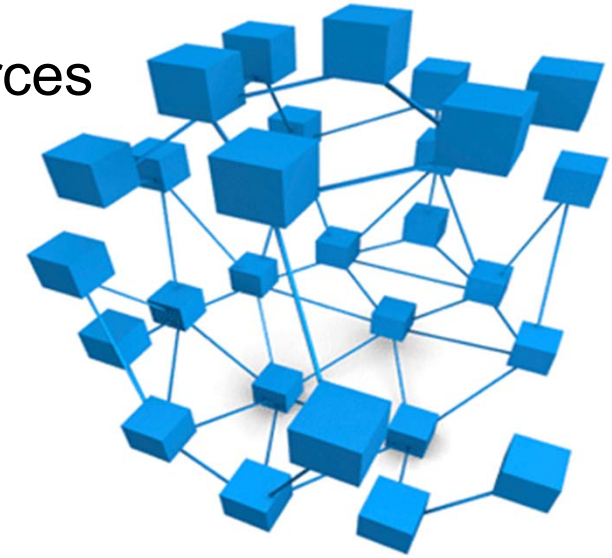
Method: Consider evaluation of effects of the "medical devices" as a whole on human tissues. Use **endpoint** tables grouped by type and duration of contact in a clinical setting to evaluate any biological safety.

Role: To serve as a framework in which to plan a biological evaluation.

1. Scope

<What is specified in JIS T0993-1>

- General principles governing the biological evaluation
- Categories of medical devices based on the nature and duration of their contact with the body
- Evaluation of existing data from appropriate sources
- Risk analysis based on identification of gaps
- Identification of additional data required
- Risk assessment of biological safety of medical devices



1. Scope

- Applicable materials and medical devices
  - Intended use: Contact with patient's body
  - Medical devices intended for protection (e.g., surgical gloves, masks and others): Including users

- Applicable medical devices
  All types of medical devices, including active, non-active, implantable and non-implantable medical devices

- This document also gives guidelines for the assessment of biological hazards arising from:
  - Risks such as changes over time
  - Exposure to new materials due to breakage

- Biological evaluation and related tests: Covered by each part of ISO 10993
- Mechanical testing: Address with device-specific standards
- Out of scope: Pathogen-related hazards

2. Normative references

ISO 10993-2:2006	Animal welfare
ISO 10993-3	Genotoxicity
ISO 10993-4	Hemocompatibility
ISO 10993-5	Cytotoxicity
ISO 10993-6	Implantation
JIS T 0993-7	Residual EO
ISO 10993-9	Degradation products
ISO 10993-10	Irritation/Sensitization
ISO 10993-11:2017	Systemic toxicity
ISO 10993-12	Sample preparation
ISO 10993-13	Degradation products from polymeric medical devices
ISO 10993-14	Degradation products from ceramics
ISO 10993-15	Degradation products from metals/alloys
ISO 10993-16	TK for degradation products
ISO 10993-17	Leachable substances
ISO 10993-18	Chemical characterization
ISO 10993-20	Immunotoxicity
JIS T 14971:2012	Risk management

With Western calendar year:
The year version described is applied.
The revised version is not applied.

Without Western calendar year:
The latest version is applied.

3 Terms and definitions

1 Biocompatibility
2 Biological risk
3 Biological safety
4 Chemical constituent
5 Data set
6 Direct contact
7 Externally communicating medical device
8 Final product
9 Geometry, device configuration
10 Implant
11 Indirect contact
12 Material
13 Material characterization
14 Medical device
15 Nanomaterial
16 Non-contacting

5
26

17 Physical and chemical information
18 Risk analysis
19 Risk assessment
20 Risk evaluation
21 Risk management
22 Toxic
23 Toxicological hazard
24 Toxicological risk
25 Toxicological threshold
26 Transitory contact

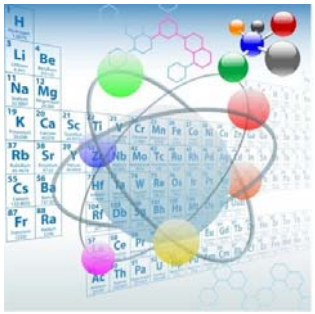
Added concept (1)

Material characterization (Sections 3.13 and 4.3)

Must be performed prior to biological testing (see Figure 1)

- A description of the chemical constituent of the medical device (Section 3.4)
- Material characterization

(including chemical characterization
See ISO 10993-18)



+ Toxicological threshold

Examination of the necessity of biological testing
Annex B
ISO 10993-17
ISO 10993-18

Added concept (2)

Categorization (Section 4.4)

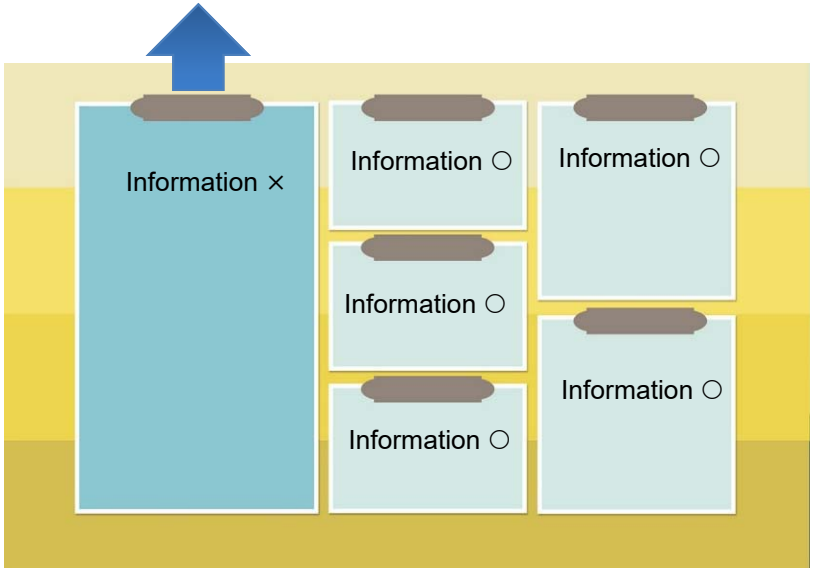
Biological evaluation shall commence with categorization of medical devices.
(See Section 5.)

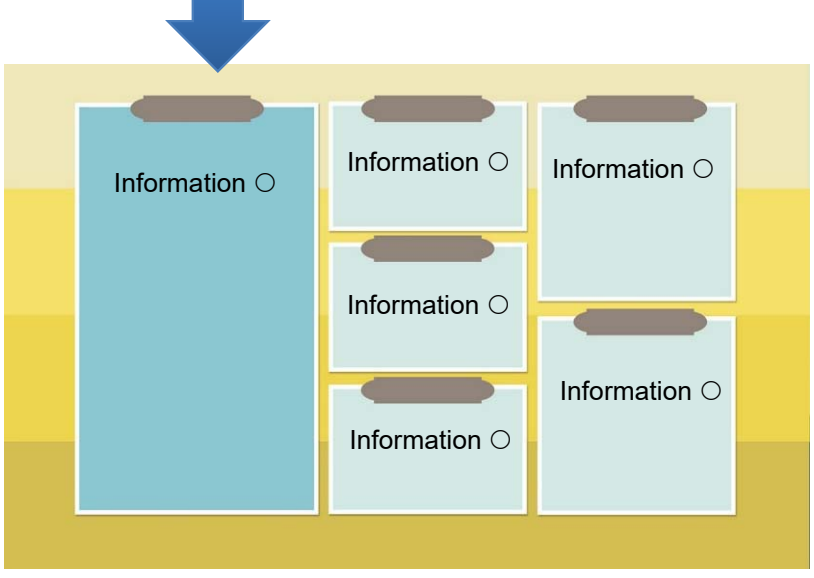
<Factors determining matters necessary for evaluation>
- Hazards identified for medical device or material
- Nature, degree, frequency and duration of exposure

Assessment of the information already available then enables a gap analysis to facilitate the selection of appropriate tests.

Testing is not necessary since sufficient information is already available for assessment.

Testing is performed for missing information.





Added concept (3)

Person responsible for evaluation (Section 4.1)

Biological evaluation is performed by knowledgeable and experienced professionals.

- Person responsible for evaluation

- **Document** the discussion (validity) from the following viewpoints (advantages/disadvantages).

a) Medical device configuration (e.g., size, geometry, surface properties)
   Listing of a medical device's materials of construction (qualitative)
   Proportion and amount (mass) of each material in the medical device (quantitative)
b) Physical and chemical characteristics of the materials of construction and their composition
c) History of clinical use or human exposure data
d) Existing toxicology and other biological safety data on product and component materials, breakdown products and metabolites
e) Test procedures

If necessary

Literature can be cited if it is already documented.

Previous approval data can be used.

Added concept (4)

Systematic approach to biological evaluation (Section 4.1)

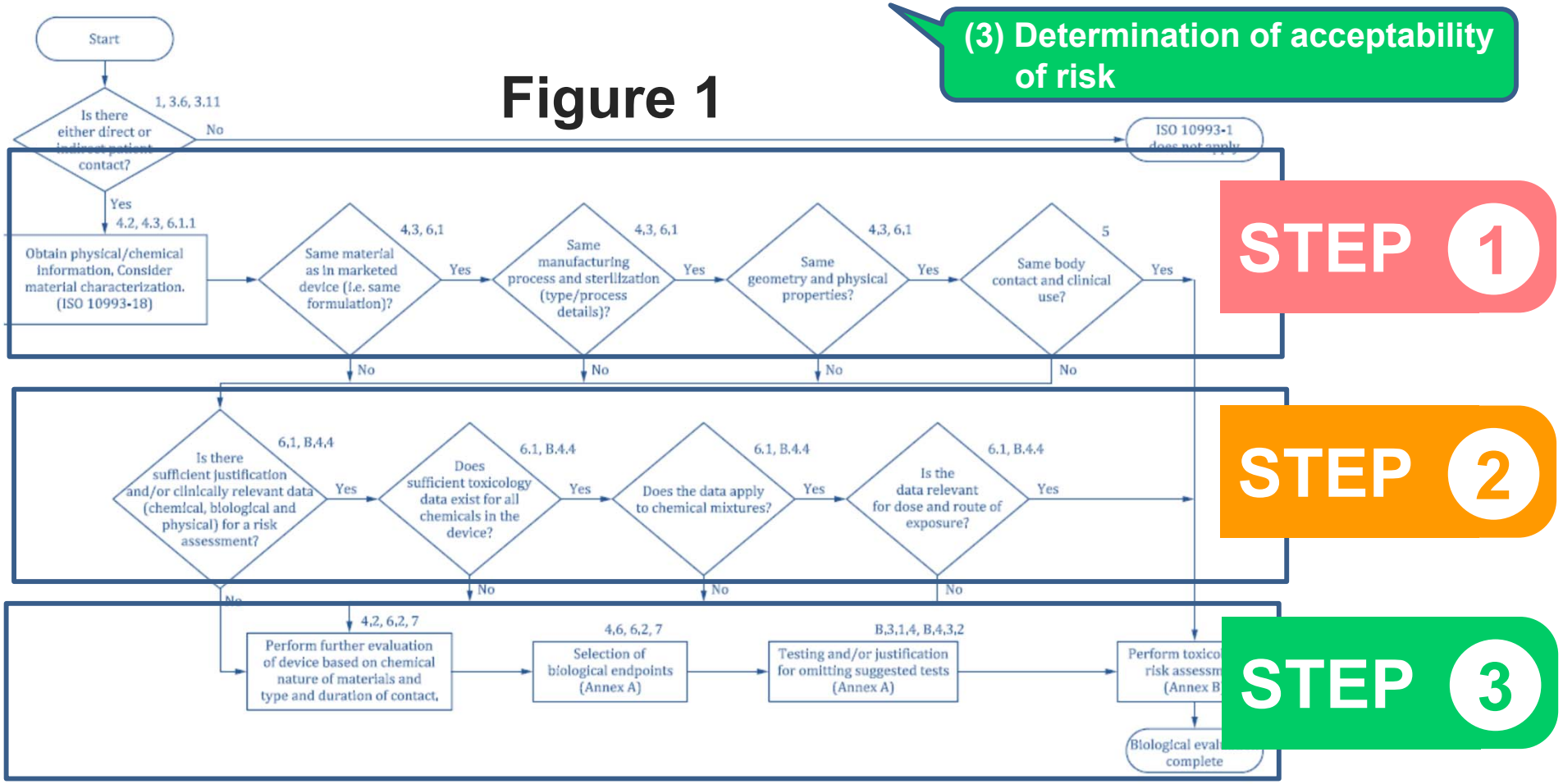
Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process

