Medical Device Biocompatibility Evaluation - An Industry Perspective

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Agenda

- Introduction to Biological Evaluation
- Biocompatibility assessment process
- Real-life examples

What is biological safety, or “biocompatibility”?

biological safety of medical devices refers to an appropriate host response to the materials in the medical device. Evaluation of biological safety is one part of the overall safety assessment of the device.

–ISO 10993-1:2009(E)

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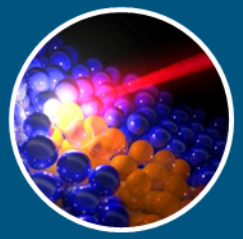
When to evaluate biocompatibility?

Patient contact material –direct or indirect contact

New materials, new devices

Change control



The source or the specification of the materials

the formulation, processing, primary packaging or sterilization of the product;

Manufacturer's instructions or storage

any change in the intended use of the product;

any evidence that the product may produce adverse effects when used in humans

Refer to ISO 10993-1 Section 4.7

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Global requirements

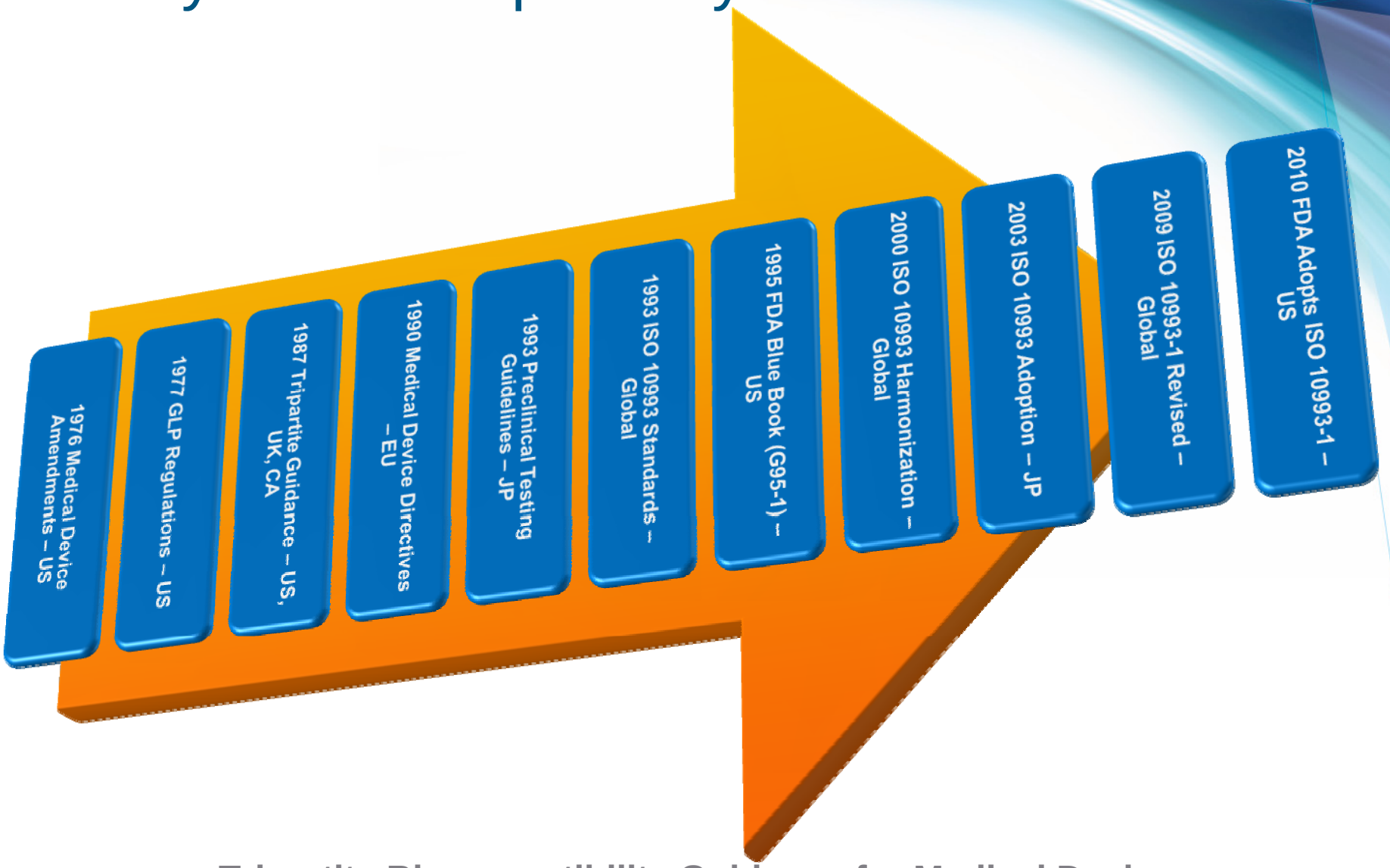
ISO-10993 series of standards.

