The Biological Evaluation Plan (BEP)

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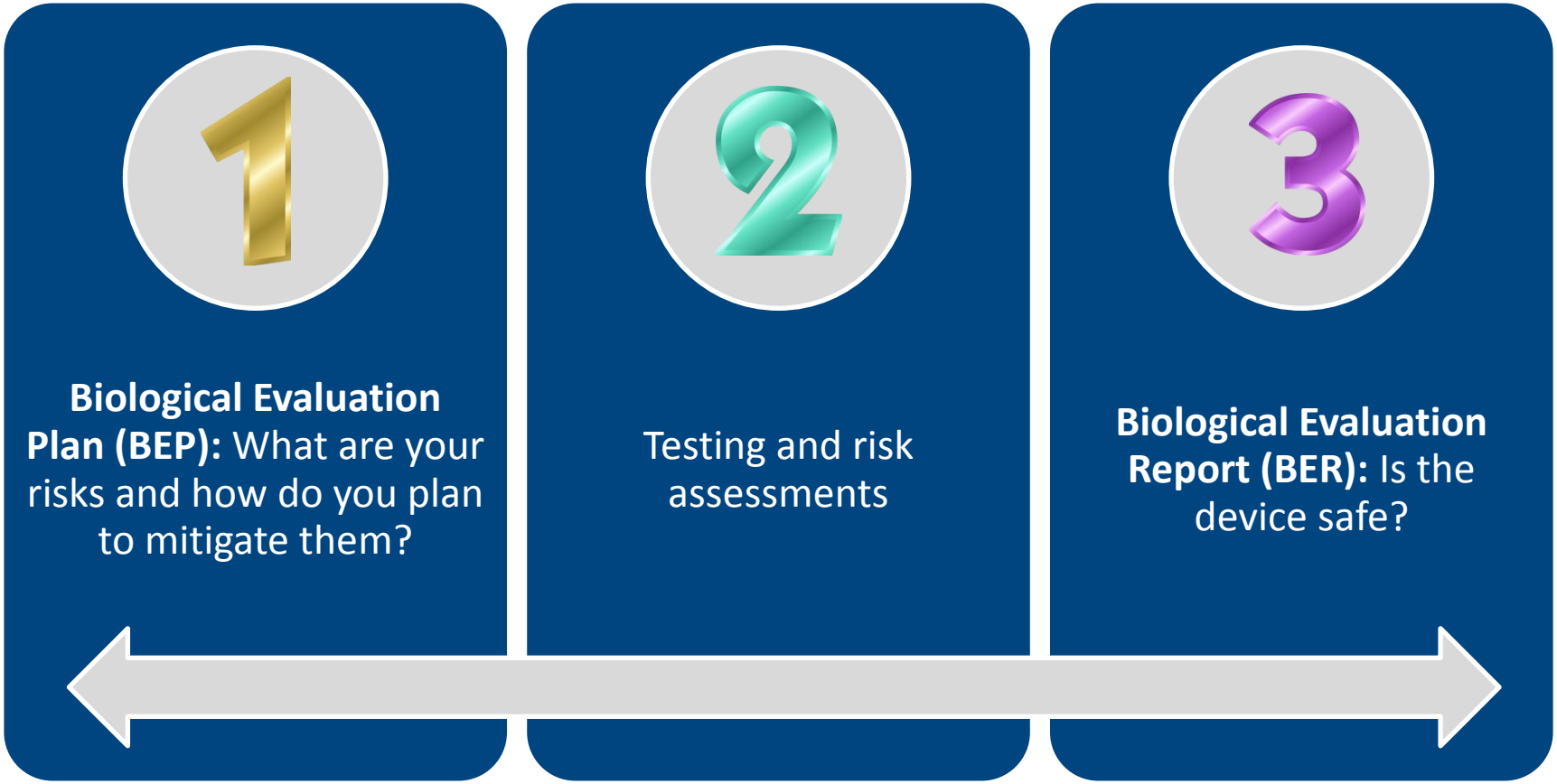
A crucial first step in the biocompatibility evaluation of a medical device

05 MAR 2020

Biological Safety Evaluation



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Introduction

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Introduction

Device contact → ***Contact time*** → ***Perform tests***

Medical device categorization by			Biological effect							
Category	Contact	contact duration (see 5.3) A – limited (⩽ 24 h) B – prolonged (> 24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Surface device	Skin	A	X [a]	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

[a] The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

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Introduction

- Didn't understand
  - Materials
  - Testing

Medical device categorization by			Biological effect							
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		C	X	X	X					
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		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
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External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

[a] The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

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Introduction

- ISO 10993-1 (2018): Biological evaluation of medical devices - Part 1: Evaluation and testing within a **risk** management process.