(1) Identification of biological hazards

(2) Estimation of biological risks

(3) Determination of acceptability of risk

Figure 1



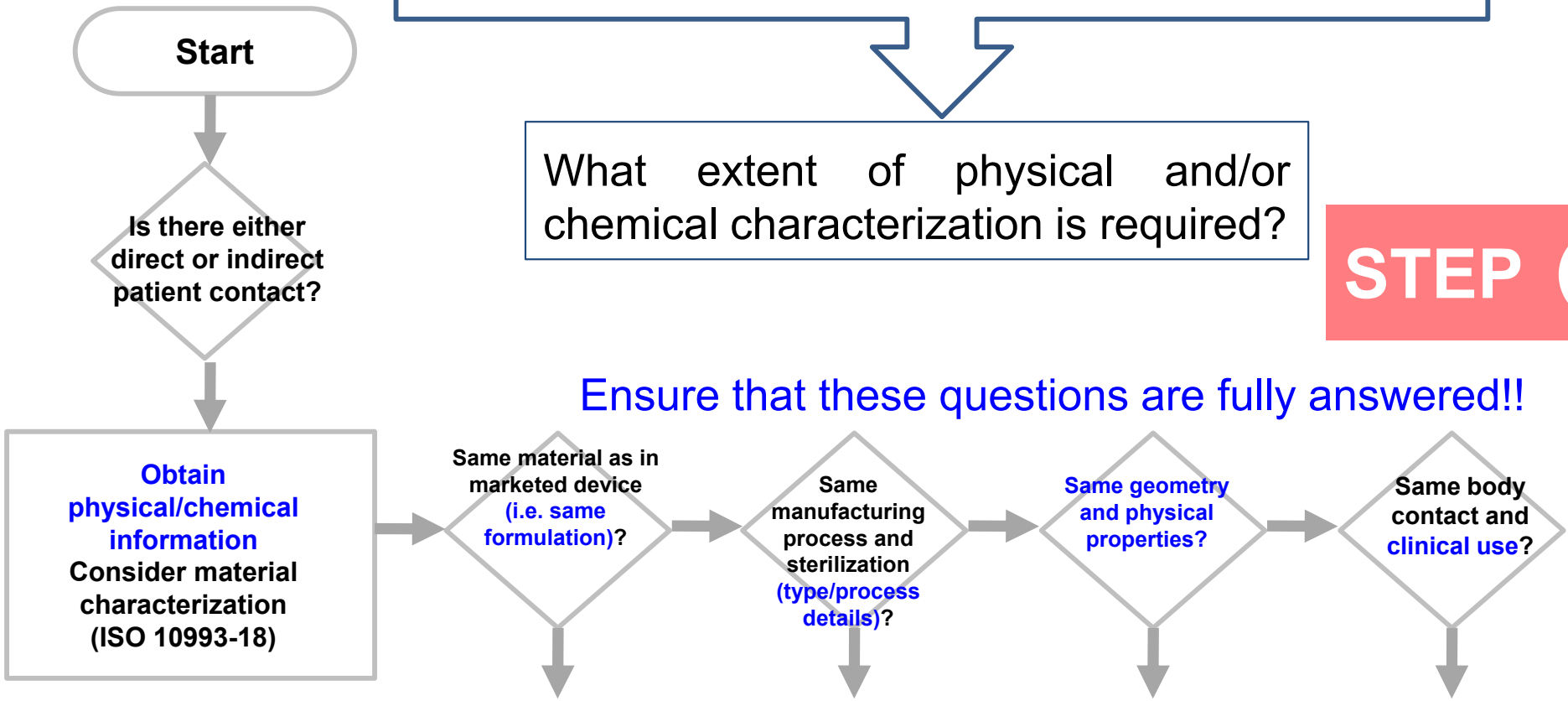
Additional assessments (1)

Physical and/or chemical information (Section 6.1)

- Material formulation
- Nature and duration of body contact of medical devices

What extent of physical and/or chemical characterization is required?

STEP 1



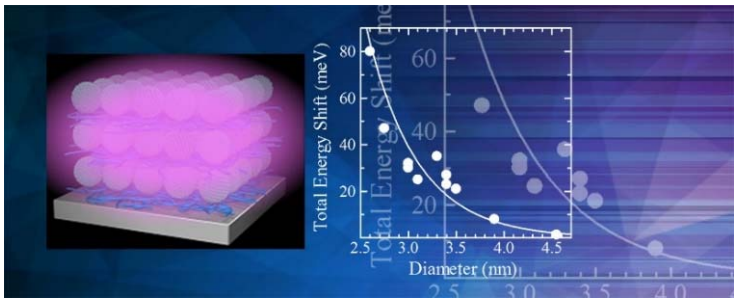
Ensure that these questions are fully answered!!

Additional assessments (2)

Expansion of application (Section 1)

- Applicable materials and medical devices
  - Intended use: Patient's body
  - Medical devices intended for protection (e.g., surgical gloves, masks and others): User's body
- This document can also be used for the assessment of biological hazards arising from
  - Risks such as changes over time
  - Exposure to new materials due to breakage

Nanomaterial (Section 3.15, Section 6.3.2)

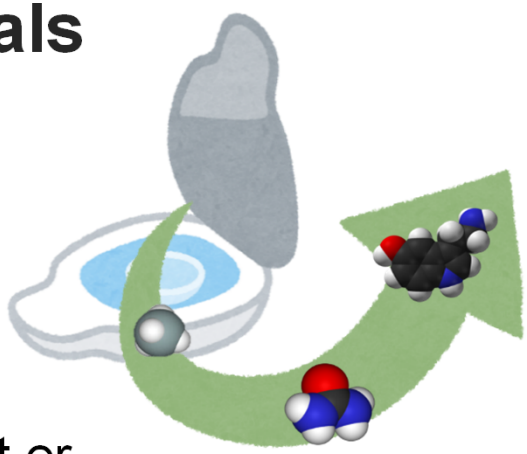


- If nanomaterial particle release is possible
  ➡ **ISO / TR 10993-22**
- Application of nanomaterial to test systems
  Interpretation of test results of nanomaterials

Specific problems may occur
Example) Assay interference
(see ISO/TR 10993-22)

Additional assessments (3)

Impact of packaging materials (Section 4.3 c)



- Direct or indirect contact with the medical device

➡ Chemicals transferred to medical device

➡ Possibility of indirect contact with patient or clinician

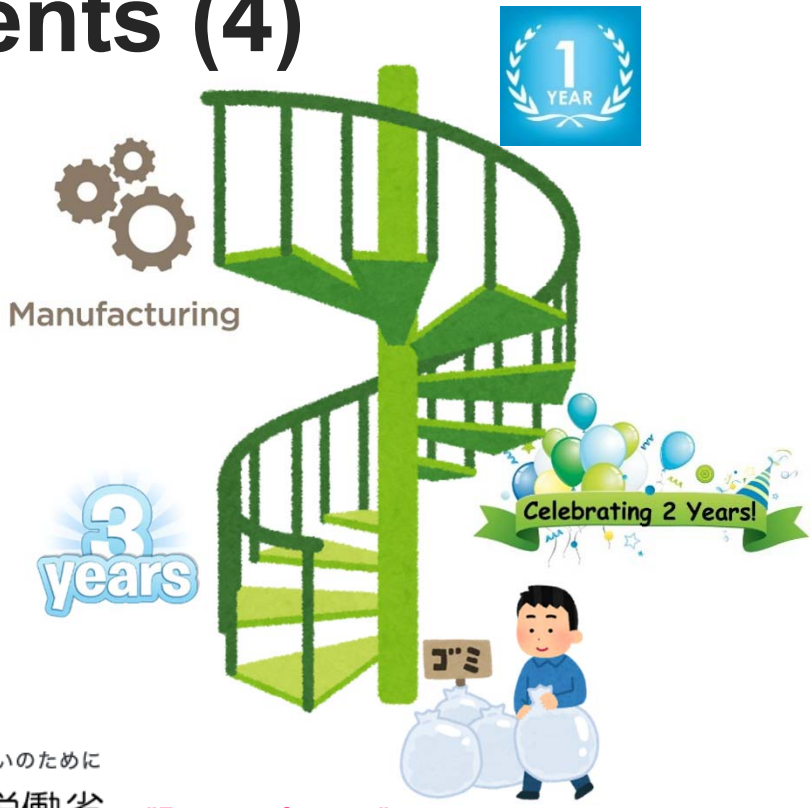
Medical devices in contact with gas (Section 5.1 Example 2)

- Gas pathway device components (with only indirect contact)

➡ Device specific standards (**ISO 18562** Biocompatibility Evaluation of Respiratory Gas Pathways in Healthcare Applications) should be used to determine the relevant type of biocompatibility evaluations.

Additional assessments (4)

Life-cycle of a medical device (Section 4.7)



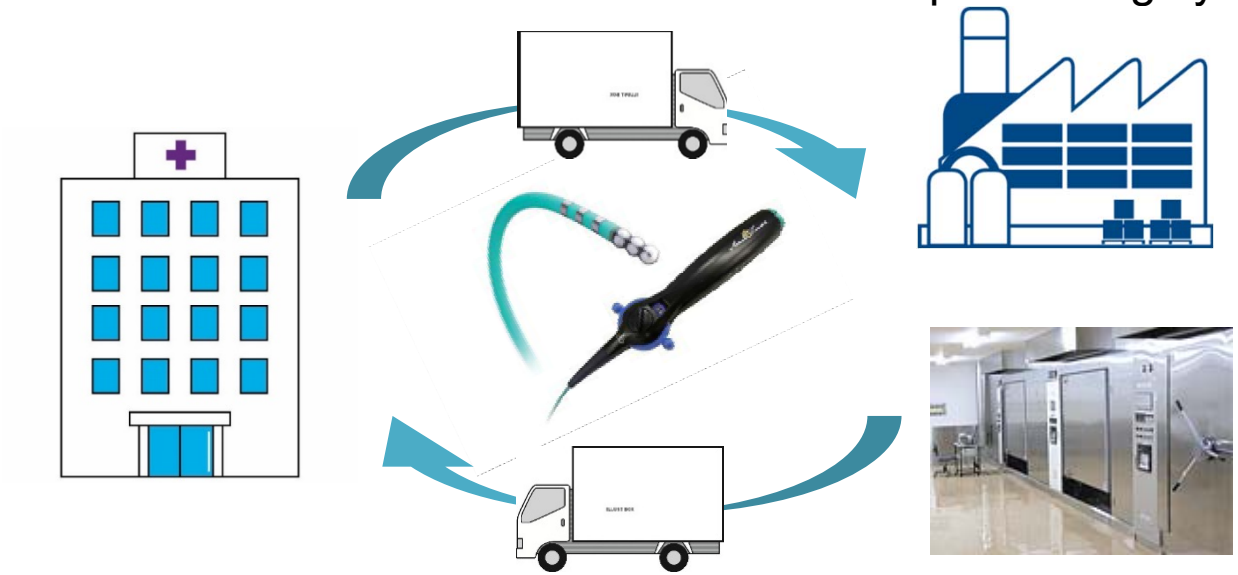
- Evaluate biological safety over the whole life-cycle

Re-usable medical device (Section 4.8)

JIS "Reuse"

ひと、くらし、みらいのために 厚生労働省 Ministry of Health, Labour and Welfare "Remanufacture"

- Evaluate for the maximum number of validated reprocessing cycles



Additional assessments (5)

Categorization by nature of body contact (Section 5.2)

- Non-contacting medical devices

Neither direct nor indirect contact with the body
➡ Biocompatibility evaluation is not needed.

