The Biological Evaluation Plan (BEP)

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

1. Biological Evaluation Plan (BEP): What are your risks and how do you plan to mitigate them?
2. Testing and risk assessments
Introduction
## Medical device categorization by nature of body contact (see 5.2)

<table>
<thead>
<tr>
<th>Contact</th>
<th>Biological effect</th>
<th>Cytotoxicity</th>
<th>Sensitization</th>
<th>Irritancy or intracutaneous reactivity</th>
<th>Systemic toxicity (acute)</th>
<th>Subchronic toxicity (subacute toxicity)</th>
<th>Genotoxicity</th>
<th>Implantation</th>
<th>Hemocompatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surface device</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal membrane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breached or compromised surface</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood path, indirect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue/bone/dentin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulating blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue/bone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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.*

---

**Device contact**

**Contact time**

**Perform tests**
### Introduction

- Didn’t understand
- Materials
- Testing

---

<table>
<thead>
<tr>
<th>Medical device categorization by</th>
<th>Biological effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>nature of body contact (see 5.2)</td>
<td>Cytotoxicity</td>
</tr>
<tr>
<td>Contact duration (see 5.3)</td>
<td></td>
</tr>
<tr>
<td>A – limited (&lt; 24 h)</td>
<td></td>
</tr>
<tr>
<td>B – prolonged (&gt; 24 h to 30 d)</td>
<td></td>
</tr>
<tr>
<td>C – permanent (&gt; 30 d)</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Contact</td>
</tr>
<tr>
<td>Skin</td>
<td>A</td>
</tr>
<tr>
<td>Surface device</td>
<td>B</td>
</tr>
<tr>
<td>Mucosal membrane</td>
<td>C</td>
</tr>
<tr>
<td>Breached or compromised surface</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
<td>X</td>
</tr>
<tr>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Blood path, indirect</td>
<td>A</td>
</tr>
<tr>
<td>External communicating device</td>
<td>B</td>
</tr>
<tr>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Tissue/bone/dentin</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
<td>X</td>
</tr>
<tr>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Circulating blood</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
<td>X</td>
</tr>
<tr>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Implant device</td>
<td>A</td>
</tr>
<tr>
<td>Tissue/bone</td>
<td>B</td>
</tr>
<tr>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Blood</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
<td>X</td>
</tr>
<tr>
<td>C</td>
<td>X</td>
</tr>
</tbody>
</table>

*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.*
Introduction


• What is risk?

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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature of body contact</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implanted medical device</td>
<td>Tissue/bone[^i]</td>
<td>A</td>
<td>X</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>X</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>X</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>A</td>
<td>X</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>X</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>X</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^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 timespans 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 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.
Introduction

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). If a medical device is manufactured from novel materials, not previously used in medical device applications, and not toxicological 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.
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.
**Introduction**

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.”
BEP – the practice
ISO 10993-1 (2018) Clause 4

Configuration
Raw materials
Historical data
Manufacturing
Packaging
Literature
Test strategy
1. Applicable guidelines

- ISO 10993
- ISO 18562
- ISO 19227
- USP 1663/1664
- FDA guidance on Container Closure Systems
- EU-MDR
2. Device description

- Dimensions
- Intended purpose
2. Device description

- Dimensions
- Intended purpose
- Frequency of use
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

- Off-label use

IFU
- Intact skin contact
- ≤ 30 days contact
- Adult 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?
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
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”

<table>
<thead>
<tr>
<th>Medical device categorization by</th>
<th>Contact duration</th>
<th>Sensitization</th>
<th>Endpoints of biological evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nature of body contact</strong></td>
<td></td>
<td></td>
<td>Acute systemic toxicity²</td>
</tr>
<tr>
<td><strong>Category</strong></td>
<td></td>
<td></td>
<td>Sub acute toxicity³</td>
</tr>
<tr>
<td><strong>Contact</strong></td>
<td></td>
<td></td>
<td>Sub chronic toxicity²</td>
</tr>
<tr>
<td><strong>A</strong> - limited (≤24 h)</td>
<td>X</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td><strong>B</strong> - prolonged (&gt;24 h to 30 d)</td>
<td>X</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td><strong>C</strong> - Long term (&gt;30 d)</td>
<td>X</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td><strong>Implant medical device</strong></td>
<td></td>
<td></td>
<td>Chronic toxicity²</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td>Implantation effects of device</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>X</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>X</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>X</td>
<td>E</td>
<td>E</td>
</tr>
</tbody>
</table>