- What is risk ?

  ISO 14971: Combination of the probability of occurrence of harm and the severity of that harm.

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Introduction

Medical device categorization by			Endpoints of biological evaluation														
Nature of body contact		Contact duration															
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (>30 d)	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/ developmental toxicity[d,e]	Degradation[f]
Implant medical device	Tissue/bone[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Blood	A	X	E	E	E	E	E				E	E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

[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.

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	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		

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Introduction

- ISO 10993-1 (2018): *The biological evaluation of any material or medical device intended for use in humans shall form part of a structured* ***biological evaluation plan*** *within a risk management process.*

  This risk management process involves identification of biological hazards, estimation of the associated biological risks, and determination of their acceptability.

- Annex B.2.2: *Since biological evaluation is a risk management activity, a Biological Evaluation Plan is required, and this forms part of the Risk Management Plan.* ***It is emphasized that simply planning to conduct testing against all of the aspects of biocompatibility identified in Annex A does not meet the requirements of ISO 14971 or this document.***

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Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process“ - Section III

*“Such a process should generally begin with assessment of the device, including the **material components**, the **manufacturing processes**, the **clinical use of the device**… Considering this information, the **potential risks from a biocompatibility perspective** should be identified. Considering the potential biological impact, a plan should be developed…**either by biocompatibility testing or other evaluations that appropriately address the risks.**”*

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BEP – the practice

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BEP – the practice

ISO 10993-1 (2018) Clause 4

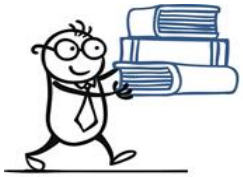
Configuration

Raw materials

Historical data

Manufacturing

Packaging



Literature

Test strategy

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1. Applicable guidelines

Guidance on ISO 10993

ISO 10993

ISO 18562

ISO 19227

USP 1663/1664
FDA guidance on Container Closure Systems

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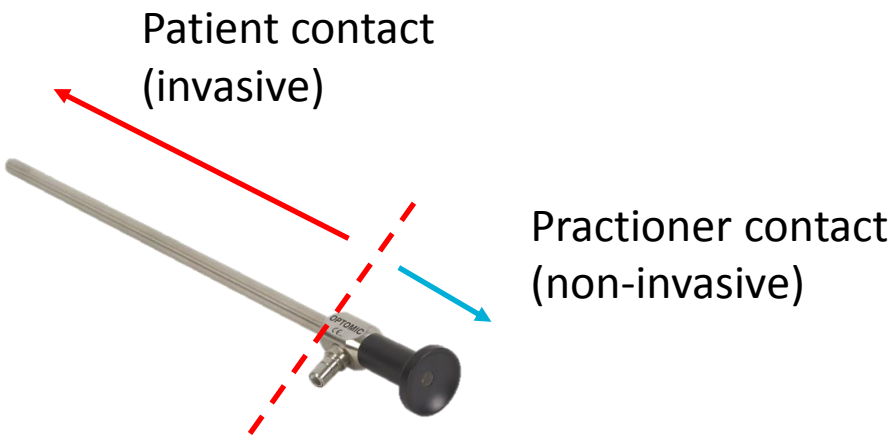
2. Device description