- Surface-contacting medical devices
  - a) Skin
  - b) Mucosal membranes
  - c) Breached or compromised surface

If it ca be made of commonly used materials with similar nature of contact
➡ No further biological evaluation is needed.



- Externally communicating medical device
  - a) Blood path, indirect
  - b) Tissue/bone/dentin
  - c) Circulating blood

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



- Implant medical devices
  - a) Tissue/bone
  - b) Blood

Clarification that assessment is not required

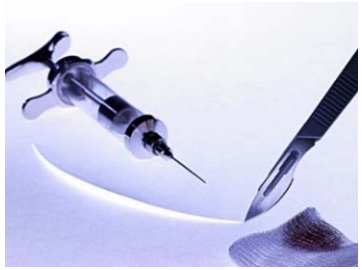
Transitory-contacting medical devices (Section 5.3.2)

Medical devices with very brief/transitory contact with the body

Example) Lancets that are used for less than one minute
Hypodermic needles
Capillary tubes

Testing to address biocompatibility is generally not required

<Attention to remaining substances> Coatings and lubricants
When some substance may remain in a patient after use of the medical device
➡ A more detailed biocompatibility assessment may be necessary.
<Cumulative use should also be considered>



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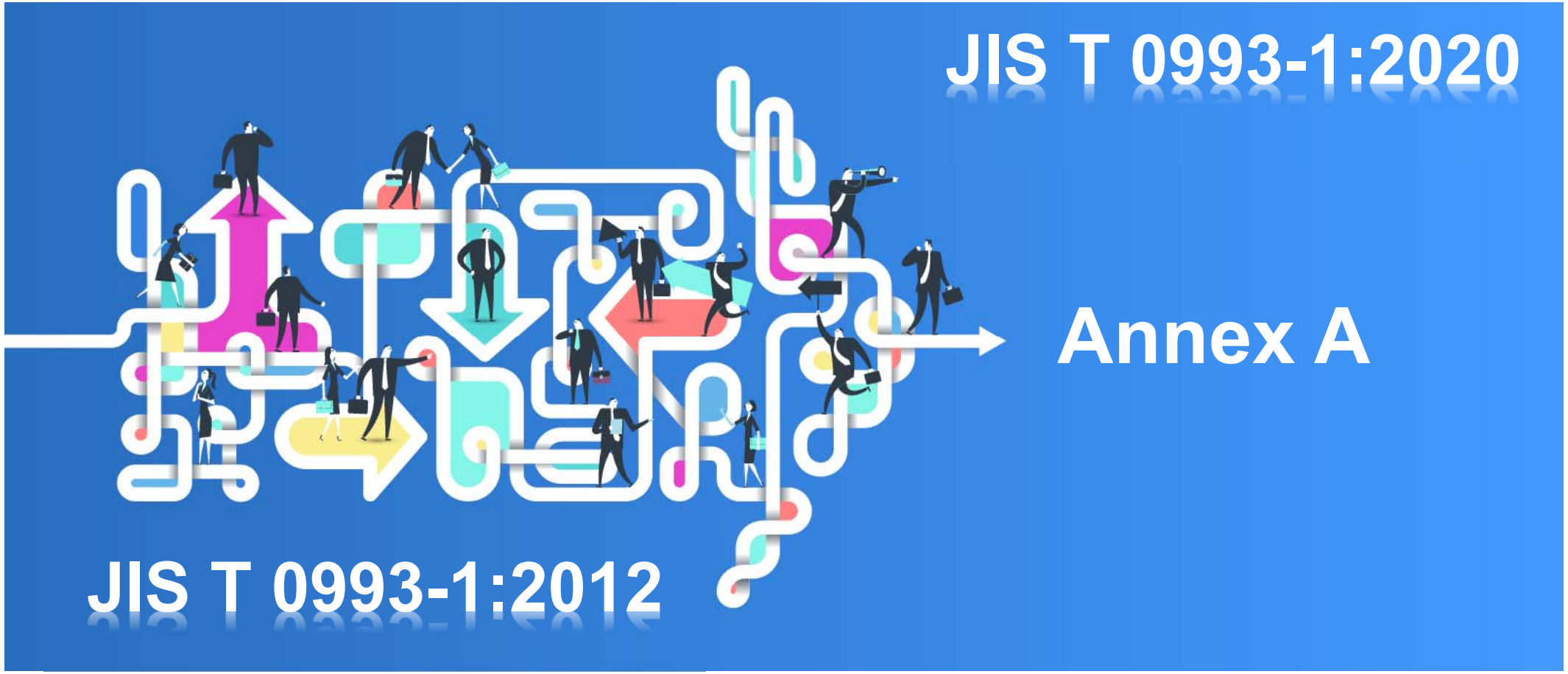

JIS T 0993-1:2020
Annex A
JIS T 0993-1:2012

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	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	Hemocompatibility	Genotoxicity	Carcinogenicity	Reproductive/developmental toxicity	Degradation
Category	Contact	A: limited (≤ 24 h) B: prolonged (> 24 h to ≤ 30 d) C: Long-term (> 30 d)															

X Information required prior to risk assessment

E Endpoints to be evaluated

A risk assessment is any of the following:

- Evaluation using existing toxicology data.
- Conduct of the biological safety tests as presented in the endpoints.
- Rationale for omission of tests, if applicable.

Use of new materials + no toxicology data available ➡ **E+α**

Characteristics of medical devices ➡ **E ± α**

Number of endpoints based on evaluation

Medical device categorization by			Endpoints of biological evaluation															
Nature of body contact		Contact duration	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	Hemocompatibility	Genotoxicity	Carcinogenicity	Reproductive/developmental toxicity	Degradation
Category	Contact	A: limited (≤ 24 h) B: prolonged (> 24 h to ≤ 30 d) C: Long-term (> 30 d)															
Surface medical device	Intact skin	A	X	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	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*			
		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 devices	Tissue/bone	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		

JIS : Yes
No. 20: No

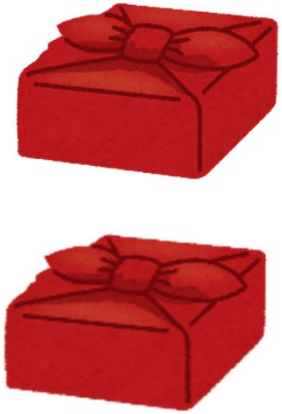
● JIS : No
No. 20: Yes

*: Applicable only to devices used for extracorporeal circulation equipment

JIS T 0993-1 and FDA guidance

Medical device categorization by			Endpoints of biological evaluation													
Nature of body contact		Contact duration	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity	Acute systemic toxicity	Subacute/Subchronic toxicity	Chronic toxicity	Implantation effects	Hemocompatibility	Genotoxicity	Carcinogenicity	Reproductive/developmental toxicity	Degradation
Category	Contact	A: limited (≤ 24 h) B: prolonged (> 24 h to ≤ 30 d) C: Long-term (> 30 d)														
Surface medical device	Intact skin	A	X	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			
	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		
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		
	Tissue/bone/dentin	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		
	Circulating blood	A	X	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		
Implant medical devices	Tissue/bone	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		
	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		

Note: "Subacute systemic toxicity" and "Subchronic systemic toxicity" are summarized as a single item in FDA guidance.



▲ JIS: No
FDA: Yes

*: Applicable only to devices used for extracorporeal circuits (JIS)

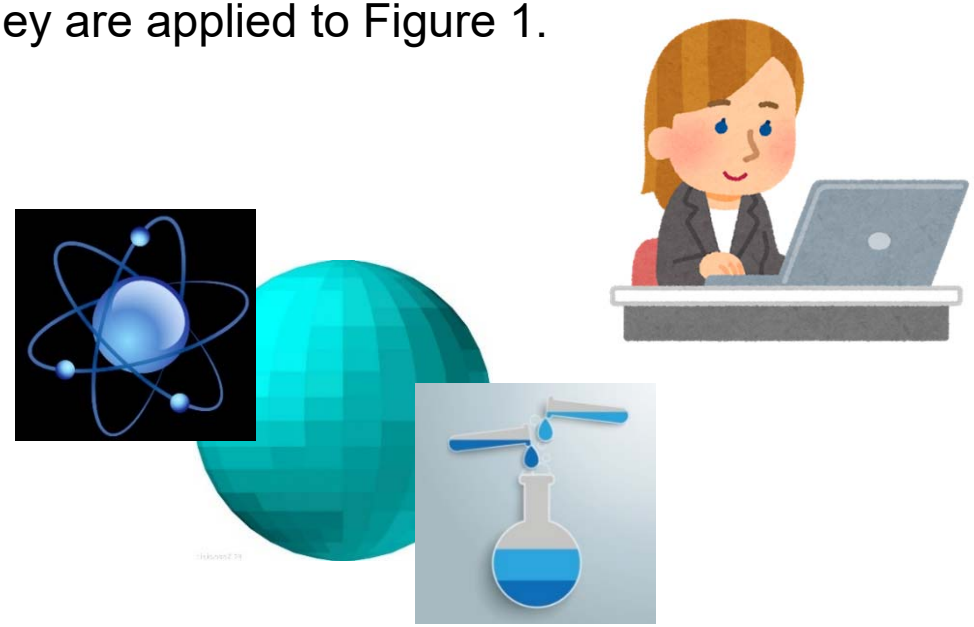
Physical and/or chemical information

Medical device categorization by			Endpoints of biological evaluation
Nature of body contact		Contact duration	
Category	Contact	A: li (≤ B: (> C: Long-term	Physical and/or chemical information
Surface medical device	Intact skin	A B C	X X X
	Mucosal membrane	A B C	X X X
	Breached or compromised surface	A B C	X X X
Externally communicating medical device	Blood path, indirect	A B C	X X X
	Tissue/bone/ dentin	A B C	X X X
	Circulating blood	A B C	X X X
Implant medical devices	Tissue/bone	A B C	X X X
	Blood	A B C	X X X

Required Item

For all medical devices, this information is used to determine whether further biological safety test is required.