GB-16886 series of standards

FDA G95-1 is the interpretation of ISO standards by US FDA
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm

Ministry of Health Labor and Welfare (MHLW) Notice #36

History of biocompatibility matrix



Tripartite Biocompatibility Guidance for Medical Devices
International Journal of Toxicology 1988 7: 504

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ISO -10993 Series

10993-1:2009	Guidance on selection of tests = Evaluation and testing *(1st-1992)*
10993-2:2006	Animal welfare requirements *(1st-1992)*
10993-3:2003	Tests for genotoxicity, carcinogenicity, reproductive toxicity *(1st-1992)*
10993-4:2002	Selection of tests for interaction with blood *(1st-1992; Am. 2006)*
10993-5:2009	Tests for cytotoxicity: *in-vitro* methods
10993-6:2007	Tests for local effects after implantation
10993-7:2008	Ethylene oxide sterilization residues
14155: 2003	Clinical investigation of medical devices
10993-9:2009	Degradation of materials related to biological testing
10993-10:2010	Tests for irritation and sensitization
10993-11:2006	Tests for systemic toxicity
10993-12:2012	Sample preparation and reference materials
10993-13:2010	Degradation products from polymeric devices
10993-14:2006	Identification and quantification of degradation products from ceramics
10993-15:2000	Identification and quantification of degradation products from metals and alloys
10993-16:2010	Toxicokinetic study design for degradation products & leachables
10993-17:2002	Establishment of allowable limits for leachable substances
10993-18:2005	Chemical characterization of materials
10093-19:2006	Physicochemical, morphological, & topographical characterization
10993-20:2006	Immunotoxicology testing of medical devices

ISO TC 194

- The international standard organization
- Technical Committee 194
- Develop ISO10993 Standards for the Biological Evaluation of Medical Devices
- Instituted over 20 years ago 1989
- Comprised of 17 Work Groups
- Currently 22 participating countries, including Europe, Asia, NA, 25 observing countries (SA, Africa, ME, etc.)
- SAC TC 248 is the counterpart committee in China

ISO10993-1 Annex A is not a Check-list

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.

Annex A
(informative)

Biological evaluation tests

Table A.1 is a framework for the development of an assessment programme and is not a checklist (see Clause 6). For particular medical devices, different sets of tests may be necessary, including either more or less testing than is indicated in the Table A.1. In addition to the framework set out in Table A.1, the following should be considered based on a risk assessment, which considers the specific nature and duration of exposure: chronic toxicity, carcinogenicity, biodegradation, toxicokinetics, immunotoxicity, reproductive/developmental toxicity or other organ-specific toxicities.

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

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.

