ISO 10993
An Introduction

Alice Ravizza
www.PGGScientific.com

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

Project teamwork

- 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

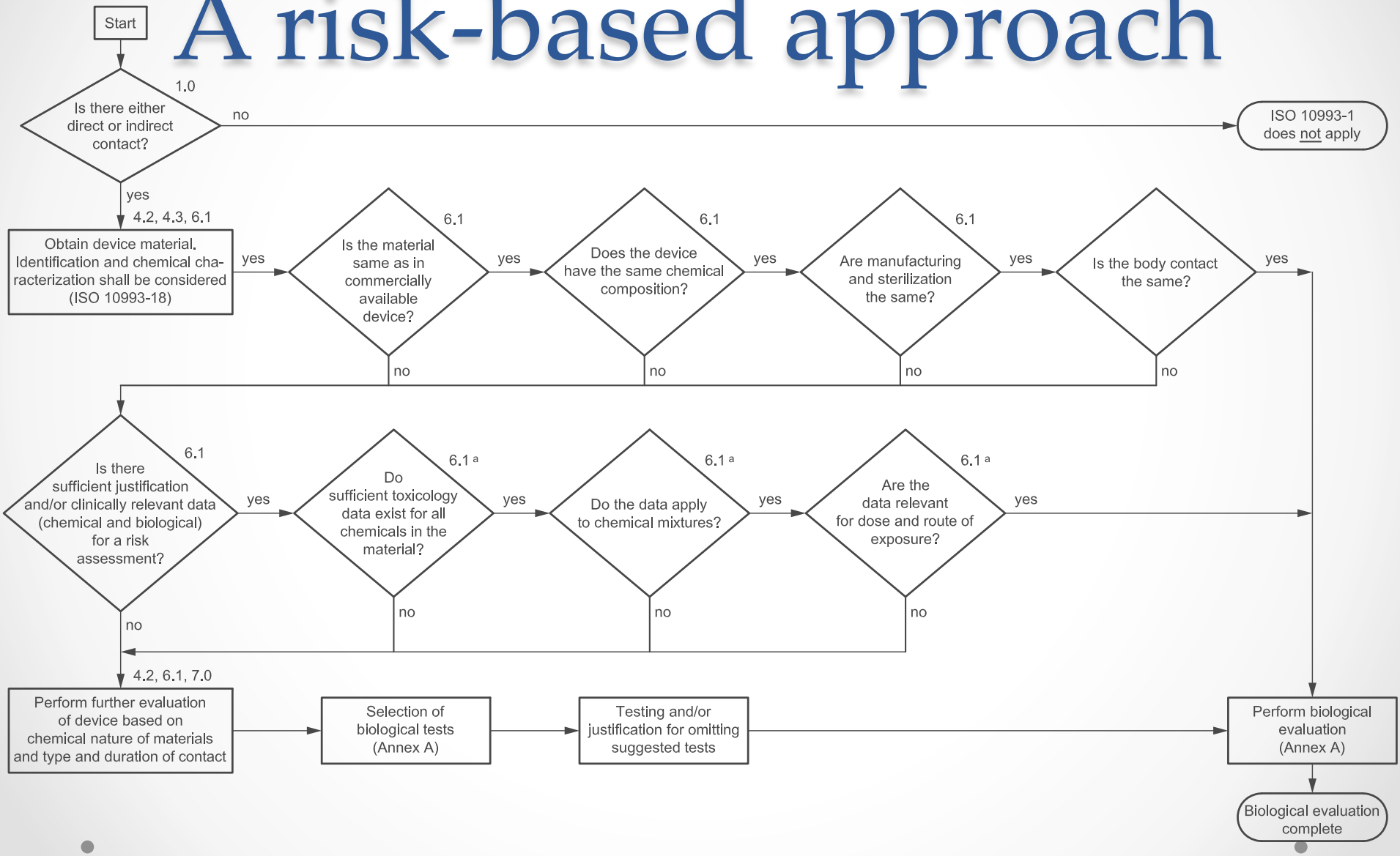
- Compliance of test methods to the methods described in the ISO 10993 series allows to avoid test validation
- Compliance of results to the limits set in the ISO 10993 series allows presumption of safety

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.
- Data from:
  - the review and evaluation of existing data from all sources with,
  - the selection and application of additional tests,
- 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

A risk-based approach



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
- Aim: anticipate the behavior of a new device in humans BUT…
  - it cannot be unequivocally concluded that the same tissue reactions will also occur in humans
  - differences in the response to the same material among individuals: some patients can have adverse reactions, even to well-established materials.