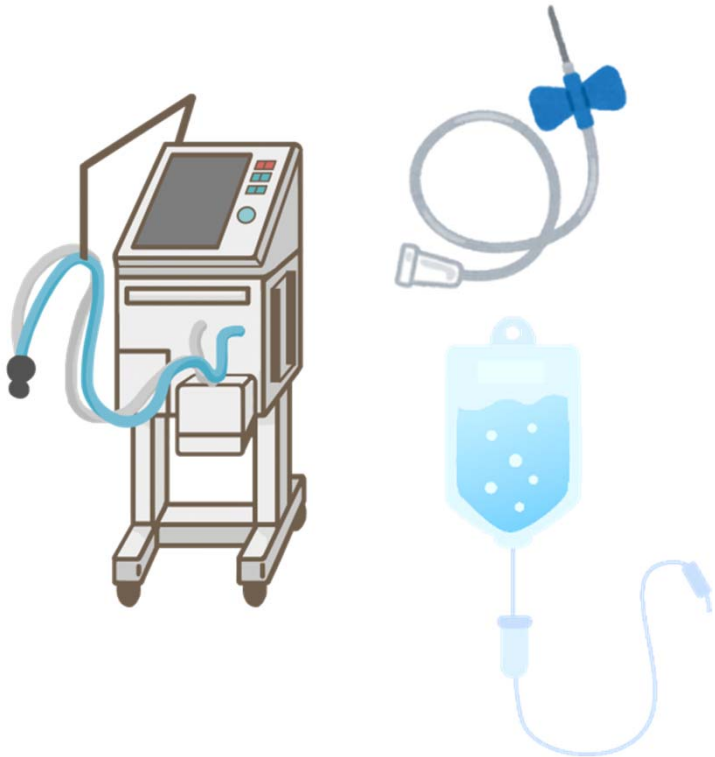
First, physical/chemical information is collected to characterize the product.
They are applied to Figure 1.



Irritation or intracutaneous reactivity

Medical device categorization by			Endpoints of biological evaluation
Nature of body contact		Contact duration	Irritation or intracutaneous reactivity
Category	Contact	A: limited B: prolonged C: Long-term	
Surface medical device	Intact skin	A	E
		B	E
		C	E
	Mucosal membrane	A	E
		B	E
		C	E
	Breached or compromised surface	A	E
		B	E
		C	E
Externally communicating medical device	Blood path, indirect	A	E
		B	E
		C	**E**
	Tissue/bone/dentin	A	E
		B	E
		C	E
	Circulating blood	A	E
		B	E
		C	E
Implant medical devices	Tissue/bone	A	E
		B	E
		C	E
	Blood	A	E
		B	E
		C	E

Components that have long term indirect contact with blood (e.g., infusion systems) can produce irritants in the blood stream.



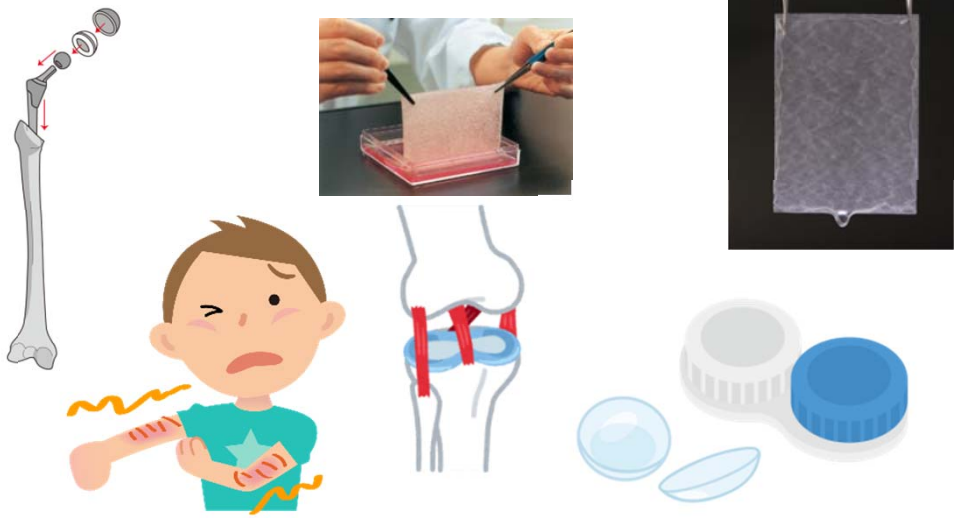
Material mediated pyrogenicity
Acute systemic toxicity

Medical device categorization by			Endpoints of biological evaluation	
Nature of body contact		Contact duration		
Category	Contact	A: limited B: prolonged C: Long-term	Material mediated pyrogenicity	Acute systemic toxicity
Surface medical device	Intact skin	A		
		B		
		C		
	Mucosal membrane	A		
		B		**E**
		C		**E**
	Breached or compromised surface	A	**E**	**E**
		B	**E**	**E**
		C	**E**	**E**
Externally communicating medical device	Blood path, indirect	A	E	E
		B	E	E
		C	E	E
	Tissue/bone/dentin	A	**E**	**E**
		B	**E**	E
		C	**E**	E
	Circulating blood	A	E	E
		B	E	E
		C	E	E
Implant medical devices	Tissue/bone	A	**E**	**E**
		B	**E**	E
		C	**E**	E
	Blood	A	E	E
		B	E	E
		C	E	E

Since the extractables or leachables can be:

- Introduced to the systemic circulation through the compromised surface.
- Introduced to the systemic circulation, lymphatic system, and/or cerebrospinal fluid via mucosal membrane.
- Introduced to the systemic circulation, lymphatic system, and/or cerebrospinal fluid from tissue fluid surrounding the tissue/bone.

Those entering the systemic circulation should also be evaluated for pyrogenicity and acute systemic toxicity.
It is also absorbed from the mucosal membrane.

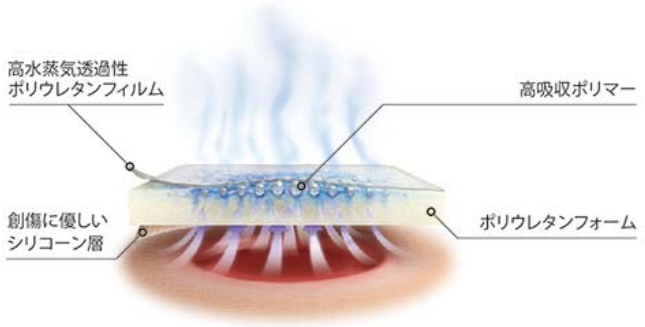


Subacute toxicity

Medical device categorization by			Endpoints of biological evaluation
Nature of body contact		Contact duration	
Category	Contact	A: limited B: prolonged C: Long-term	Subacute toxicity
Surface medical device	Intact skin	A B C	
	Mucosal membrane	A B C	 **E** E
	Breached or compromised surface	A B C	 **E** E
Externally communicating medical device	Blood path, indirect	A B C	 **E** E
	Tissue/bone/ dentin	A B C	 E E
	Circulating blood	A B C	 E E
Implant medical devices	Tissue/bone	A B C	 E E
	Blood	A B C	 E E

Use of medical devices or components for more than 24 hours may result in uptake of extractables or leachables to the systemic circulation, lymphatic system, and/or cerebrospinal fluid.

If the extractables can be introduced to the body for more than 24 hours, subacute toxicity should be evaluated.

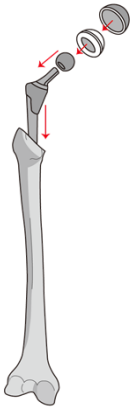


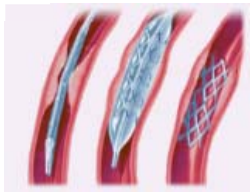
Subchronic toxicity
Chronic toxicity

Medical device categorization by			Endpoints of biological evaluation	
Nature of body contact		Contact duration	Subchronic toxicity	Chronic toxicity
Category	Contact	A: limited B: prolonged C: Long-term		
Surface medical device	Intact skin	A B C		
	Mucosal membrane	A B C	E	**E**
	Breached or compromised surface	A B C	E	**E**
Externally communicating medical device	Blood path, indirect	A B C	E	**E**
	Tissue/bone/dentin	A B C	E	**E**
	Circulating blood	A B C	E	**E**
Implant medical devices	Tissue/bone	A B C	E	**E**
	Blood	A B C	E	**E**

Use of medical devices or components for more than 30 days may result in uptake of extractables or leachables into the systemic circulation, lymphatic system, and/or cerebrospinal fluid.

Longer than 30 days = chronic





Implantation effects

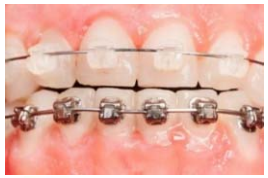
Medical device categorization by			Endpoints of biological evaluation
Nature of body contact		Contact duration	Implantation effects
Category	Contact	A: limited B: prolonged C: Long-term	
Surface medical device	Intact skin	A B C	
	Mucosal membrane	A B C	 **E** **E**
	Breached or compromised surface	A B C	 **E** **E**
Externally communicating medical device	Blood path, indirect	A B C	 **E**
	Tissue/bone/dentin	A B C	 E E
	Circulating blood	A B C	 E E
Implant medical devices	Tissue/bone	A B C	 E E
	Blood	A B C	E E E

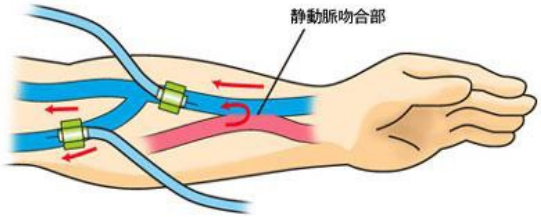
Because it is desirable to examine local and systemic effects when the device is implanted in the body

Rather than implantation, local reaction of tissues should be evaluated.

When the medical device with direct contact is used in combination, the extractables or leachables that are taken into the blood stream from the components that have indirect contact with blood may affect the inflammatory reaction caused by direct contact with the medical device used in combination.

➡ Evaluation of systemic toxicity + implantation in direct contact site



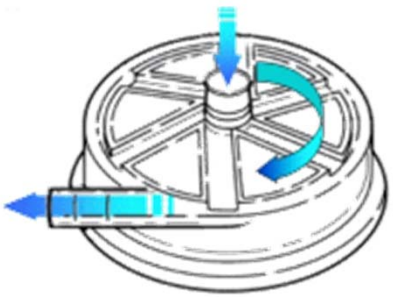


Genotoxicity

Medical device categorization by			Endpoints of biological evaluation
Nature of body contact		Contact duration	
Category	Contact	A: limited B: prolonged C: Long-term	Genotoxicity
Surface medical device	Intact skin	A B C	
	Mucosal membrane	A B C	E
	Breached or compromised surface	A B C	E
Externally communicating medical device	Blood path, indirect	A B C	E
	Tissue/bone/dentin	A B C	E E
	Circulating blood	A B C	**E** E E
Implant medical devices	Tissue/bone	A B C	E E
	Blood	A B C	**E** E E

Since the extractables or leachables may be taken into the blood stream and remain in the body even after the medical device is removed

Risk that the contact area is large, and the leachables enter at once and remain. Plasticizers, etc.

