Biocompatibility: a risk based approach

Legal framework

- 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*

ISO 10993: structure 4/5

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*

ISO 10993: structure 5/5

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 stake- holders
- 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

Medical device categorization by			Biological effect							
nature of body contact (see 5.2) **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		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.

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?