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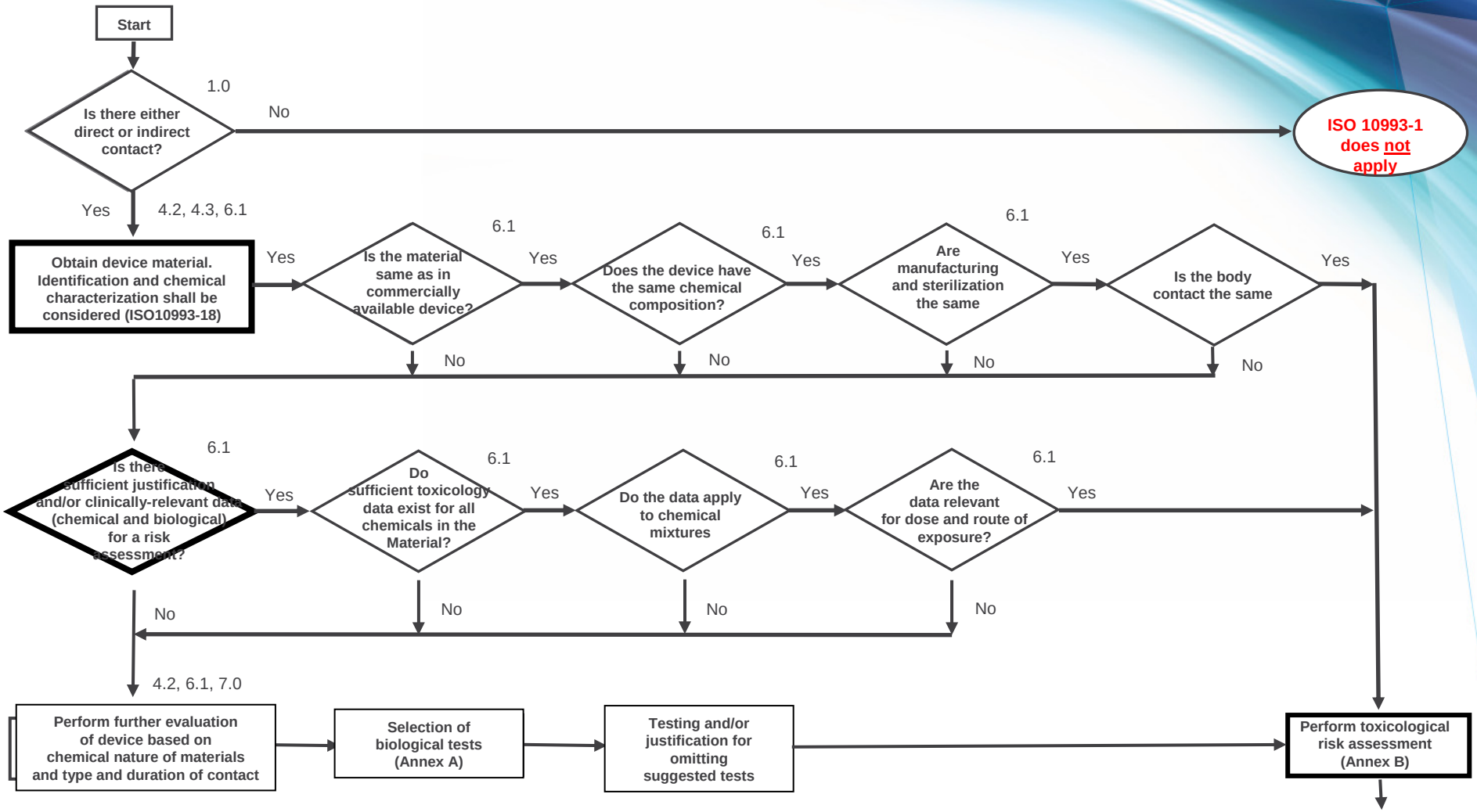
Biological Evaluation Tests

- Cytotoxicity
- Sensitization
- Irritation
- Acute Systemic Toxicity
- Subacute/Subchronic Toxicity
- Genotoxicity
- Implantation
- Haemocompatibility
- Chronic Toxicity
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Biodegradation
- Toxicokinetic studies
- Immunotoxicology

Figure 1 — Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process ISO 10993-1:2009(E)



New Flow Chart – emphasizing Material Characterization and Toxicological Risk Assessment

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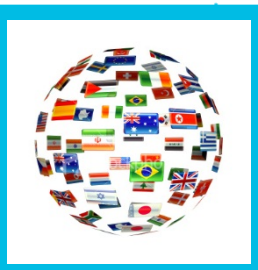
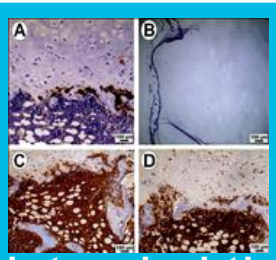
The Evaluation Process-Plan



Market geographies



The intended tissue contact and duration

Prototype device and drawing

Existing Data

Clinical History of the device and materials

Material information (chemical characterization data, material supplier, processing details, sterilization, potential material interactions)

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The Evaluation process-Execution

Biological safety testing (as discussed in the following section). Use qualified contract research organizations, GLP.

Chemical analysis to characterize the material(s)

Toxicological Risk Assessments (as discussed in a following section).