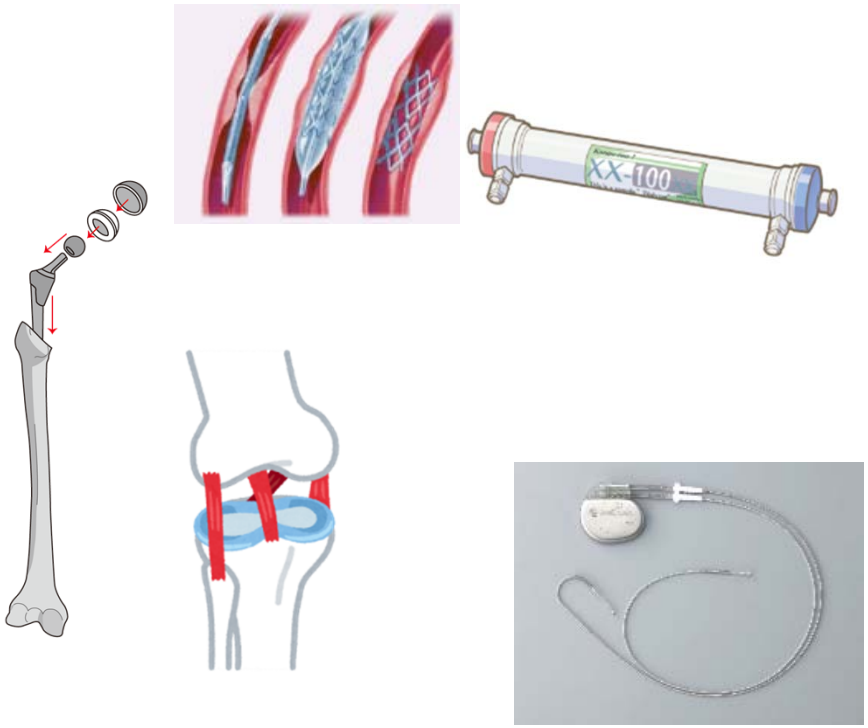


Carcinogenicity

Medical device categorization by			Endpoints of biological evaluation
Nature of body contact		Contact duration	Carcinogenicity
Category	Contact	A: limited B: prolonged C: Long-term	
Surface medical device	Intact skin	A B C	
	Mucosal membrane	A B C	
	Breached or compromised surface	A B C	E
Externally communicating medical device	Blood path, indirect	A B C	E
	Tissue/bone/dentin	A B C	E
	Circulating blood	A B C	E
Implant medical devices	Tissue/bone	A B C	E
	Blood	A B C	E

Since the extractables or leachables s can be introduced to the systemic circulation, lymphatic system, and/or cerebrospinal fluid

Carcinogenic risk should be evaluated in the first place.



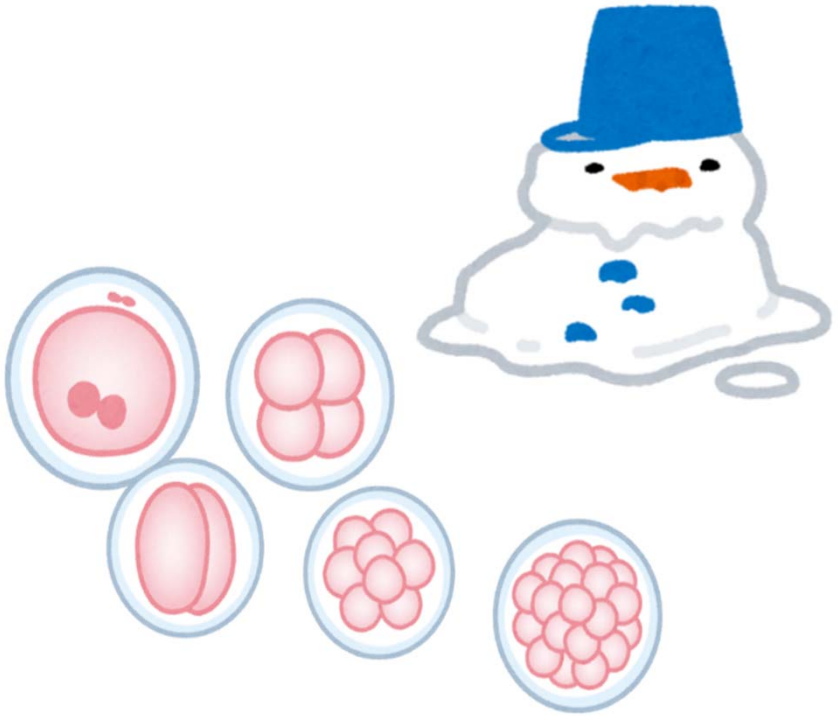
Reproductive/developmental toxicity Degradation

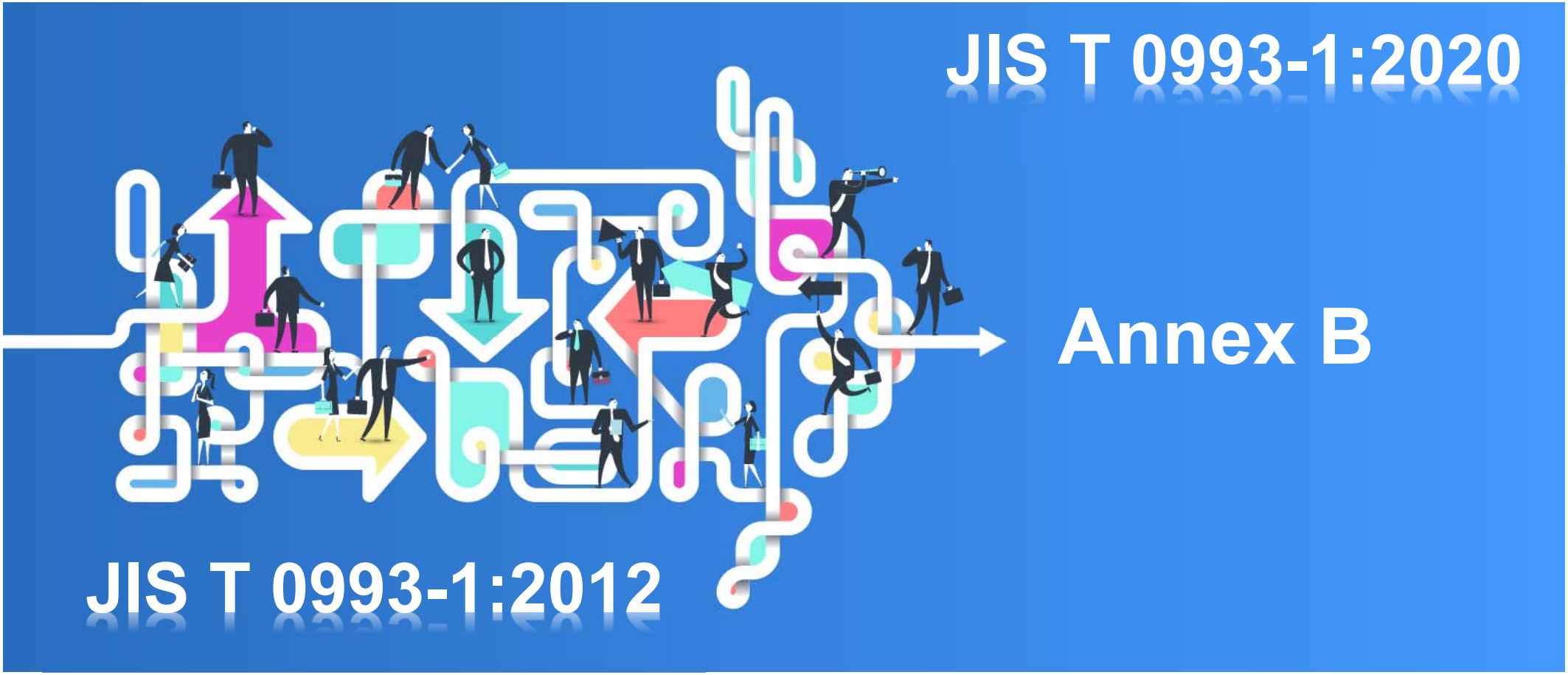
Medical device categorization by			Endpoints of biological evaluation	
Nature of body contact		Contact duration		
Category	Contact	A: limited B: prolonged C: Long-term	Reproductive/developmental toxicity	Degradation
Surface medical device	Intact skin	A B C		
	Mucosal membrane	A B C		
	Breached or compromised surface	A B C		
Externally communicating medical device	Blood path, indirect	A B C		
	Tissue/bone/ dentin	A B C		
	Circulating blood	A B C		
Implant medical devices	Tissue/bone	A B C		
	Blood	A B C		

Investigate the effect on the next generation

Investigate the effect of changes in the properties of the device

If no leachable substances/degradation products have been identified, risk assessment is required.
Both reproductive/developmental toxicity and degradation are important.




JIS T 0993-1:2020
Annex B
JIS T 0993-1:2012

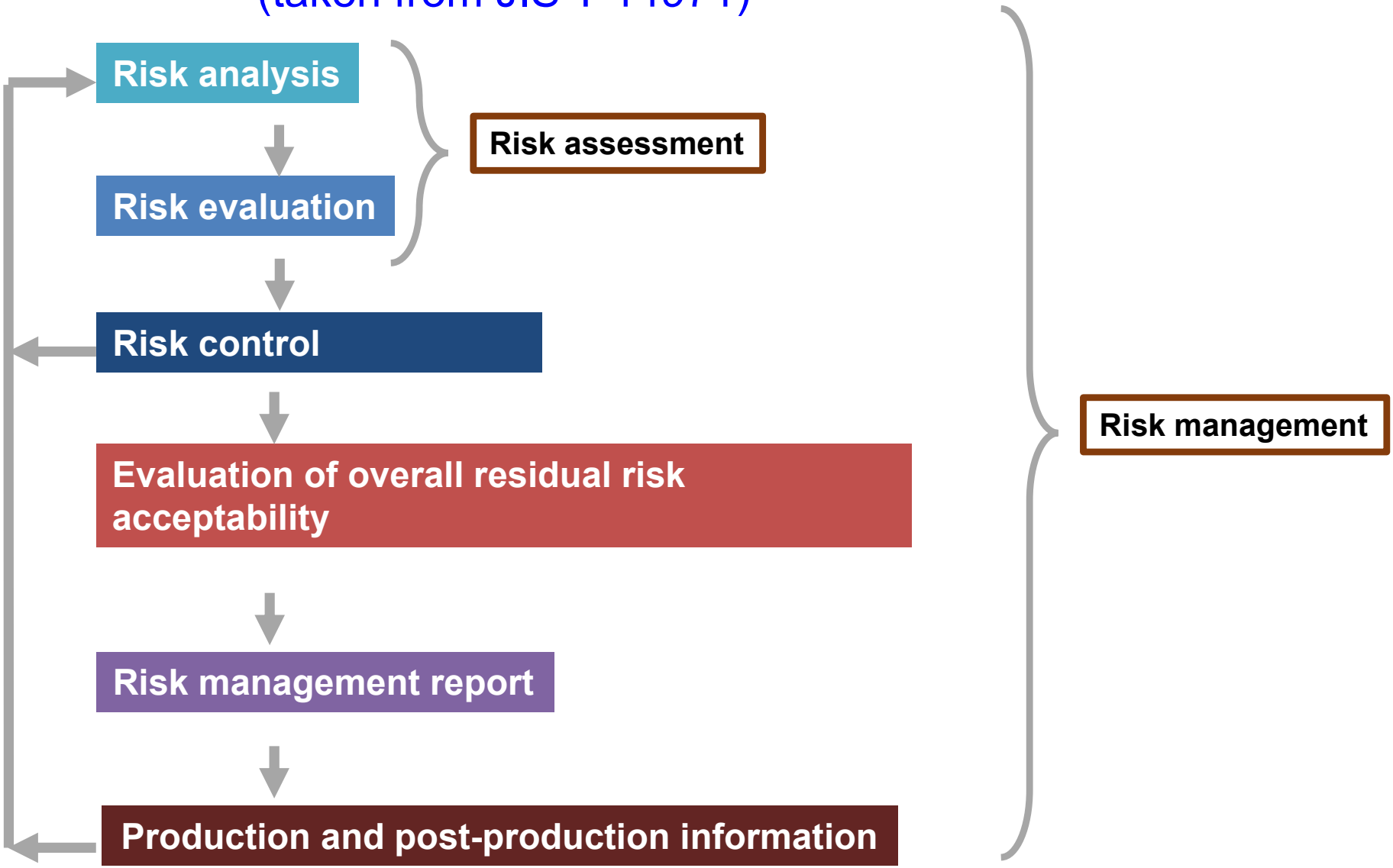
Annex B

Guidance on the conduct of biological evaluation within the risk management process

Guidance for biological safety evaluation based on JIS T 14971

B.3 Guidance on risk management

Figure B.1 A shematic representation of the risk management process (taken from JIS T 14971)



Risk analysis

Risk analysis Risk analysis

1. Intended use and identification of characteristics related to the safety of the medical device
2. Identification of hazards
3. Estimation of the risk for each hazardous situation

➡ **Clarify the purpose of development, subjects, and problems in use of medical devices.**

- The amount of data required for risk analysis and the depth of analysis differ depending on the intended use.
- Safety requirements differ depending on the nature and duration of contact with the tissue.