- Dimensions
- Intended purpose



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2. Device description

- Dimensions
- Intended purpose
- Frequency of use

Medical device categorization by			Endpoints of biological evaluation														
Nature of body contact		Contact duration															
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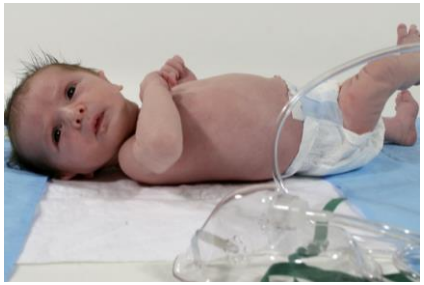
	Blood	A	X	E	E	E	E	E				E	E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

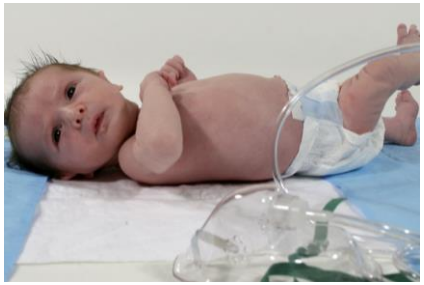
2. Device description

- Dimensions
- Intended purpose
- Frequency of use
- Patient population



2. Device description

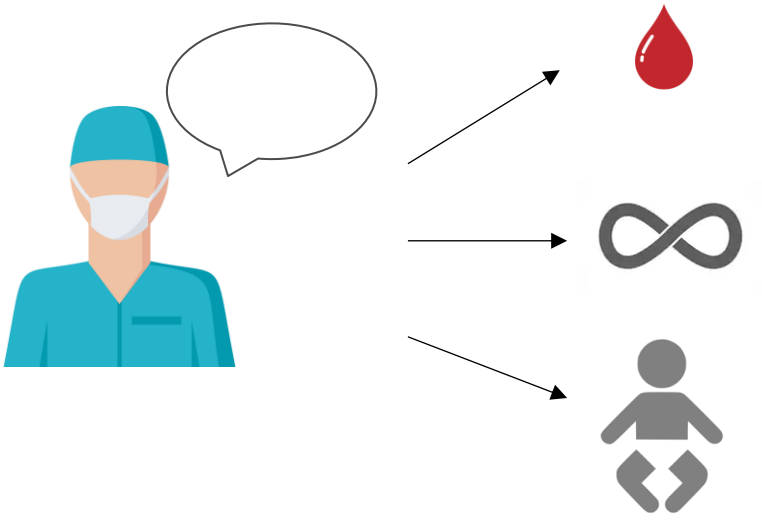
- Dimensions
- Intended purpose
- Frequency of use
- Patient population
- Off-label use



2. Device description

IFU
Intact skin contact
≤ 30 days contact
Adult use

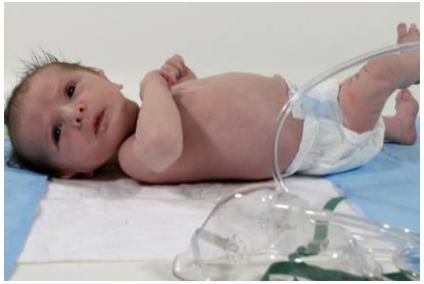
- Off-label use



Risk evaluation !

2. Device description

- Dimensions
- Intended purpose
- Frequency of use
- Patient population
- Off-label use
- …



Device Categorization

3. Material characterisation

List of all materials used: standard materials ?

Cleaning validation as per ISO 19227 ?

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3. Material characterisation

"The extent of characterization required is determined by the **invasiveness** and **duration** of clinical exposure in the intended use…"

ISO 10993-18

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3. Material characterisation

- Chemical characterisation needed ?
  - ISO 10993-1: “The choice of test procedures shall take into account that certain biological tests (i.e. those designed to assess **systemic effects**) **are not justifiable** where the presence of leachable chemicals has been **excluded** (in accordance with ISO 10993-18), or where chemicals have **a known and acceptable toxicity profile**, allowing the safe use by evaluation in accordance with ISO 10993-17 and risk assessment in accordance with ISO 14971”

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3. Material characterisation

"The extent of characterization required is determined by the **invasiveness** and **duration** of clinical exposure in the intended use…"

ISO 10993-18

Limited contact: identify materials and processing; use biocompatibility testing to support safety.

Prolonged contact: Use biocompatibility testing to support safety. Maybe chemical characterization if materials are new.