Rationales to analyze existing data and justify not doing certain biological tests

The Evaluation Process-Report

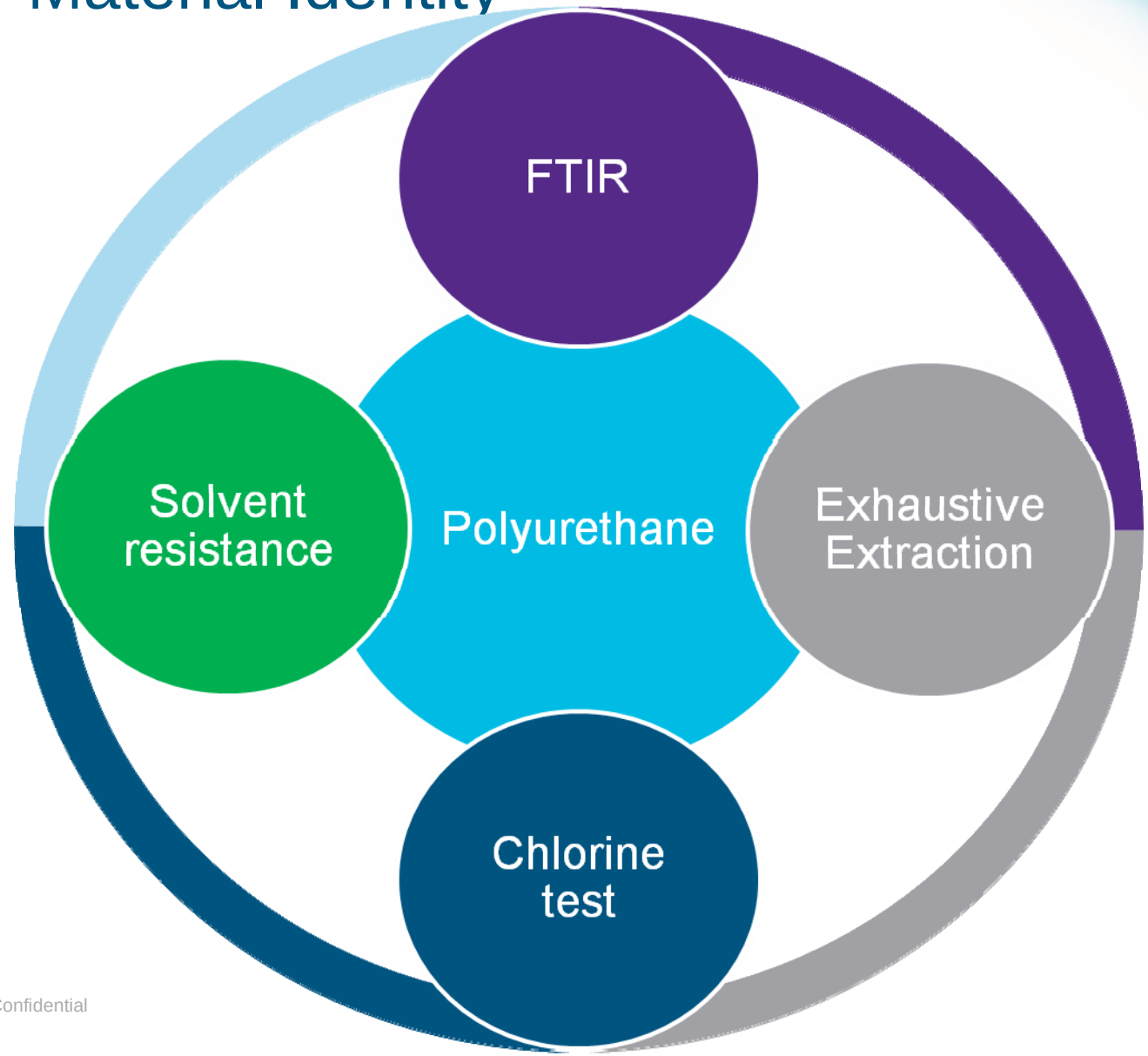
- Descriptions of the device and components
- Chemical characterization of materials
- Manufacturing and processing information
- Biological safety information needs
- Biological safety testing results
- Rationale for selecting specific t
- Additional relevant data
- Toxicological risk assessment
- Conclusion
- Review and approval signatures

