Agenda

ISO 10993 Series of Standards – Regulatory Updates and Requirements

- Introduction
- Biocompatibility Testing
- Changes in the Regulations
- Summary
ISO 10993 Series of Standards – Regulatory updates and requirements

- Introduction
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- Summary
Introduction

? What is meant with the term “biocompatibility”?

? What standards have to be considered when testing for biocompatibility?

? What are the requirements regarding the test specimens?
Introduction

Some Definitions from ISO TIR 15499:2012

Biocompatibility
Ability of a material to perform with an appropriate host response in a specific application

Biological risk
Potential for a substance to cause harm to health by virtue of its toxicity

Biological safety
Freedom from unacceptable biological risk
Introduction

Biocompatibility

Evaluated according to ISO 10993-1:2009 - Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management system

Additional documents:
## Introduction

### ISO 10993-1 Biological Evaluation of Medical Devices

<table>
<thead>
<tr>
<th>Biological Testing</th>
<th>Chemical Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td><strong>Additional Documents</strong></td>
</tr>
</tbody>
</table>
Introduction

Influences on Biocompatibility – Life Cycle of a MD

Polymerization, injection molding, …

Material processing, like CNC turning, cutting, drilling, polishing, gluing, cleaning

Packaging

Sterilization

Transport and Storage

Raw materials → Components → Medical Device → Packed Medical Device → Final Medical Device → Application of Medical Device

Additives, like fillers, reinforcement composites, UV blocker, flame retardants, release agents, internal lubricants, pigments & dyes, catalysts, modifiers, plasticizers, stabilizers, …

Lubricants, coating, glue, polishing agent, cleaning agents, …

Packaging materials, labels (glue, dye, solvents), …

Sterilization agent, process conditions, …

Temperature, humidity, UV light, aging, …
Introduction

Unintended biological effects (hazards):
- Physical and morphological characteristics
  - Rough or sharp edges (irritation, damaging of tissues)
  - Surface properties, like roughness (implantation or thrombogenicity effects)
- Particles (common and nanoparticles)
- Leachables
Introduction

Testing Specimen

ISO 10993-1, sub clause 6.2.1:
• Sterile final product, or
• Representative samples from the final product or
• Materials processed in the same manner as the final product (including sterilization)
Agenda

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Biocompatibility Testing

- Do I need to perform all tests, which are marked in ISO 10993-1, Table 1? Which order shall I choose?
- Is it needed to perform biocompatibility, partly animal experimental, tests if the material characterization does not show abnormalities?
- Is the aspect of biocompatibility finished, when I have all biological data?
- What kind of test(s) should I perform if I use material of another supplier?
- How can I prove the biocompatibility at the end of the shelf-life?
Biocompatibility Testing

Classification by nature of contact

Surface devices
- Skin
- Mucosal membrane
- Breached or compromised surface

External communicating devices
- Blood path, indirect
- Tissue, bone, dentin
- Circulating blood

Implant devices
- Tissue, bone
- Blood
Biocompatibility Testing

Classification by contact duration

Limited exposure (A):
Devices whose single or multiple use or contact is likely to be up to 24 h

Prolonged exposure (B):
Devices whose single, multiple or long-term use or contact is likely to exceed 24 h but not 30 days

Permanent contact (C):
Devices whose single, multiple or long-term use or contact exceeds 30 days

Note:
1. Repeated device application requires appropriate testing
2. In-situ polymerizing or biodegradable devices require testing of final polymer, starting materials, intermediate and degradation products
## Biocompatibility Testing

<table>
<thead>
<tr>
<th>Medical device categorization by nature of body contact</th>
<th>Contact duration</th>
<th>Cytotoxicity</th>
<th>Sensitization</th>
<th>Irritation or intracutaneous reactivity</th>
<th>Systemic toxicity (acute)</th>
<th>Subchronic toxicity (subacute toxicity)</th>
<th>Genotoxicity</th>
<th>Implantation</th>
<th>Haemocompatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>A - limited (≤ 24 h)</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B - prolonged (&gt; 24 h to 30 d)</td>
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</tr>
<tr>
<td>C - permanent (&gt; 30 d)</td>
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</tr>
</tbody>
</table>