Permanent contact : Perform chemical characterization testing with a toxicological risk assessment.

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3. Material characterisation

- Chemical characterisation needed ?
  - Which strategy ?
  - Which solvents ?
  - Which techniques ?
  - Toxicological evaluation of the detected compounds

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4. Biocompatibility test selection and rationale

- Selection of each test

Medical device categorization by			Endpoints of biological evaluation														
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		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		

- Cytotoxicity needed ?
  - MEM Elution
  - L929 MTT/XTT
  - L929 MTT/XTT with dilutions
  - V79 colony assay

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4. Test selection and rationale

- Justification out of testing

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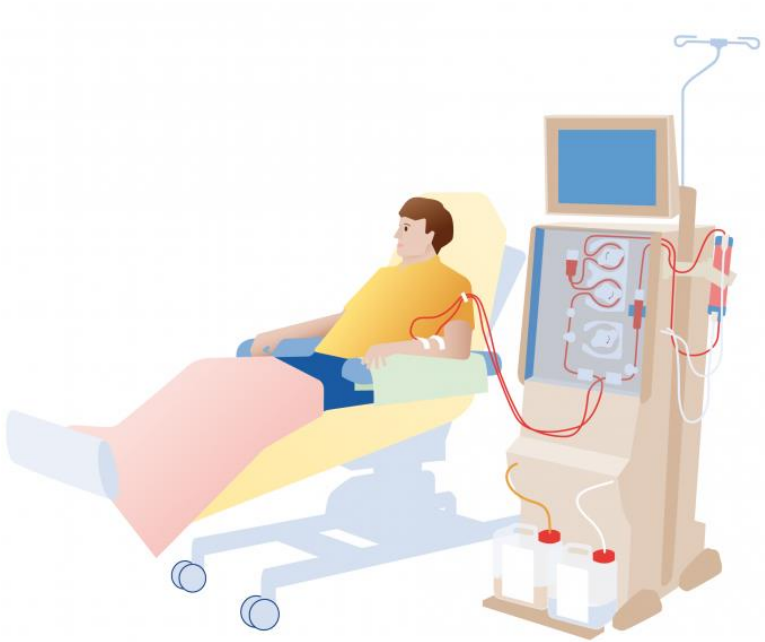
5. Test sample selection

Representative product

Coupons



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5. Test sample selection

Representative product → Coupons → Family grouping → "Monster" product

5. Test sample selection

- Representative product
- Coupons
- Family grouping
- "Monster" product
- Exclusion of components
- No patient contact
- Removal of electronic components

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5. Test sample selection

- Representative product
- Coupons
- Family grouping
- "Monster" product
- Exclusion of components
- No patient contact
- Removal of electronic components
- Contacting manner

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6. Test sample extraction

- Solvent: polar and apolar
- Ratios: surface area has preference
- Time and temperature

37°C for 24 hours

37°C for 72 hours

50°C for 72 hours

70°C for 24 hours

121°C for 1 hours

Cytotoxicity
(72 hrs for implants)

Typical recommended extraction condition for other in-vitro/in-vivo tests

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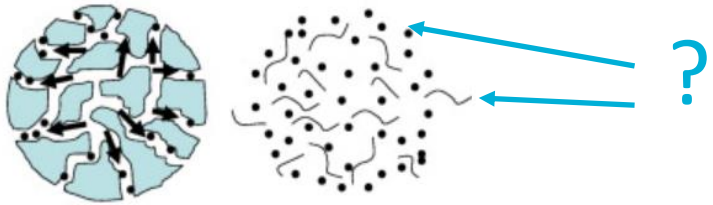
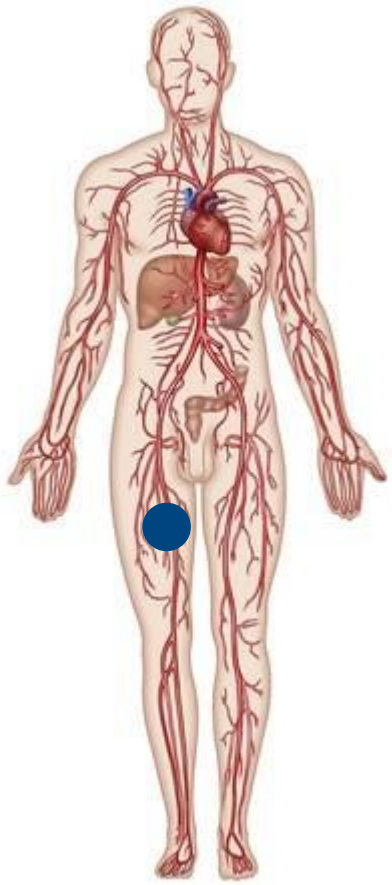
7. Extra considerations ?