Material Evaluation Real-life Example 1: Verify Material Identity

Molded parts

Supplier claim: the material is a halogenated polyolefin

Material Evaluation Real-life Example 1: Verify Material Identity



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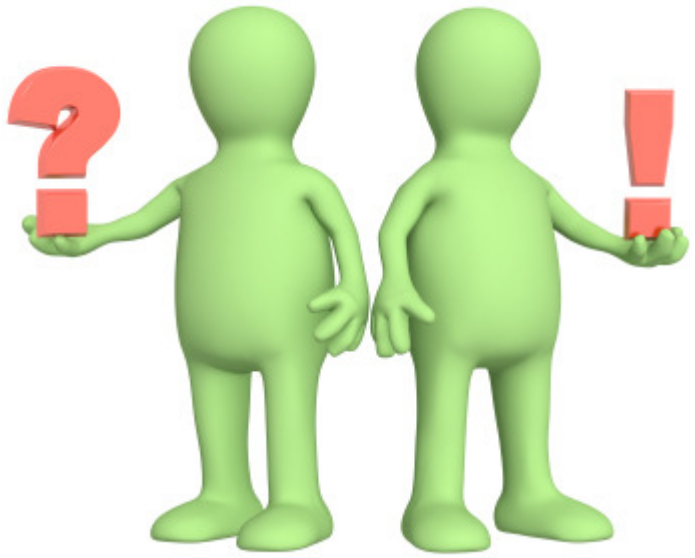
Material Evaluation Real-life Example 2. To Show Material Equivalence

- Supplier initiated material change
- Prolonged tissue contact material (Cyto, Sens, Irri, Acute sys, Subacute/Subchronic sys, Genotox, Implantation)
- Same CAS # and percentages according to MSDS
- HPLC on water, IPA and PEG400 extracts of the original and replacement material
- FTIR, DSC and TGA tests on the two materials
- All test samples were EO sterilized

Assessment

All test results showed material equivalence.

Existing data on existing material are applicable to the replacement material.



Device Evaluation Real-life Example 1

Antimicrobial coated catheter

Prolonged contact with circulating blood

All patient contact materials are from existing devices on the market

Device release on US and EU market

Elements of biological evaluation

Collect material and patient contact information, perform gap analysis on existing data.

Biology test according to ISO10993-1:2009(E):

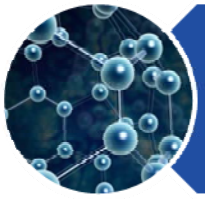
- Device level: Cytotoxicity*, Sensitization, Irritation, Acute systemic toxicity, Subacute/subchronic systemic toxicity, Genotoxicity*(Ames, Mouse Lymphoma), material-mediated pyrogenicity*, hemocompatibility (hemolysis, dog thrombogenicity*, PT, UPTT, complement activation)
- Component level: Implantation*

Risk assessments: Antimicrobial elution and toxicological risk assessment.

New Trends

Leachables and Extractables

Combination Products



Nanomaterials

Alternative Testing

Summary

Introduction to Biological Evaluation

Biocompatibility assessment process

3 Real-life examples

“Medical Grade” Plastics or USP Plastic Classification

USP <88>Six Plastic Classes are defined (see Table 1). This classification is based on responses to a series of in vivo tests for which extracts, materials, and routes of administration are specified. These tests are directly related to the intended end-use of the plastic articles.

Table 1. Classification of Plastics

Plastic Classes[a]						Tests to be Conducted			
I	II	III	IV	V	VI	Test Material	Animal	Dose	Procedure[b]
x	x	x	x	x	x	Extract of *Sample* in *Sodium Chloride Injection*	Mouse	50 mL/kg	A (iv)
x	x	x	x	x	x		Rabbit	0.2 mL/animal at each of 10 sites	B
	x	x	x	x	x	Extract of *Sample* in *1 in 20 Solution of Alcohol in Sodium Chloride Injection*	Mouse	50 mL/kg	A (iv)
	x	x	x	x	x		Rabbit	0.2 mL/animal at each of 10 sites	B
		x		x	x	Extract of *Sample* in *Polyethylene Glycol 400*	Mouse	10 g/kg	A (ip)
				x	x		Rabbit	0.2 mL/animal at each of 10 sites	B
		x	x	x	x	Extract of *Sample* in *Vegetable Oil*	Mouse	50 mL/kg	A (ip)
			x	x	x		Rabbit	0.2 mL/animal at each of 10 sites	B
			x		x	Implant strips of *Sample*	Rabbit	4 strips/animal	C
			▲x		x	Implant *Sample*	Rat	2 *Samples*/animal	C▲USP35

[a] Tests required for each class are indicated by “x” in appropriate columns.