### Surface device

#### Skin

- A:
  - Cytotoxicity: X
  - Sensitization: X
  - Irritation or intracutaneous reactivity: X

- B:
  - Cytotoxicity: X
  - Sensitization: X

- C:
  - Cytotoxicity: X

#### Mucosal membrane

- A:
  - Cytotoxicity: X
  - Sensitization: X

- B:
  - Cytotoxicity: X
  - Sensitization: X
  - Irritation or intracutaneous reactivity: X

- C:
  - Cytotoxicity: X
  - Sensitization: X
  - Irritation or intracutaneous reactivity: X

#### Breached or compromised surface

- A:
  - Cytotoxicity: X

- B:
  - Cytotoxicity: X

- C:
  - Cytotoxicity: X

### External communicating device

#### Blood path, indirect

- A:
  - Cytotoxicity: X
  - Sensitization: X
  - Irritation or intracutaneous reactivity: X

- B:
  - Cytotoxicity: X
  - Sensitization: X

- C:
  - Cytotoxicity: X

### Tissue/bone/dentin

- A:
  - Cytotoxicity: X
  - Sensitization: X

- B:
  - Cytotoxicity: X
  - Sensitization: X

- C:
  - Cytotoxicity: X

### Circulating blood

- A:
  - Cytotoxicity: X
  - Sensitization: X

- B:
  - Cytotoxicity: X
  - Sensitization: X

- C:
  - Cytotoxicity: X

### Implant device

#### Tissue/bone

- A:
  - Cytotoxicity: X

- B:
  - Cytotoxicity: X

- C:
  - Cytotoxicity: X

#### Blood

- A:
  - Cytotoxicity: X

- B:
  - Cytotoxicity: X

- C:
  - Cytotoxicity: X

---

**Note:** The “X” indicates data endpoint that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

**Evaluation Table from ISO 10993-1**
## Biocompatibility Testing

### Medical device categorization by Nature of Body Contact and Contact Duration

<table>
<thead>
<tr>
<th>Category</th>
<th>Contact Duration</th>
<th>Biological Effect *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A - limited (≤ 24 h)</td>
<td>Cryptotoxicity</td>
</tr>
<tr>
<td></td>
<td>B - prolonged (&gt; 24 h to 30 d)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C - permanent (&gt; 30 d)</td>
<td></td>
</tr>
<tr>
<td><strong>Surface device</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Mucosal membrane</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Breached or compromised surface</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td><strong>External communicating device</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood path, indirect</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Tissue/bone/dentin +</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Circulating blood</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td><strong>Implant device</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue/bone</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Blood</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>X</td>
</tr>
</tbody>
</table>

### Notes:
- X: ISO Evaluation tests for consideration
- O: Additional categories which should be addressed in FDA submissions, either by inclusion of the testing or a rationale for its omission
- Tissue includes tissue fluids and subcutaneous spaces
- For all devices used in extracorporeal circuits
- "X" indicates data endpoint 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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**Evaluation Table from FDA Draft Guidance Document**
Biocompatibility Testing

ISO 10993-1, Chapter 4:
General principles applying to biological evaluation of medical devices

“The biological evaluation of any material or medical device intended for use in humans shall form part of a structured biological evaluation programme within a risk management process in accordance with ISO 14971 […].

The rigour necessary in the biological evaluation is principally determined by the nature, degree, duration and frequency of the exposure and the hazards identified for the material.

Selection of any in vitro or in vivo tests shall be based on end-use applications. […]

In vitro test methods, which are appropriately validated, reasonably and practically available, reliable and reproducible shall be considered for use in preference to in vivo tests. Whenever possible, in vitro screening shall be carried out before in vivo tests are commenced.”
Biocompatibility Testing

Cleaning within manufacturing process of well-known materials:

- Sufficient diminishing of substances used (adherent, cutting oils, detergents, etc.) → Demonstrate biocompatibility
- Microorganisms (sterile products)
- Endotoxin (implants)
- Particles

Therefore, a validation of the (end) cleaning within the production process is essential.
Biocompatibility Testing

Particulate Contamination

Consideration is required for non-active implants (ISO 14630) and active implants (ISO 14708-X/EN 45502-X). Acceptance limits are partly missing.