- Biodegradation



7. Extra considerations ?

- Biodistribution



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7. Extra considerations ?

- Drug/device interaction
- …

Conclusion

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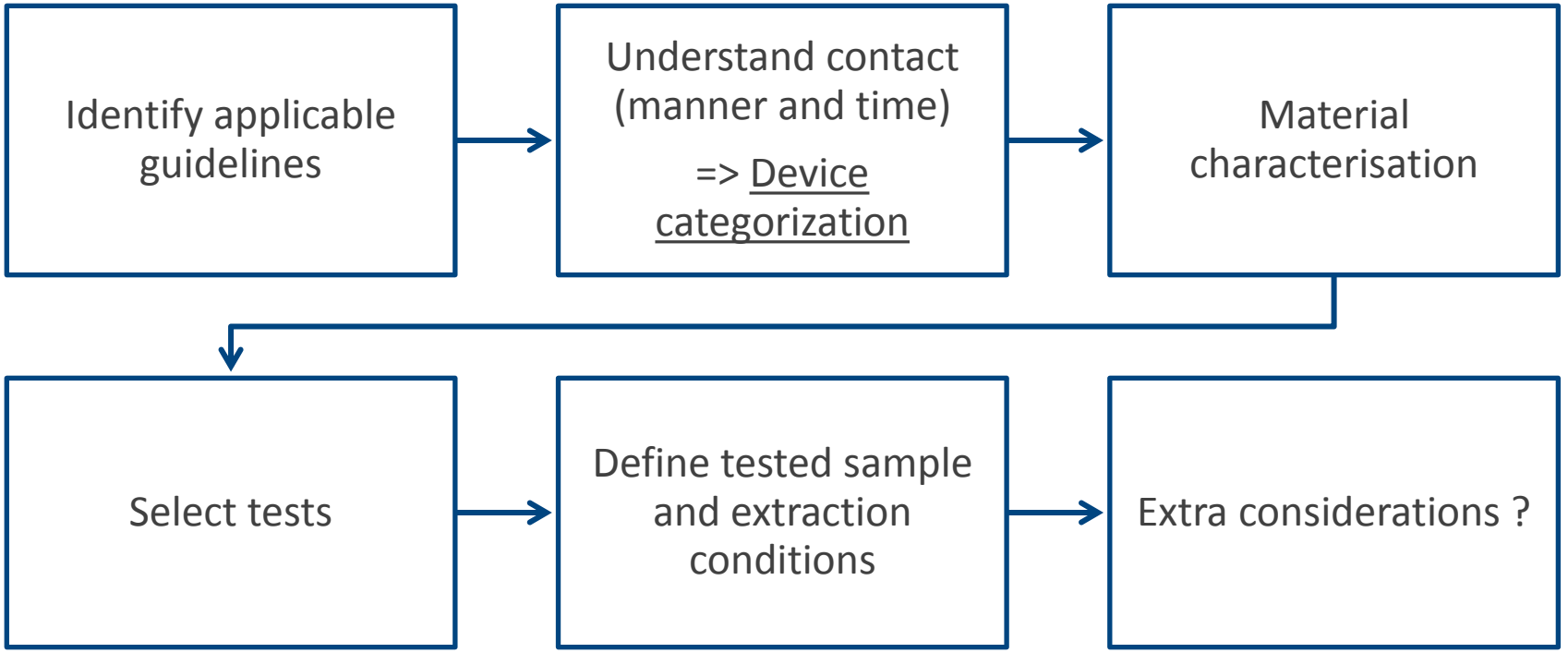
Conclusion