[b] Legend: A (ip)—Systemic Injection Test (intraperitoneal); A (iv)—Systemic Injection Test (intravenous); B—Intracutaneous Test (intracutaneous); C—Implantation Test (intramuscular ▲or subcutaneous▲USP35 implantation).

Individual material vs. whole device testing

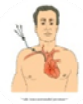
Testing shall be performed on the sterile final product, or representative samples from the final product or materials processed in the same manner as the final product (including sterilization).

Some situations for using dummy devices or materials include:


Very small devices


Very large device or surface area


Samples difficult to obtain


Multiple types of patient contact


Challenging geometries

Sample preparation, ISO 10993-12:2012

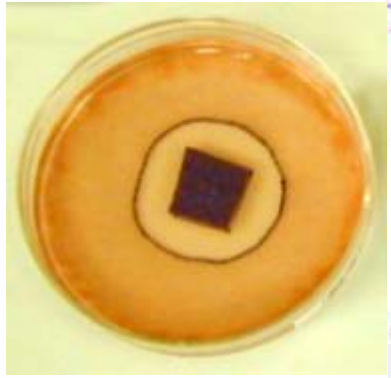
- Extraction Conditions
  - a)(37 ± 1) ° C for (72 ± 2) h;
  - b) (50 ± 2) ° C for (72 ± 2) h;
  - c) (70 ± 2) ° C for (24 ± 2) h;
  - d) (121 ± 2) ° C for (1 ± 0,1) h.
- Extraction Vehicles, polar, non- polar
- Extraction Ratio , Table 1
- Extraction with agitation. Use extracts immediately, without filtration or centrifuge,

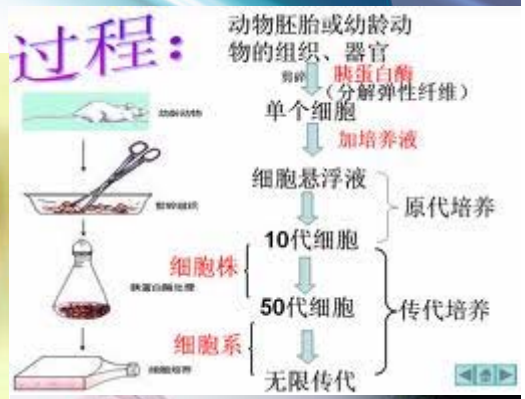
Sample preparation, ISO 10993-12:2012

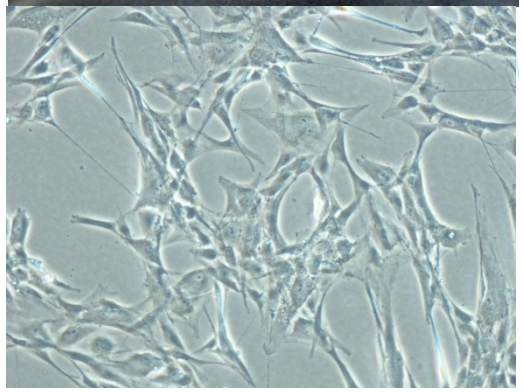
- For solution and soluble materials, select extraction conditions to mimic exaggerated exposure. Pre-test maybe necessary, test neat solution if possible,
- If the material is an aqueous solution and used in this form, it shall be tested directly and not extracted,
- Where fluids circulate through the device under normal conditions of use, e.g. extra-corporeal devices, extraction via re-circulation may be used. When possible, one or more of the conditions shall be exaggerated, e.g. temperature, time, volume, flow rate. The rationale for the extraction chosen shall be reported.

Cytotoxicity ISO10993-5:2009(E)

- Qualitative
  - MEM Elution (L929)
  - Direct Contact (L929)
  - Agarose overlay(L929)
- Quantitative
  - MTT (L929)
  - V79 Colony Formation (V79)
  - NRU (3T3)







Acceptance Criteria

ISO10993-5:1999

Qualitative evaluation: examine the cells microscopically, using cytochemical stain if desired. Assess

changes in, for example, general morphology, vacuolization, detachment, cell lysis and membrane integrity.

