Biocompatibility of Raw Materials for Medical Devices

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SPE 2020

Overview

- ISO 10993-1: How this applies to raw materials
- Medical Device Regulation: discuss regarding carcinogens, mutagens, and reproductive toxins (CMRs)

- Who is responsible for testing?
- What information and testing on raw materials is useful for medical device companies?

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STANDARDS AND REGULATIONS

ISO 10993-1: 2018	• Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
MDR	• Regulation (EU) 2017/745 of the European Parliament and of the Council of 05 April 2017 on Medical Devices. (MDR)

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ISO 10993-1

Section 4.3

“The following shall be taken into account for their relevance to the overall biological evaluation of the medical device:

a) the material(s) of construction (i.e. all direct and indirect tissue contacting materials);

b) intended additives, process contaminants and residues (for example, testing for ethylene oxide sterilization residuals shall be conducted in accordance with ISO 10993-7);

c) packaging materials that directly or indirectly contact the medical device can transfer chemicals to the medical device and then indirectly to the patient or clinician;”

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Table A.1 — Endpoints to be addressed in a biological risk assessment

Medical device categorization by			Endpoints of biological evaluation														
Nature of body contact		Contact duration															
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (>30 d)	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/developmental toxicity[d,e]	Degradation[f]
Surface medical device	Intact skin	A	X[g]	E[h]	E	E											
		B	X	E	E	E											
		C	X	E	E	E											
	Mucosal membrane	A	X	E	E	E											
		B	X	E	E	E		E	E			E					
		C	X	E	E	E		E	E	E	E	E		E			
	Breached or compromised surface	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E	E		
Externally communicating medical device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue/ bone/ dentin[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulating blood	A	X	E	E	E	E	E					E	E[j]			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

Table A.1 *(continued)*

Medical device categorization by			Endpoints of biological evaluation														
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Implant medical device	Tissue/bone[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Blood	A	X	E	E	E	E	E				E	E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

[a] Refer to ISO 10993-11:2017, Annex F.

[b] Information obtained from comprehensive implantation assessments that include acute systemic toxicity, subacute toxicity, subchronic toxicity and/or chronic toxicity may be appropriate if sufficient animals and timepoints are included and assessed. It is not always necessary to perform separate studies for acute, subacute, subchronic, and chronic toxicity.

[c] Relevant implantation sites should be considered. For instance medical devices in contact with intact mucosal membranes should ideally be studied/ considered in contact with intact mucosal membranes.

[d] If the medical device can contain substances known to be carcinogenic, mutagenic and/or toxic to reproduction, this should be considered in the risk assessment.

[e] Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, medical devices with relevant target populations (e.g. pregnant women), and/or medical devices where there is the potential for local presence of device materials in the reproductive organs.

[f] Degradation information should be provided for any medical devices, medical device components or materials remaining within the patient, that have the potential for degradation.

[g] X means prerequisite information needed for a risk assessment.

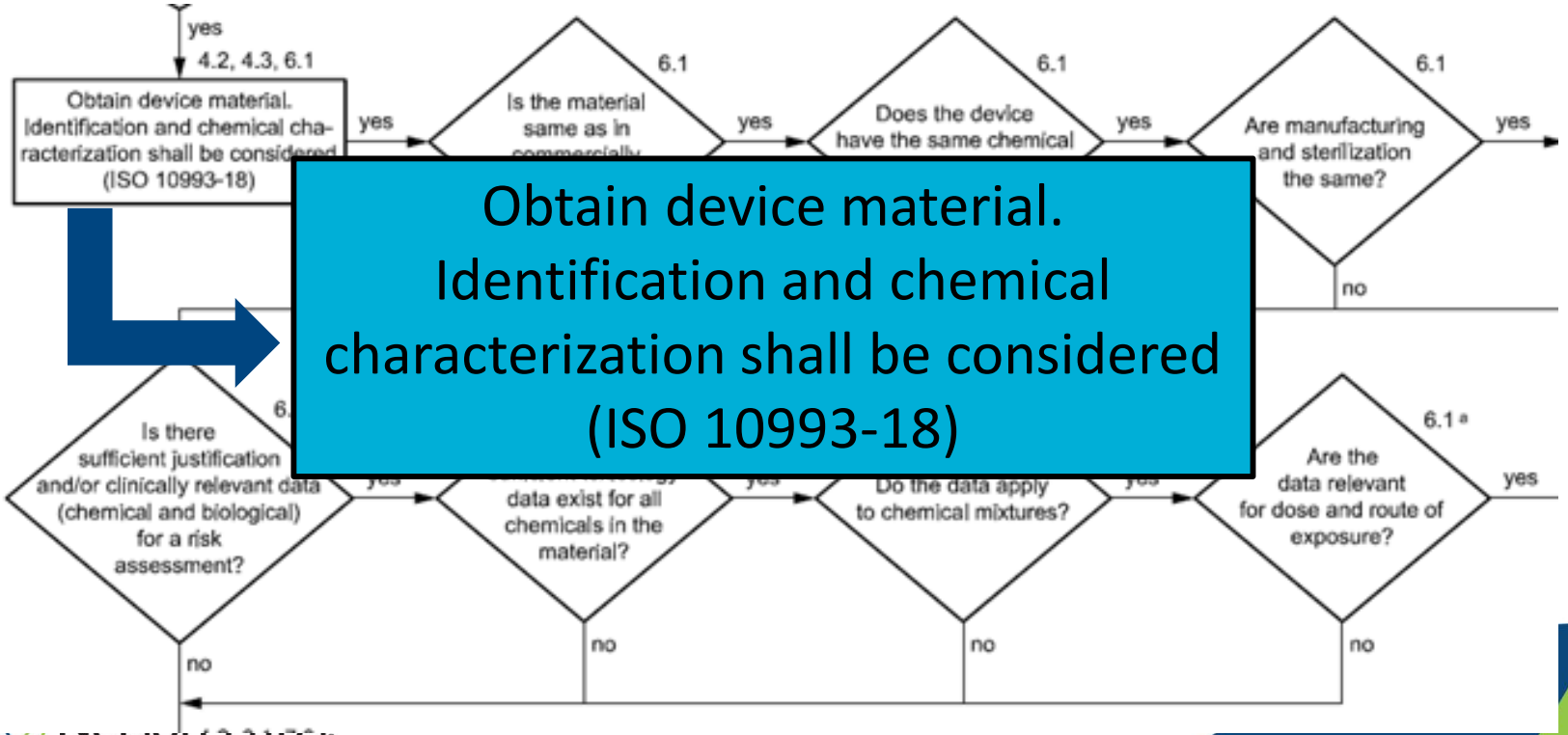
[h] E means endpoints to be evaluated in the risk assessment (either through the use of existing data, additional endpoint-specific testing, or a rationale for why assessment of the endpoint does not require an additional data set). If a medical device is manufactured from novel materials, not previously used in medical device applications, and no toxicology data exists in the literature, additional endpoints beyond those marked "E" in this table should be considered. For particular medical devices, there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated.