Risk evaluation

Risk evaluation

B.3.1.4 Risk evaluation

The step following the risk analysis

- As a result of risk analysis, the significance of identified risks is evaluated.
- Requirements and opportunities to control (mitigate) the risk are identified.

  - Biocompatibility must be evaluated under conditions specific to the medical device.
  - Consider the toxicity of extractable/leachable chemicals by taking into account information on routes and duration of exposure, uptake rate in the body, etc.
  - Clinical use history and data on similar approved products are useful.

Biological risk evaluation:
Conducted by assessors with the necessary knowledge and expertise who can strictly evaluate available data. (Person who can make appropriate judgments in response to requests for additional tests)

Risk control

Risk control

B.3.2 Risk control

Process of identifying and implementing measures to reduce risks

When **risk control** leads to design change:

- Reduce exposure time.
- Change surface properties (shape) to minimize areas of thrombus formation.
- Prevent production of harmful substances (particulation, coating delamination).
- Change material containing toxic substances or reformulation.
- Change production processes to reduce hazardous residues or additives.

×N

Implementation of risk control ➡ Evaluation of residual risk
Risk benefit analysis

Risk analysis

Identification of new risks arising as a result of risk control

"Risk control" is finally completed.

Evaluation of overall residual risk acceptability

Evaluation of overall residual risk acceptability

B.3.3 Evaluation of residual risk acceptability

Review the findings of these preceding activities and document the residual risk, disclosure of such residual risks (labeling, cautions or warnings)

Risks with uncertainty identified in risk controls are mitigated by warnings and contraindications.

Risk management report

Risk management report

Risk management report

7. Interpretation of biological evaluation data and overall biological risk assessment

a) Strategy and plan for biological evaluation of the medical device

b) Criteria to determine whether the material is acceptable for its intended use in line with the risk management plan

c) Adequacy of material characterization

d) Rationale for selection/waiving of tests

e) Interpretation of existing data and test results

f) Necessity of additional data to complete the biological evaluation

g) Overall conclusion on biological safety of the medical device

Collection of production and post-production information

Production and post-production information

B. 3.4 Post-production monitoring

To be updated with new information that becomes available from post market monitoring of medical device performance and safety in actual clinical use.

This monitoring should include information on adverse events of medical devices of concern, the latest findings on similar medical devices and materials, ongoing review of relevant scientific literature, etc.

1. History and Points of Revision of JIS T0993-1 (Text)

2. Revisions in JIS T0993-1 (Annexes A and B)

3. Impact of the revisions including the revisions to the Japanese guidance (2020)

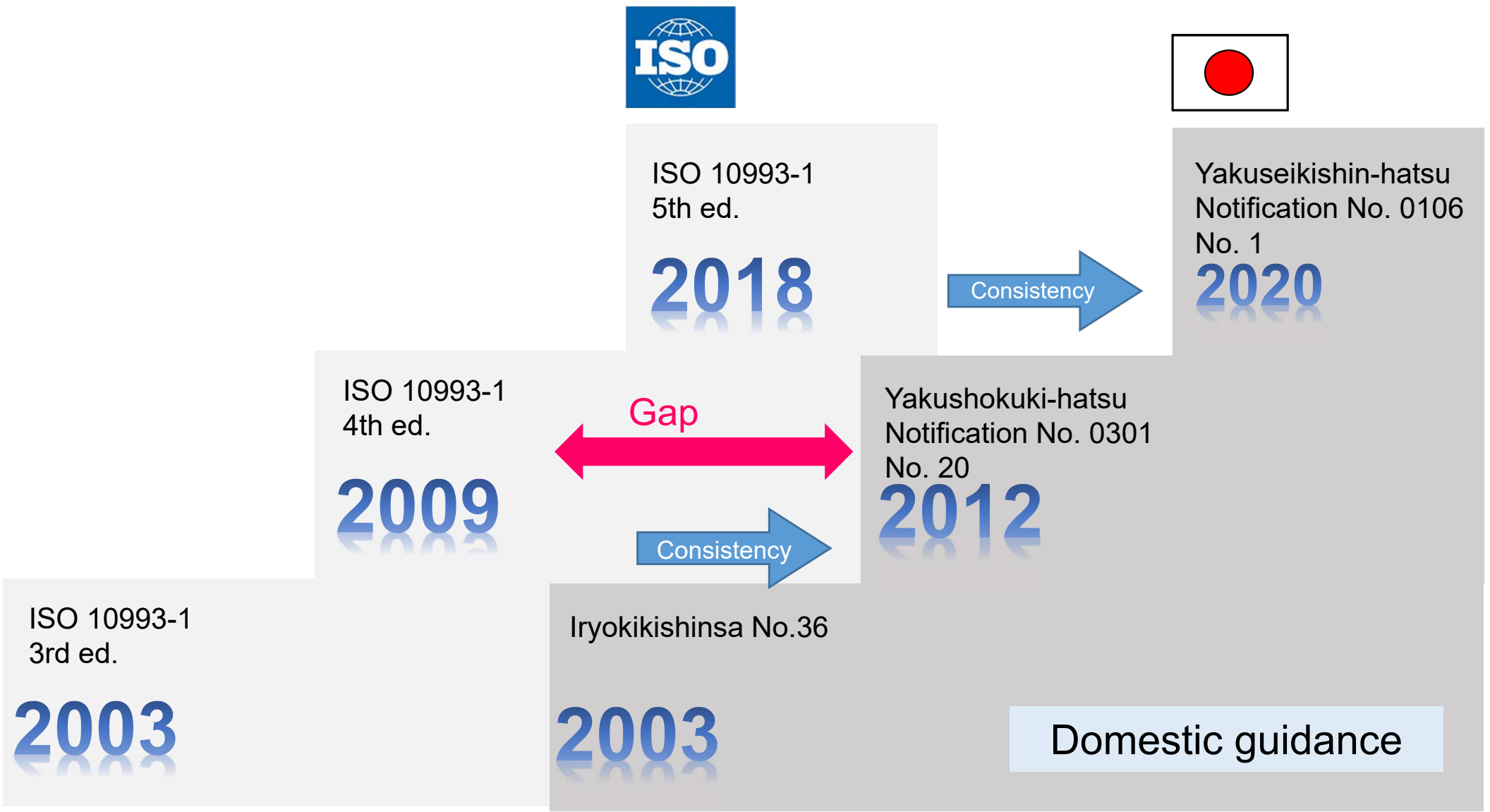
Gaps left

Japan and overseas: Differences in concept

Gap to ISO 10993-1: 2009

Good-bye to No. 20 Characteristics of domestic guidance

Gap structure



Japan and overseas: Differences in concept (1)

Gap to ISO 10993-1: **2009**

Part 1
Responsibilities for medical device malfunction

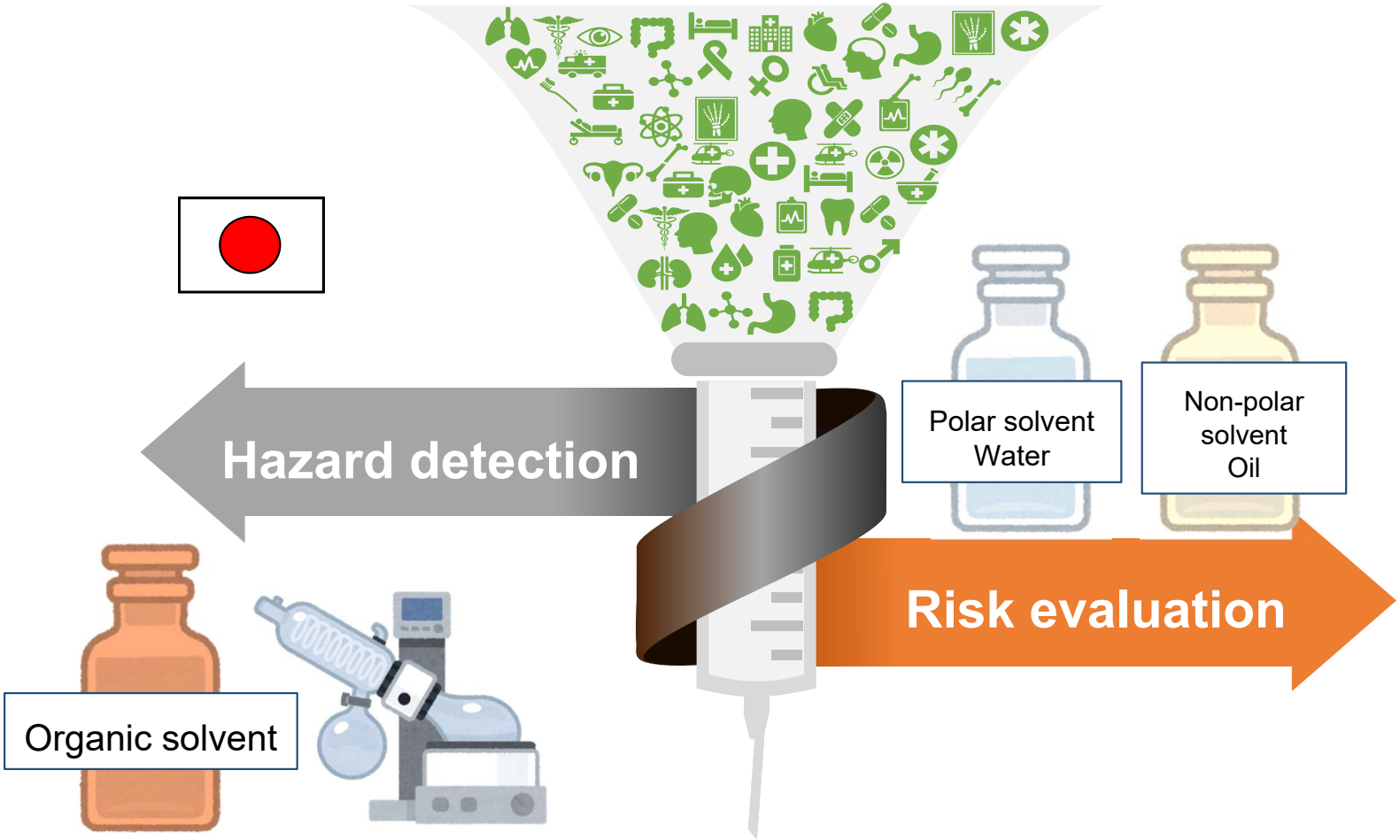
ひと、くらし、みらいのために
厚生労働省
Ministry of Health, Labour and Welfare

Medical device manufacturer/ distributor

Japan and overseas: Differences in concept (2)

Gap to JIS T 0993-1: **2012**

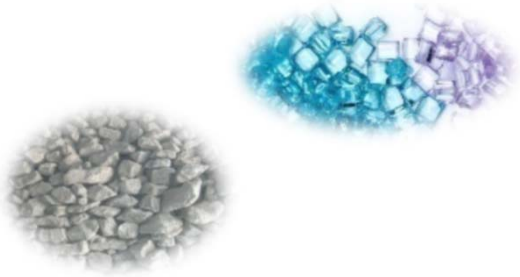
Part 2
Hazards and risks
Exhaustive extraction and clinical application