The change from normal morphology shall be recorded in the test report descriptively or numerically. A useful

way to grade test materials is presented below. (1999)

Cytotoxicity scale Interpretation

0 Noncytotoxic

1 Mildly cytotoxic

2 Moderately cytotoxic

3 Severely cytotoxic

Acceptance Criteria

ISO 10993-5:2009(E)

Table 1 — Qualitative morphological grading of cytotoxicity of extracts Grade Reactivity Conditions of all cultures

0 None Discrete intracytoplasmatic granules, no cell lysis, no reduction of cell growth

1 Slight Not more than 20 % of the cells are round, loosely attached and without intracytoplasmatic granules, or show changes in morphology; occasional lysed cells are present; only slight growth inhibition observable.

2 Mild, Not more than 50 % of the cells are round, devoid of intracytoplasmatic granules, no extensive cell lysis; not more than 50 % growth inhibition observable.

3 Moderate, Not more than 70 % of the cell layers contain rounded cells or are lysed; cell layers not completely destroyed, but more than 50 % growth inhibition observable.

4 Severe Nearly complete or complete destruction of the cell layers.

Table 2 — Reactivity grades for agar and filter diffusion test and direct contact test

Grade Reactivity Description of reactivity zone

0 None No detectable zone around or under specimen

1 Slight Some malformed or degenerated cells under specimen

2 Mild Zone limited to area under specimen

3 Moderate Zone extending specimen size up to 1,0 cm

4 Severe Zone extending farther than 1,0 cm beyond specimen

The achievement of a numerical grade greater than 2, based on Tables 1 and 2, is considered a cytotoxic effect.

Acceptance Criteria

Quantitative evaluation: Measure cell death, inhibition of cell growth, cell proliferation or colony formation. The number of cells, amount of protein, release of enzymes, release of vital dye, reduction of vital dye or any other measurable parameter may be quantified by objective means. The objective measure and response shall be recorded in the test report. Reduction of cell viability by more than **30 %** is considered a cytotoxic effect. Other criteria, including different cut-off points or an acceptable ratio of test-to-control result shall be justified for alternate cell lines or multi-layered tissue constructs. The criteria shall be justified and documented.

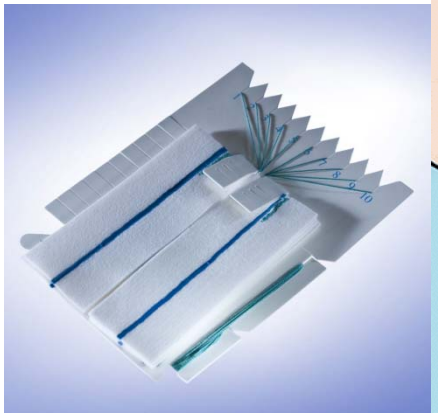
Trouble-shooting cytotoxicity study failure

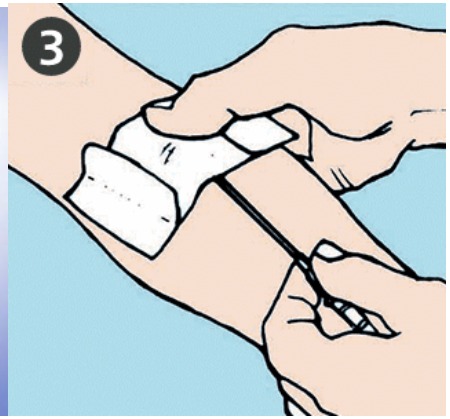
Find out the cause: additives, metals, adhesives, bleach, bonding agents, detergents, processing aids. Determine if there is any patient risk.

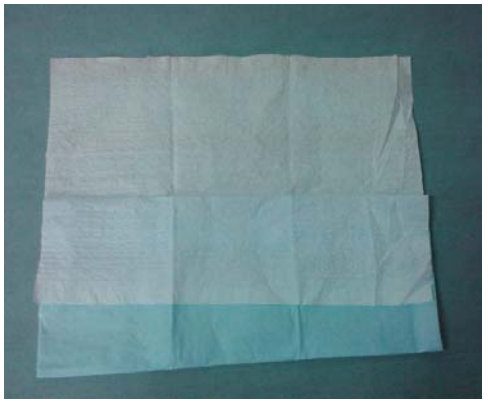
Select appropriate test methods. Or modify methods to mimic patient exposure.

Perform in vivo studies.

If test article failed qualitative study, then perform quantitative study to assess risk.







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