**Notes:**
- X: Test is required.
- E: Test is excluded.

---

**Sensitization:**
- **Physical irritation or cutaneous reactivity**
- **Material mediated pyrogenicity**
- **Acute systemic toxicity**
- **Sub acute toxicity**
- **Sub chronic toxicity**
- **Chronic toxicity**
- **Implantation effects of device**
- **Hemocompatibility**
- **Genotoxicity**
- **Carcinogenicity**
- **Reproductive/developmental toxicity**
- **Degradation**

---

**Company Information:**
- Nelson Labs®
- A Sotera Health company

**Confidential**
- © 2020 Nelson Laboratories, LLC | ALL RIGHTS RESERVED

---

22
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.
3. Material characterisation

- Chemical characterisation needed?
  - Which strategy?
  - Which solvents?
  - Which techniques?
  - Toxicological evaluation of the detected compounds
4. Biocompatibility test selection and rationale

• Selection of each test

<table>
<thead>
<tr>
<th>Medical device categorization by</th>
<th>Contact duration</th>
<th>Physical and/or chemical information</th>
<th>Cytotoxicity</th>
<th>Irritation or intracutaneous reactivity</th>
<th>Material mediated pyrogenicity</th>
<th>Acute systemic toxicity</th>
<th>Sub acute toxicity</th>
<th>Sub chronic toxicity</th>
<th>Chronic toxicity</th>
<th>Implantation effects</th>
<th>Hemocompatibility</th>
<th>Genotoxicity</th>
<th>Carcinogenicity</th>
<th>Reproductive/developmental toxicity</th>
<th>Degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue/bone¹</td>
<td>A - Exposed (≤24 h)</td>
<td>X E E E E E E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B - prolonged (&gt;24 h to 30 d)</td>
<td>X E E E E E E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C - Long term (&gt;30 d)</td>
<td>X E E E E E E E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>A</td>
<td>X E E E E E E E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>X E E E E E E E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>X E E E E E E E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

➢ Cytotoxicity needed?
  ❖ MEM Elution
  ❖ L929 MTT/XTT
  ❖ L929 MTT/XTT with dilutions
  ❖ V79 colony assay
4. Test selection and rationale

- Justification out of testing
5. Test sample selection

Representative product → Coupons
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
5. Test sample selection

- Representative product
- Coupons
- Family grouping
- “Monster” product

- Exclusion of components
- No patient contact
- Removal of electronic components

- Contacting manner
6. Test sample extraction

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

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>37°C</td>
<td>24 hours</td>
</tr>
<tr>
<td>37°C</td>
<td>72 hours</td>
</tr>
<tr>
<td>50°C</td>
<td>72 hours</td>
</tr>
<tr>
<td>70°C</td>
<td>24 hours</td>
</tr>
<tr>
<td>121°C</td>
<td>1 hour</td>
</tr>
</tbody>
</table>

Cytotoxicity (72 hrs for implants)

Typical recommended extraction condition for other in-vitro/in-vivo tests
7. Extra considerations?

• Biodegradation
7. Extra considerations?

- Biodistribution
7. Extra considerations?

- Drug/device interaction
- ...
Conclusion

Identify applicable guidelines

Understand contact (manner and time) => Device categorization

Material characterisation

Select tests

Define tested sample and extraction conditions

Extra considerations?
Biological Safety Evaluation

1. Biological Evaluation Plan (BEP): What are your risks and how do you plan to mitigate them?

2. Testing and risk assessments