<table>
<thead>
<tr>
<th>Document</th>
<th>Product</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO 15798</td>
<td>Viscosurgical devices</td>
<td>no</td>
</tr>
<tr>
<td>ISO 14949</td>
<td>Two-part addition-cure silicone elastomers for implants</td>
<td>yes</td>
</tr>
<tr>
<td>ISO 8871-3</td>
<td>Elastomeric parts for parenterals and for devices for pharmaceutical use</td>
<td>no</td>
</tr>
<tr>
<td>ISO 8536-4</td>
<td>Infusion sets</td>
<td>yes</td>
</tr>
<tr>
<td>ISO 14708-1/EN 45502-1</td>
<td>Active implantable medical devices</td>
<td>Yes</td>
</tr>
<tr>
<td>ISO 14630</td>
<td>Non-active surgical implants</td>
<td>No</td>
</tr>
</tbody>
</table>
Biocompatibility Testing

ISO 10993-1, Chapter 7 „Interpretation of biological evaluation data and overall biological safety assessment “

Expert assessors with necessary knowledge and experience in view of biocompatibility and medical devices shall determine and document following aspects:

a) the strategy and program content for the biological evaluation of the medical device;

b) the criteria for determining the acceptability of the material for the intended purpose, in line with the risk management plan;

c) the adequacy of the material characterization;

d) the rationale for selection and/or waiving of tests;

e) the interpretation of existing data and results of testing;

f) the need for any additional data to complete the biological evaluation;

g) overall biological safety conclusions for the medical device.
Biocompatibility Testing

“Bridging” approach for raw materials and final products

Examples:

- Evaluation of the biocompatibility at the end of the shelf-life
- Minor changes to the manufacturing process
- New suppliers of identical or similar raw materials
- New cleaning or reprocessing procedures
- New packaging materials
- Proof of the batch-to-batch homogeneity
- Incoming goods controls of suppliers
- Proof of „substantial equivalence“ for „predicate devices“
Biocompatibility Testing

Typical test strategy within “Bridging” approach

- GC/MS and/or ICP fingerprint after extraction
- Cytotoxicity as biological endpoint
- For products, where genotoxicity studies are requested: AMES test
Agenda

ISO 10993 Series of Standards – Regulatory updates and requirements

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Changes in the Regulations

? Can I use the same approach for CE mark and FDA Approval?

? Will the actual standards be modified?
Changes in the Regulations

Difference in Approach for CE Mark and FDA Approval

Sensitization Testing (ISO 10993-10)

CE Mark - Main tests
• Guinea Pig Maximization Test (GPMT) according to Magnusson and Kligman
• Local Lymph Node Assay (LLNA)

FDA Approach - Main tests
• Guinea Pig Maximization Test (GPMT) according to Magnusson and Kligman
• Local Lymph Node Assay (LLNA). FDA will evaluate whether to accept such reports on a case-by-case basis; especially for materials comprised of chemical mixtures
Changes in the Regulations

Difference in Approach for CE Mark and FDA Approval
Genotoxicity Testing (ISO 10993-3)

CE Mark - two *in vitro* tests
• Gene mutations in bacteria (Bacterial Reverse Mutation Test, “Ames” Test)
  AND EITHER
• Clastogenicity in mammalian cells (*In Vitro* Mammalian Chromosome Aberration Test)
  OR
• Gene mutations in mammalian cells (e. g. *In Vitro* Mouse Lymphoma Assay)
  OR
• Clastogenicity in mammalian cells (*In Vitro* Micronucleus Test).
Changes in the Regulations

Difference in Approach for CE Mark and FDA Approval

Genotoxicity Testing (ISO 10993-3)

FDA Approach – three test models

- Gene mutations in bacteria (Bacterial Reverse Mutation Test, “Ames” Test)
- \textit{In vitro} mammalian genotoxicity assay (choose one):
  - Mouse Lymphoma gene mutation assay (preferred);
  - \textit{In vitro} chromosomal aberration (CA) assay; or
  - \textit{In vitro} micronucleus assay.
- \textit{In vivo} cytogenetics assay (choose one):
  - Bone marrow micronucleus (MN) assay;
  - Bone marrow chromosomal aberration (CA) assay; or
  - Peripheral blood MN assay.
Changes in the Regulations