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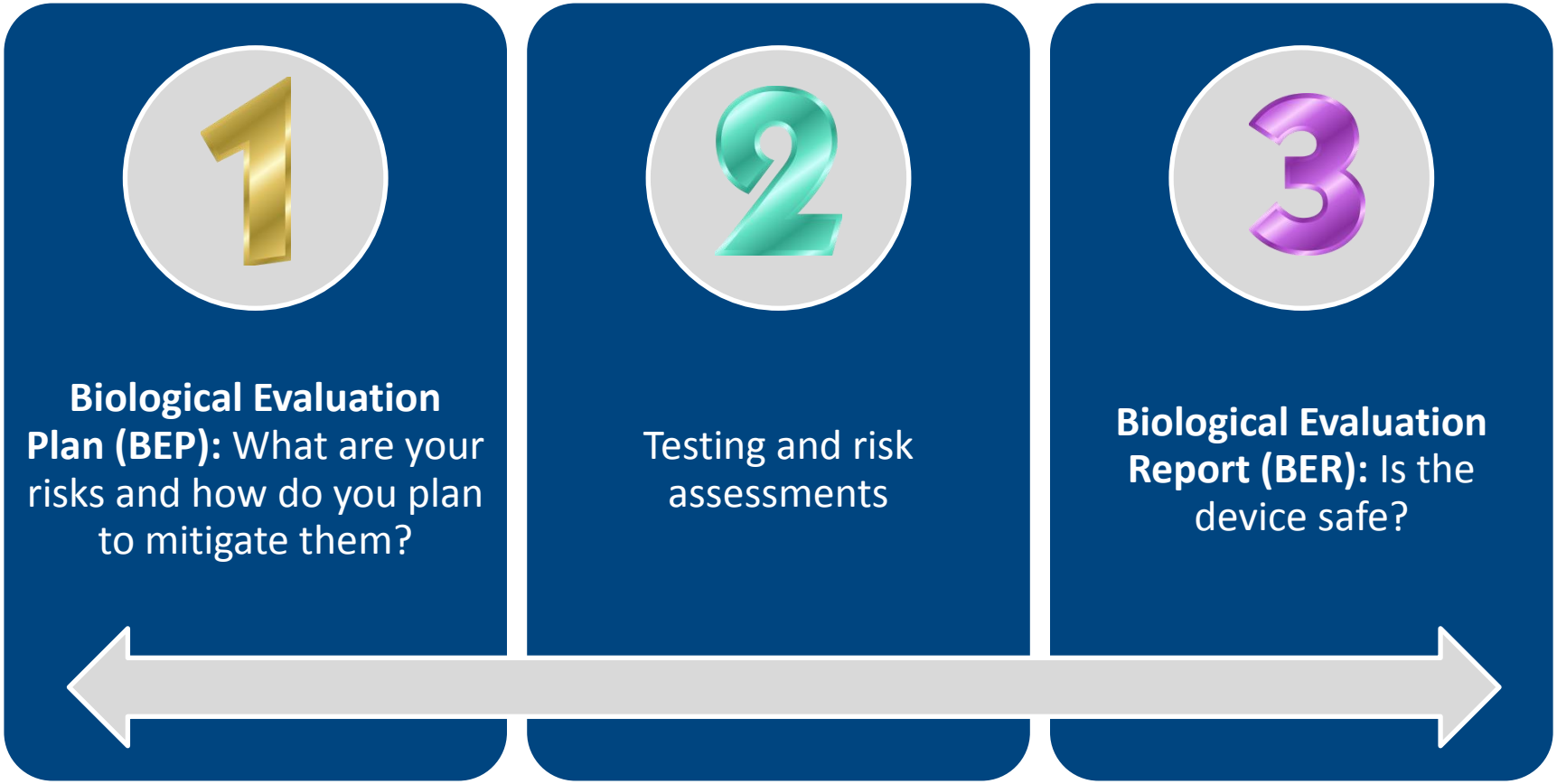
Biological Safety Evaluation



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