Biocompatibility: a risk based approach
The regulatory requirements include:

- Demonstration of safety
- Demonstration of efficacy
- Positive balance of risk and benefit

The regulatory requirements can be met by means of:

- Compliance to international norms (ISO, AAMI)
- Pre-validated testing
ISO 10993-1: Contents

• The risk based approach

• Categorization of medical devices
  • nature of body contact
  • duration of contact

• Biological evaluation process
  • Material and subproducts characterization
  • Biological evaluation tests

• Interpretation of results

• Test planning (annex A and B)

• Literature review guidance (annex C)
Project teamwork

clause 4.1

- Project leader
  - Define prototype status
  - Approve test results

- Regulatory expert
  - Identify minimum required testing

- Engineer
  - Provide manufacturing methods
  - Provide product specifications

- Biologist and biotechnologist
  - Test protocol
  - Testing
  - Test results comment
ISO 10993: A FAMILY OF NORMS

- Scope: all medical devices

- Aim: planning appropriate testing to ensure safety of the materials and of the device

- Acceptance: recognized world-wide, if applied by:
  - certified labs (ISO 17025 or similar accreditation)
  - According to Good Laboratory Practices
ISO 10993: structure 1/5

A series of norms on planning

- **Part 1**: *Evaluation and testing within a risk management process*: a main norm for
  - Identification
  - Planning
  - Reporting

- **Part 12**: *Sample preparation and reference materials*: a general norm on GLP
ISO 10993: structure 2/5

A series of norms on standard biocompatibility testing:

• Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
• Part 4: Selection of tests for interactions with blood
• Part 5: Tests for in vitro cytotoxicity
• Part 6: Tests for local effects after implantation
• Part 10: Tests for irritation and skin sensitization
• Part 11: Tests for systemic toxicity
• Part 20: Principles and methods for immunotoxicology testing of medical devices (Technical Specification)
ISO 10993: structure 3/5

A series of norms on leachables:

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

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

- Part 18: Chemical characterization of materials
- Part 19: Physico-chemical, morphological and topographical characterization of materials (Technical Specification)
Norm relevance

- Compliance of test methods to the methods described in the ISO 10993 series allows to avoid test validation.
- Compliance of results to the limits set in the ISO 10993 series allows presumption of safety.

SHORTCUT TO PROOF OF SAFETY
ISO 10993-01 for Risk management

- Guidance for the biological evaluation within a risk management process, as part of the design of each device.
  - protection of humans from potential biological risks arising from the use of medical devices.
  - concerning the biological evaluation of medical devices.
Aim of ISO 10993-01

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

clause 4.1

- Review and evaluation of existing data from all sources
  - Literature
  - Company data on similar devices
  - Supplier declarations
- Selection and application of additional tests
Object of ISO 10993-1
clause 6.2.1

- Significant device
  - sterile final product,
  - OR representative samples from the final product (smaller?)
  - OR materials processed in the same manner as the final product (including sterilization) (significant prototype)
ISO 10993-01 for Test Planning

- Biological evaluation is based on:
  - Material and raw material identification data
  - Data from literature
  - Testing

- Biological testing is based on:
  - in vitro
  - ex vivo test methods
  - animal models
Ex vivo and animal models

- Minimize the number and exposure of test animals
- Preference to chemical constituent testing and in vitro models, IF these methods yield equally relevant information
- Dedicated norm: – *Part 2: Animal welfare requirements*: a general norm for animal testing
  - Applies to all animal models and all tests
  - Integrated by local law
EU Directive
2010/63/EU

- 3R principle: the replacement and reduction of the use of animals in procedures and the refinement of the breeding, accommodation, care and use of animals in procedures;

- Authorization of experiments by external committee
Human application

- Allowed only if the estimated benefit over-weights the risk
  - Benefit: on clinical conditions, including quality of life
  - Risk: on all the stakeholders

- MDD: No device can be put on the market or even used as part of a clinical trial if the risk benefit ratio isn’t favorable
  - Marketing: Notified Body review
  - Clinical trials: Ethics Committee
The risk based approach 1/2

Annex B

- Device identification: based on known information
  - Intended use
  - Known materials

- Assess hazards
  - From materials, additives, leachables
  - Toxicology data, dose-response rate
  - Nature of exposure (time, path, total exposure over the clinical life)
The risk based approach 2/2

Annex B

- Estimate risk
  - On patient health
  - Use past experience to estimate probability of occurrence

- Lower risk where possible

- Evaluate overall risk-benefit ratio
Device identification

- MDD: classification by the intended use
- ISO 10993: Classification by the kind of body contact
  - Nature
  - Duration
Nature of body contact 1/2
clause 5.2

- **Surface**
  - skin, (band-aids, electrodes)
  - mucose, (contact lenses, intra vaginal devices,...)
  - breached surface (wound dressing)

- **External path**
  - indirect blood path (IV sets)
  - tissue as path (laparoscopes, draining tubes)
  - blood circuits (ECMO)
Nature of body contact 2/2
clause 5.2

- Implant devices
  - Tissue (filling gel, pacemakers)
  - Bone (replacement joints, bone cement)
  - Blood (heart valves, stents)
Duration of body contact
clause 5.3

- A: Limited - 24h or less
  - Needles
  - Internal defibrillation electrodes
- B: Prolonged – 24h to 30 d
  - Catheters
- C: Permanent – 30d plus (even intermittent)
  - Implants
  - Repeated use devices
Biological testing

- Only if no past data are available
- On the (sterile) final product, form commercial manufacturing
- Test planning as per annex A
- Test protocol to identify correct procedures
- VS positive or negative control
- According to GLP and/or ISO 17025
- The test results should be reproducible (intralaboratory) as well as repeatable (interlaboratory) and robust.
## Test planning

### Table A.1 — Evaluation tests for consideration

<table>
<thead>
<tr>
<th>Medical device categorization by</th>
<th>Biological effect</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>
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*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.*
Interpretation of results

- interpretation of existing data and results of testing;
- Comparison of results for the device under examination to the results for positive/ negative controls
- need for any additional data to complete the biological evaluation;
- overall biological safety conclusions for the medical device
- Impact on risk-benefit ratio
Got doubtZ?