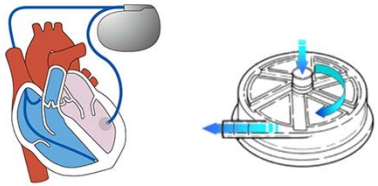


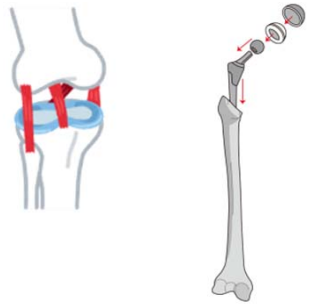
Japan and overseas: Differences in concept (3)

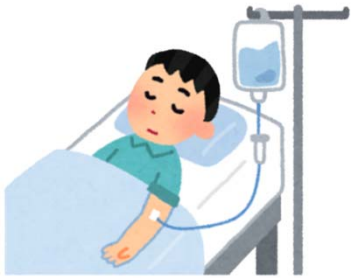
Gap to ISO 10993-1: **2009**

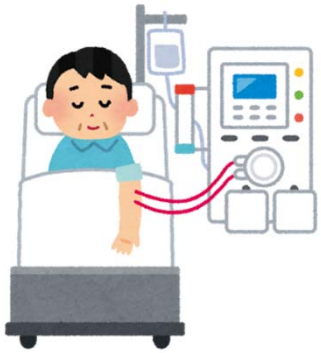
Part 3
Raw materials and final products



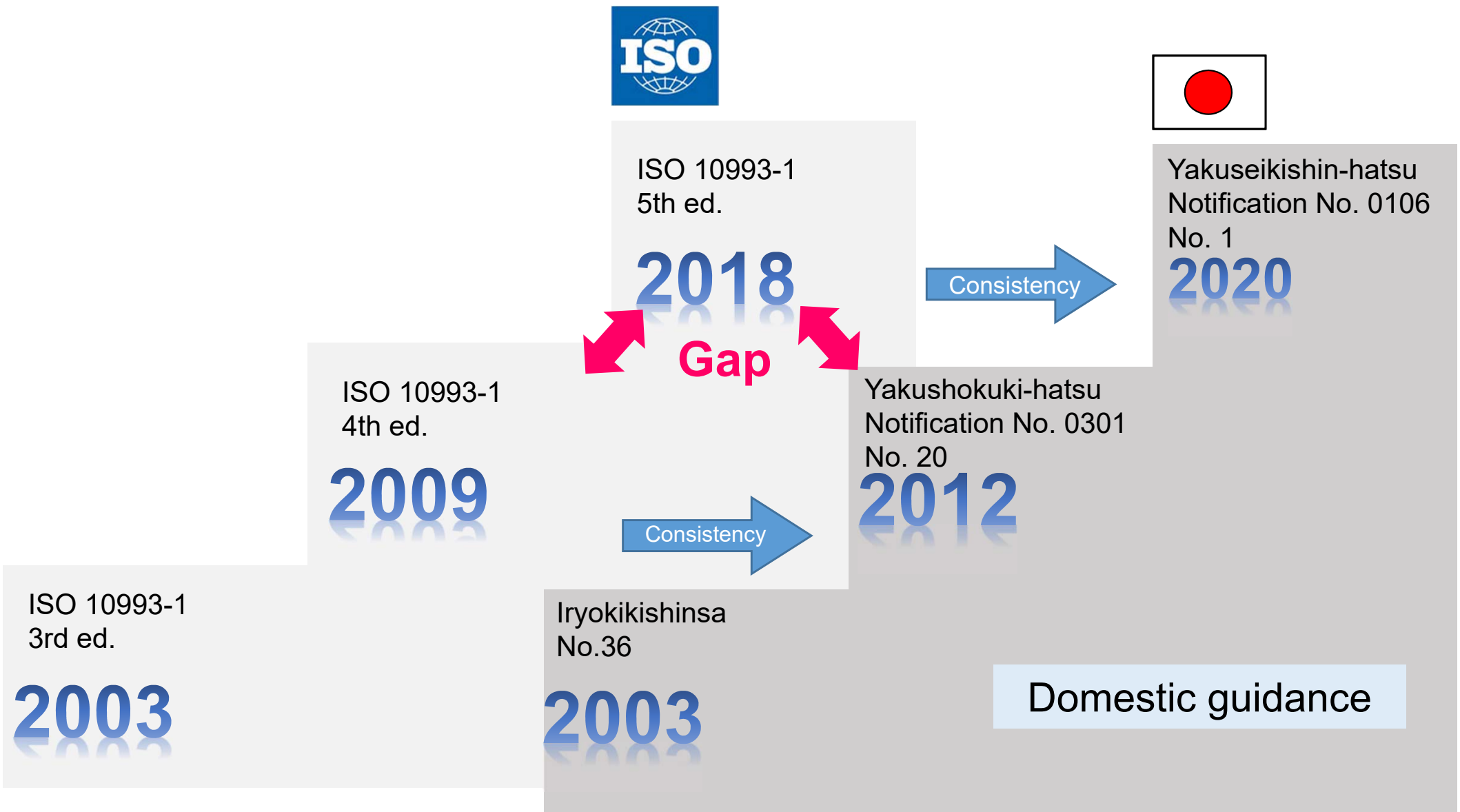








Gap structure



Revisions from Yakushokuki-hatsu Notification No. 0301-20

In consideration of harmonization with JIS T 0993-1, the following revisions were mainly made.

1) Added that the biological safety evaluation of medical devices shall be performed as a part of verification work in the risk management process of JIS T 14971 or ISO 14971.

2) Ensured consistency with the definitions, terms, and evaluation procedure specified in JIS T 0993-1.

3) Described precautions for reusable medical devices, nanomaterials, transitory-contacting medical devices, biodegradation evaluation, reproductive and developmental toxicity, and carcinogenicity evaluation.

4) Added that the study should be conducted in compliance with GLP in principle.

Differences in concept still remain.

Impact of revision (1)

Annex B

B.4 Guidance on specific aspects of biological evaluation

B.4.1 Material characterization

B.4.1.1 Chemical characterization

Chemical characterization is effective when:

- The issues of proprietary nature can be resolved.
- A small number of chemical constituents are changed.
- Toxicity data are readily available for chemical constituent(s).
- Extraction and analytical chemistry studies are easily conducted.

Impact of revision (2)

Annex B

B.4 Guidance on specific aspects of biological evaluation

B.4.4 Biological safety assessment

B.4.4.2 What constitutes "sufficient toxicity data" including dose and route relevance?

Chemical characterization may identify a number of chemical compounds from leachable substances, but appropriate toxicity data may not be available for all of them.

Although methods are available to conduct a route-to-route extrapolation of dose, these approaches should be used with caution.

Caution is required in interpreting effects observed in tests at very high dose levels relative to the actual exposure in clinical use.

See ISO 10993-17

Impact of revision (3)

Annex B

B.4 Guidance on specific aspects of biological evaluation

B.4.5 General guidance

B.4.5.3 Biocompatibility evaluation **documentation**

- A general description or drawing of the medical device
- Quantitative information on the material composition/formulations and quantitative or qualitative information on physical characteristics for all device components with direct or indirect contact as defined in **5.2**
- Description of processing conditions that could introduce manufacturing contaminants
- A review of available toxicity and prior use data (e.g., clinical use experience) relevant to each medical device component with direct/indirect tissue contact as defined in **5.2**
- Reports of biological safety tests
- An assessment of the data
- A statement confirming the risk analysis and risk controls have been completed.

Revision of JIS T 0993-1

Reform of biological safety evaluation method

(1) Conduct the test according to the endpoint tablle
(2) If any positive reaction is found, perform risk assessments.

JIS T 0993-1
2012

JIS T 0993-1
2020

(1) Planning an overall risk assessment
(2) Collecting information needed for risk assessment
(3) If a complete assessment cannot be made, consider to conduct testing:
1st Chemical and physical characterization
2nd *in vitro* tests
3rd in vivo tests

Supplement

Supplementary information

i. For products in categories with increased endpoints (in many cases), it is acceptable to evaluate the added endpoints by description.

ii. Analysis using ISO 10993-18 is optional.

iii. Literature is available for evaluation of biological safety.

iv. The analytical tests specified in the JIS cited from the certification standards such as the elution test are conducted in the conventional method as before. (A consultation with PMDA is not necessary.)

i. For products in categories with increased endpoints (in many cases), it is acceptable to evaluate the added endpoints by description.

There are categories with increased endpoints in the revised standard.

Example: Material mediated pyrogenicity, acute systemic toxicity, chronic, carcinogenicity, etc.

Medical device categorization by			Endpoints of biological evaluation																
Nature of body contact		Contact duration	Physical and/or chemical informa ion	Cytotoxicity	Sensitization	Irrita ion or intracutaneous reactivity	Material mediated pyrogenicity	Acute systemic toxicity	Subacute toxicity	Subchronic toxicity	Chronic toxicity	Implantation effects	Hemocompatibility	Genotoxicity	Carcinogenicity	Reproductive/developmental toxicity	Degradation
Category	Contact	A: limited (≤ 24 h) B: prolonged (> 24 h to ≤ 30 d) C: Long-term (> 30 d)															
Surface medical device	Intact skin	A	X	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 communica ing 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	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			
		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 devices	Tissue/bone	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		

i. For products in categories with increased endpoints (in many cases), it is acceptable to evaluate the added endpoints by description.

Reasons why material mediated pyrogenicity and acute systemic toxicity were added

Since the extractables or leachables may:

- Circulate throughout the body through the **damaged surface.**
- **Become incorporated into systemic circulation, lymphatic system, and/or cerebrospinal fluid via** mucosal membrane.
- Become incorporated into systemic circulation, lymphatic system, and/or cerebrospinal fluid in **externally communicating medical devices and implant medical devices.**

All of those entering the systemic circulation should also be assessed for pyrogenicity and acute systemic toxicity.
It is also absorbed from the mucosal membrane.

i. For products in categories with increased endpoints (in many cases), it is acceptable to evaluate the added endpoints by description.

<Example of a case where the evaluation is performed based on the description without testings>

- **Acute systemic toxicity**: This product is a medical device **that comes in contact with the breached or compromised surface for a limited time**. The eluate does not enter the body in large quantities in a short time. No positive reaction was observed in a cytotoxicity test using an extract with high sensitivity. Therefore, it is considered very unlikely that acute systemic toxicity is observed.

- **Material mediated pyrogenicity**: The raw materials of this product are **PTFE and PU**, which have been used extensively as the raw materials of medical devices used in blood vessels. In addition, this product is used **for a short time**, and a large amount of leachable substances of the final product is not expected to be eluted. Therefore, it is considered very unlikely that material mediated pyrogenicity is observed.

From the group work in the training for certification bodies

Q2: How about performing biological safety evaluation of long-term systemic toxicity without performing a (sub) chronic systemic toxicity test or carcinogenicity test?

A2:

(1) Information on chemical substances that may have biological effects should be available.

- Raw material identity of approved/certified products
- Equivalence of manufacturing process and sterilization (If the manufacturing process is different, is there any impact?)
- The risk of the site of use and duration of use is equivalent or lower.
- Information on adverse events in clinical practice

(2) Chemicals from the final product considered to affect the living body are known, and their long-term toxicity evaluation can be confirmed based on literature, toxicity database, toxicity test results, etc.

The test(s) may be waived if the above evaluation has been performed appropriately and an description has been given.

https://www.pmda.go.jp/files/000240347.pdf

Additional explanation about waiver of acute systemic toxicity test

JIS T0993-1

6.3.2.6 Acute systemic toxicity

It is stated that "If feasible, acute systemic toxicity can be combined with subacute and subchronic toxicity and implantation test protocols."