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

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)

The risk based approach (annex B)

- Risk analysis 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)
- Estimate risk
  - On patient health
  - Use past experience to estimate probability of occurrence
- Lower risk where possible
- Evaluate overall risk-benefit ratio

CLASSIFICATION

- By nature of body contact
  - Surface (skin, mucose, breached surface)
  - External path (indirect blood path ex IV sets, tissue as path ex laparoscopes, blood circuits)
  - Implant devices (tissue or bone, blood)
- By duration of contact
  - A: Limited - 24h or less
  - B: Prolonged – 24h to 30 d
  - C: Permanent – 30d plus (even intermittent)

Before testing…

- Material characterization
  - Chemical constituents
  - Process residuals
  - Combination of known raw materials
    - REF: ISO 10993-18 and ISO/TS 10993-19
- Leachables and degradation products
  - Impact of leachables from materials and on materials
    - REF: ISO 10993-17 For the acceptable level of leachables (risks arising from toxicologically hazardous substances)
  - Presence and nature of degradation products
    - REF: ISO 10993-9, ISO 10993-13, ISO 10993-14, and ISO 10993-15 (identification of degradation product in different materials)

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)		**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**
Category	**Contact**									
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.

Test overview 1/5

- Cytotoxicity (cell culture) -5
  - lysis of cells (cell death),
  - inhibition of cell growth,
  - colony formation

- Delayed-type hypersensitivity (rabbit) -10
  - estimate the potential for contact sensitization
  - NOTE: These tests are important because exposure or contact to even minute amounts of potential leachables can result in allergic or sensitization reactions.
  - NOTE: an in vitro test is validated only for pure chemicals and is under validation for devices
  - NOTE: if any irritation is expected, only 1 animal is to be used: if this animal shows irritation, no further testing is required and the device fails

- Irritation(rabbit) -10
  - For external contact devices: skin, eye and mucous membrane with appropriate route and time of contact
  - For implanted: intracutaneous reactivity test

Test overview 2/5

- Systemic toxicity (acute, subacute and subchronic, chronic) (mouse, rat or rabbit)(from 5 to 40 animals, for 24h up to a major amount of the life span of the animal) -11
  - used where contact allows potential absorption of toxic leachables and degradation
  - Dermal. Implantation, inalation, intradermal, intramuscolar, intraperitoneal, intravenous, oral, subcutaneous
  - Observation of clinical signs on the mai phisiological parameters (examples: dysphneas, slower reflexes, bradicardia or tachicardia,…)
  - Pyrogenicity tests are included. (No single test can differentiate pyrogenic reactions that are material-mediated from those due to endotoxin contamination).
  - May be combined and may be extended for implantation testing
- Genotoxicity (in vitro, mammalian cell coltures) -3
  - gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities
  - If any of the in vitro tests are positive, either in vivo mutagenicity tests shall be performed or the presumption shall be made that the material is mutagenic

Test overview 3/5

- Implantation (appropriate animal model: ex. Rabbit for bone) -6
  - Assess the local pathological effects on living tissue, at both the gross level and microscopic level, of a sample of a material or final product that is surgically implanted or placed in an implant site or tissue appropriate to the intended application
  - These tests shall be appropriate for the route and duration of contact.
- Haemocompatibility (in vitro or bench) -4
  - Effects blood or blood components.
  - haemolysis, determines the degree of red cell lysis and the release of haemoglobin caused by medical devices, materials, and/or their extracts in vitro.
  - Other specific haemocompatibility tests may also be designed to simulate the geometry, contact conditions and flow dynamics of the device or material during clinical applications

Test overview 4/5

- Carcinogenicity (rodents) -3 (major portion of life-span of the test animal; lifetime) (possible transgenic models)
  - determine the tumorigenic potential from either single or multiple exposures or contacts
  - appropriate for the route and duration of exposure or contact
  - may be designed to examine both chronic toxicity and tumorigenicity in a single experimental study,
  - they are anyways very uncommon in practice as they are not justified for material that are genotoxic and as they require sham surgery on the control animals. Industry usually prefers to change materials

- Reproductive and developmental toxicity -3
  - Evaluate effects on reproductive function, embryonic development (teratogenicity), and prenatal and early postnatal development.
  - considered for devices/materials used during pregnancy and early infancy or if there is suspect from the degradation or leachable studies (example: phthalates)

- Biodegradation (in vitro and in vivo) -9, specifics in -13 14 and -15
  - For biodegradable or long term implanted devices
  - Biodegradation should be simulated in vitro but In vivo tests may be necessary for complex device-tissue interaction

Test overview 5/5

- Toxicokinetic studies (theoretical, in vitro, possibly in vivo) -16
  - Bioresorbable, permanent contact, with reactive degradation productsor leachables
  - evaluate the absorption, distribution, metabolism and excretion (ADME) of a chemical that is known to be toxic or whose toxicity is unknown.
  - Also determine the delivered dose to the target organ(s) in order to assess any health hazards using the physiologically based pharmacokinetic (PBPK) modelling. The extrapolation of test results across gender, age, species and doses/exposure may be possible,
  - The release from metals, alloys and ceramics is usually too low to justify toxicokinetic studies, unless the material is designed to biodegrade.
- Immunotoxicology -20
  - immunotoxicological effects or if the immunogenic potential

Interpretation of results

- Results are evaluated after approving:
  - criteria for determining the acceptability
  - adequacy of the material characterization;
  - rationale for selection and/or waiving of tests;

- Results are approved by means of:
  - 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