Expected Changes in ISO 10993 Standards

- Revision of biocompatibility strategy in ISO 10993-1 for respiratory and other devices (ISO/DIS 18562)

<table>
<thead>
<tr>
<th>Medical device categorization by</th>
<th>Contact duration</th>
<th>VOC &amp; PM</th>
<th>Extractables in aqueous solution</th>
<th>Cytotoxicity</th>
<th>Sensitization</th>
<th>Irritation</th>
<th>Systemic Toxicity (acute)</th>
<th>Subchronic Toxicity (subacute Toxicity)</th>
<th>Genotoxicity</th>
<th>Implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>Contact</td>
<td>A — limited (≤ 24 h)</td>
<td>X</td>
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<td>B — prolonged (&gt; 24 hrs to 30 days)</td>
<td>X</td>
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<td>C — permanent (&gt; 30 days)</td>
<td>X</td>
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<td></td>
<td></td>
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<tr>
<td>Medical Device with contact to breathing gas</td>
<td>Gas dry gas only</td>
<td>A</td>
<td>X</td>
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<tr>
<td></td>
<td>Gas + condensate</td>
<td>If condensate can form in breathing pathways which can then reach the patient</td>
<td>A</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>

# = Test is only for consideration when the evaluation of the result of the chemical analysis of extractables does not lead to a definite conclusion
VOC = Volatile Organic Compounds
PM = Particulate Matter
Changes in the Regulations

Expected Changes in ISO 10993 Standards

• Revision of ISO 10993-2 Animal Welfare:
  Update EU Directive 2010/63/EU: Protecting of animals used for scientific purposes

• ISO 10993-3 Genotoxicity Testing:
  - New standard issued in 2014-10
  - In preparation: Guidance document ISO TS 10993-33 “Supplement to ISO 10993-3: Guidance on tests to evaluate genotoxicity”
Changes in the Regulations

Expected Changes in ISO 10993 Standards

• Revision of ISO 10993-4 Hemocompatibility Testing:
  - Inclusion of evaluation strategy
  - Reworking of Table 1 and 2: Improving identification critical vs. optional testing
  - New table for only relevant/commonly used methods
  - Use of anticoagulants consistent with clinical condition
  - Remove of Annex D (coagulation) and Annex E (platelet activation)
  - Thrombosis test: only for devices with direct contact with circulating blood
Changes in the Regulations

Expected Changes in ISO 10993 Standards

- Revision of ISO 10993-5 Cytotoxicity Testing:
  - New definition of cytotoxicity: The extent to which an agent can cause damage to living cells.
  - Remove of the extraction media DMSO
  - Nanomaterials based devices not covered by the standard
  - Possibly: Modification of grading results quantitative
Changes in the Regulations

Expected Changes in ISO 10993 Standards

• Revision of ISO 10993-6 Implantation Testing:
  - Modification of scope: “Implantation should be mainly be performed on devices to be implanted”
  - Informative Annex for resorbable/degradable materials
  - Will be recognized by US/FDA
  - Implantation period of $\geq 12$ weeks suggested for stable materials. Degradable materials: Implantation test at different degradation stages

• Revision of ISO 10993-10 Irritation and Skin Sensitization Testing:
  - Inclusion of *in vitro* irritation test with EpiDerm™
Changes in the Regulations

Expected Changes in ISO 10993 Standards

• Revision of ISO 10993-11 Systemic Toxicity Testing:
  - Reduction of number animals for chronic toxicity testing
  - New Annex G: Protocol for concurrent administration of both polar and nonpolar MD extracts (approved by FDA)

• Development of standard ISO 10993-22 for Nanomaterials

• Preparation of new ISO TS 29741 Development of tolerable intake values for Di(2-ethylhexyl)phthalate (DEHP)
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Summary

Important Aspects to Consider:

- Evaluate biocompatibility within risk management system
- Use already FDA Draft Guidance (2013) for FDA approval
- Material characterization results may result into omitting of biological tests
- Don’t forget final evaluation of overall biological safety
THANK YOU FOR YOUR ATTENTION

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