=>Acute toxicity is a test to evaluate the toxicity of a solution or extract of the product when the solution or the extract is administered with a large amount at a time by intravenous (intraperitoneal) injection. Evaluation after administration on Day 1 is not sufficient because the dose is higher than the usual repeated dose toxicity test. Immediately after the implantation day in the implantation test, evaluation is not possible because the effects of implantation surgery strongly persist.

Therefore, "if feasible" does not exist!

ii. Analysis using ISO 10993-18 is optional.

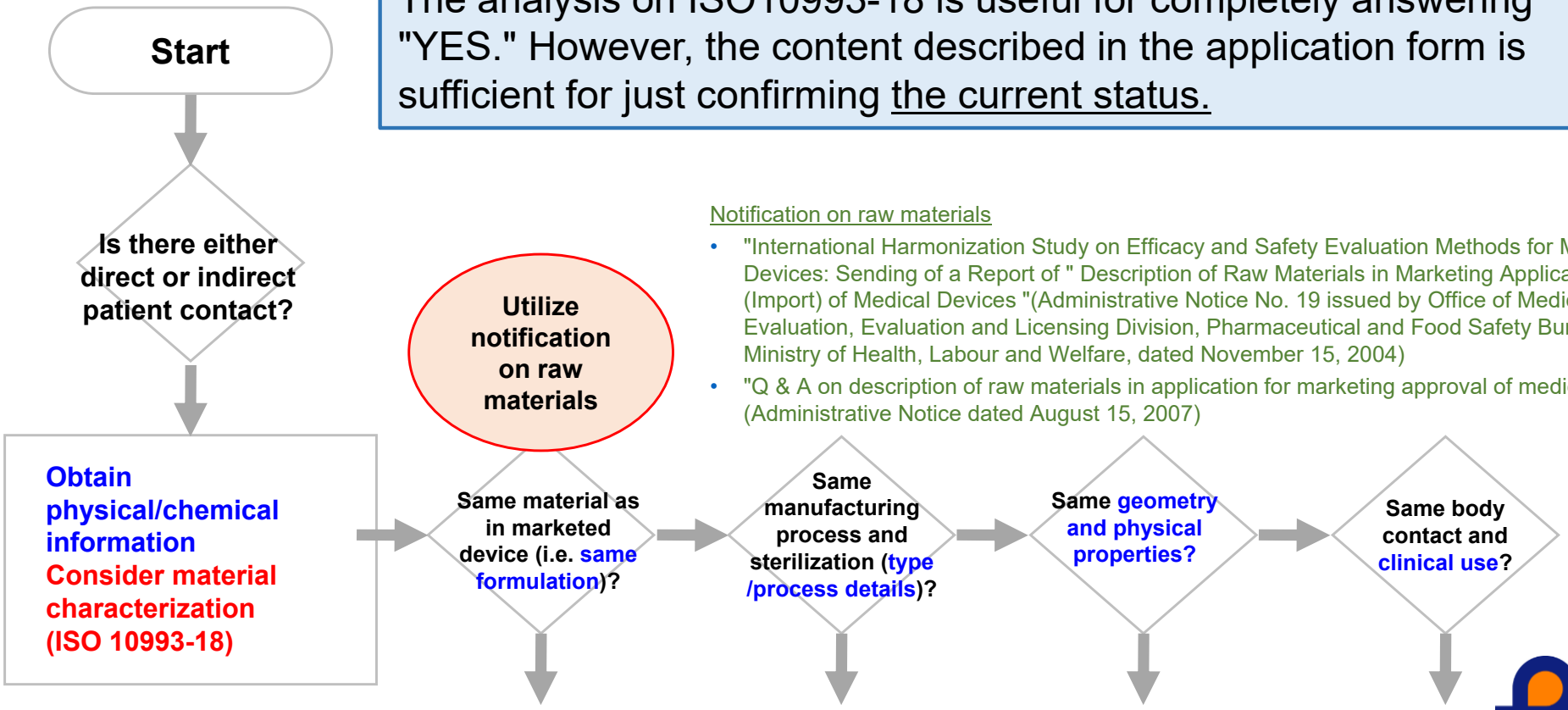
For "Obtain physical-chemical information. Consider material characterization (ISO10993-18) as needed" provided at the beginning of the flow chart when the evaluation is performed in accordance with the Figure 1 - summary of the systemic approach to a biological evaluation of a medical device as part of a risk management process.

If it can be evaluated based on other information (tests) as described, material characterization is not essential.

ii. Analysis using ISO 10993-18 is optional.

Physical and/or chemical information (Section 6.1)
Figure 1 – Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process <Flow Chart>

The analysis on ISO10993-18 is useful for completely answering "YES." However, the content described in the application form is sufficient for just confirming the current status.



Notification on raw materials

- "International Harmonization Study on Efficacy and Safety Evaluation Methods for Medical Devices: Sending of a Report of " Description of Raw Materials in Marketing Application (Form) (Import) of Medical Devices "(Administrative Notice No. 19 issued by Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated November 15, 2004)
- "Q & A on description of raw materials in application for marketing approval of medical device" (Administrative Notice dated August 15, 2007)

ii. Analysis using ISO 10993-18 is optional.

- Clearly understand which information is available and which information is inadequate, and think about what is best to make up for the insufficiency.
- In order to completely scientifically describe the equivalence, the results of analytical tests performed using appropriate procedures and methods are required. (Chemical analysis based on ISO 10993-18)
- Performing chemical analysis in accordance with ISO 10993-18 alone does not constitute an assessment of toxicity. Toxicity should be evaluated in accordance with ISO10993-17.

Expertise in analytical and toxicological evaluation is required to perform toxicological evaluation based on chemical analysis.

From the group work in the training for certification bodies

Q3: Which part of the following evaluation results is acceptable and which part is unacceptable?

<Contents of evaluation described in STED>

1. Tests were performed for cytotoxicity, sensitization, irritation, pyrogenicity, and implantation, and no problematic results were obtained.
2. Elution testing and chemical analysis were performed for

acute systemic toxicity, subacute systemic toxicity, subchronic systemic toxicity, chronic systemic toxicity, genotoxicity, and carcinogenicity. The risk is acceptable because no data suggesting the toxicity of each substance have been obtained in each analysis result and no new substance derived from raw materials has been detected in the elution test.

<Overview of chemical analysis performed (with analysis report attached)>

(1) Inorganic compounds (metals): Extraction with water at 50°C for 24 hours, qualitative and quantitative determination by ICP-MS

(2) Volatile substances among organic compounds: Extraction with water/ethanol/hexane at 50°C for 24 hours, qualitative and quantitative determination by GC-MS

(3) Semi-volatile/non-volatile substances among organic compounds: Extraction with water/ethanol/hexane at 50°C for 24 hours, qualitative and quantitative determination by LC-MS

https://www.pmda.go.jp/files/000240347.pdf

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Q3: Results of biological safety evaluation including chemical analysis data

A3:
Regarding (1), it is possible to accept the results of the test conducted.

(2) is not acceptable.
Primary reason:

- Unclearly explaining validity of the type of analysis appropriate for the purpose of analysis
  ->It is unclear what to analyze in the first place.
- Whether the extracts used for ICP-MS, GC-MS, and LC-MS are separated appropriately is unknown
  ->The appropriate extraction method is unknown because it is unclear what to analyze.
- It is unknown whether only mass spectrometry could identify all constituents.
- Unclear description about validity of the analytical system
- It is unknown whether the calculation method and validity of the obtained threshold values are adequately described.
- Risk evaluation (toxicological evaluation) of chemical substances is not clear.

There are still many points to be pointed out.
->In other words, evaluation using analysis is not as easy as conducting ISO/JIS testing.

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Those that can be detected by each analytical method

Analyte	Analytical method
Main component, polymer (polyethylene, polyvinyl chloride, etc.)	• FT-IR (Fourier transform infrared spectroscopy) • Weight of nonvolatile residue
Volatile substance (Residual monomer, residual solvent, etc.)	• GC/MS (Gas chromatography/mass spectrometry) • LC/MS (Liquid chromatography/mass spectrometry)
Refractory substance (Plasticizer, antioxidant, etc.)	• LC/MS (Liquid chromatography/mass spectrometry)
Metal component (Zinc, magnesium, nickel, etc.)	• ICP (inductively coupled plasma)

- Chemical analysis is a means to detect the object of analysis when the analyte is identified.

➢ It is necessary to set the optimal analysis conditions for the analyte (extraction solvent, detector, column, etc.).

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The risk of a chemical substance must be accurately evaluated by appropriate procedures and methods, depending on the nature, characteristics, usage, etc. of the substance.

Analyzing blindly leads to no answer and no resolution!

Actually, especially for devices with a low contact risk, it is cost-effective to perform the test conventionally!

iii. Literature is available for evaluation of biological safety.

Biological safety should be evaluated based on much existing information rather than tests.

Literature information can be used as a method of evaluation of biological safety. (See JIST0993-1: 2020 Annex C, Suggested procedure for literature review)

However, it is necessary to describe the equivalence between the materials (products) used in the literature and the raw materials (products) of this product or to provide the rationale for the availability of the literature.

(Bridging information is required.)

iii. Literature is available for evaluation of biological safety.

Example: When a catheter coated with hydrophilic coating agent is newly commercialized:

- Same as approved products except coating agent.
- Coating method is a general method of coating (with approval precedent).
- There is literature on coating agents (literature on safety and efficacy as chemical substances).

What is the equivalence between the coatings used in the literature and those used in this product?

The generic name and CAS No. used for identification of raw materials are the same.

Based on the clinical history and information on malfunctions overseas, there is no safety concern derived from the coating agent in particular.

iv. The analytical tests specified in the JIS cited from the certification standards such as the elution test are conducted using the conventional method as before. (A consultation with PMDA is not required.)

"See Tripartite consultation (Bulletin) No. 202001 (September 17, 2020)"

Chemical analysis accepted so far as evaluation other than biological safety is accepted as it is.

This is not considered as evaluation by Chemical Characterization, so it is not necessary to recommend consultation with PMDA.

Tripartite consultation (Bulletin) No. 202001

Q1
In A6 of "Questions and Answers (Q & A) on Basic Principles of Biological Safety Evaluation Required for Application for Approval to Market (Import) Medical Devices (Part 2)" (Yakuseikishin-hatsu Notification No. 0106-4 dated January 6, 2020), it is described "It is possible to waive a biological safety test by using the results of chemical analysis evaluation." What are the cases in which it is possible to waive a biological safety test for an approval application?
In addition, there are cases where evaluation using chemical analysis methods separately from biological safety is specified in certification standards, etc., but is it acceptable to perform the evaluation as before?

A1
In view of the current situation where there are few experiences of toxicological risk evaluation by chemical characterization using chemical analysis in Japan, it is possible that judgment of the appropriateness of waiver of the biological safety test may result in differences in the judgment among registered certification bodies. Therefore, if at the face-to-face consultation with PMDA it is judged possible to waive all or part of the biological safety tests required to be evaluated before the application for certification (when the conformity to the certification standards has not been confirmed) for the time being, based on the toxicological risk evaluation by chemical analysis, it is possible to waive the tests by attaching the said consultation record to the certification application form. If the use of a face-to-face consultation with PMDA is considered, first receive general consultation or preparatory consultation. In addition, if the case is similar (for example, the same event in the same JMDN) and the validity of utilizing the said consultation record can be confirmed by the certification body, a new consultation is not necessary.
For non-toxicological evaluation using chemical analysis methods specified by certification standards, etc. (evaluation different from chemical analysis evaluation to waive biological safety test; for example, elution test specified in JIS cited in certification standards), the same operation as before is acceptable, and consultation with PMDA is not necessary.