[i] Tissue includes tissue fluids and subcutaneous spaces. For gas pathway devices or components with only indirect tissue contact, see device specific standards for biocompatibility information relevant to these medical devices.

[j] For all medical devices used in extracorporeal circuits.

ISO 10993-1

Identify Risks by identifying what we already know



ISO 10993-1

3.17 physical and chemical information

- knowledge regarding formulation, manufacturing processes, geometric and physical properties and type of body contact and clinical use that is used to determine whether any additional biological or material characterization testing is needed

3.13 material characterization

- broad and general process of collecting existing information about a material's chemistry, structure and other properties, and if appropriate, new data, to facilitate the evaluation of these properties

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MDR

shall only contain the following substances in a concentration that is above 0,1 % weight by weight (w/w) where justified pursuant to Section 10.4.2:

(a) substances which are carcinogenic, mutagenic or toxic to reproduction ('CMR'), of category 1A or 1B, in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament and of the Council[1], or

(b) substances having endocrine-disrupting properties for which there is scientific evidence of probable serious effects to human health and which are identified either

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Understanding the 0.1% CMR requirement

Applies to devices with direct and indirect (delivery of liquids or gases), invasive contact.

YES: IV Tubing, surgical tool, implant, breathing tube.

NO: Any wearable device with intact skin contact.

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CMR lists

From the MDR

- "Category 1A or 1B, in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament and of the Council"
  - Harmonized classification and labeling of hazardous substances list from ECHA: https://echa.europa.eu/information-on-chemicals/annex-vi-to-clp
  - Some compounds are not CMRs so the list needs to be filtered

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CMR lists

Alternate lists

- REACH: broad set of chemical with various human and environmental impact - not specific enough to address CMRs
- Prop 65: list of compounds known to cause cancer or reproductive toxicity. Excludes mutagens –not inclusive enough.
- COSING Annex II: prohibited cosmetic ingredients (compounds already included in Annex VI CLP list)

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How to address CMRs

Best Practice

- Supplier provided certificate
- Can protect IP
- Generated in house

Alternate Option*

- High level screening chemistry
- Based on patient exposure, not device make-up

*Not known if this approach is accepted by notified bodies.

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How to address CMRs

Supplier provided certificate

Review materials used in manufacture of material – all compounds

Compare against CLP Annex VI list

Generate a CMR Statement

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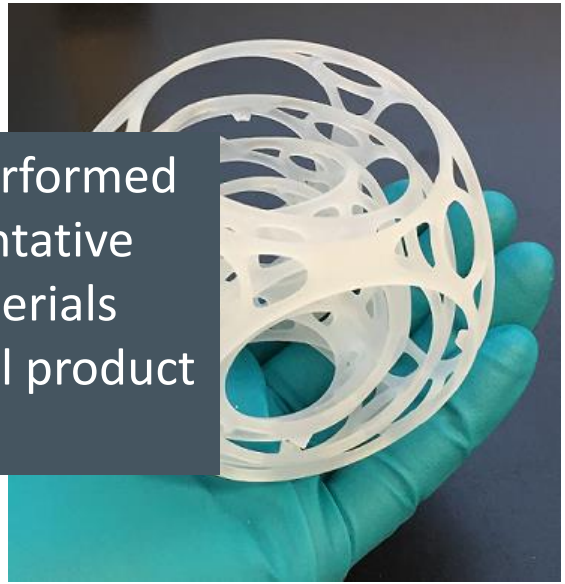
Testing responsibility

Raw Material

ISO 10993-1, 6.2.1 a) “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).”



Finished Device

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		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

Physical/Chemical Information

Supplier information

ISO 10993 compliance

USP Class VI

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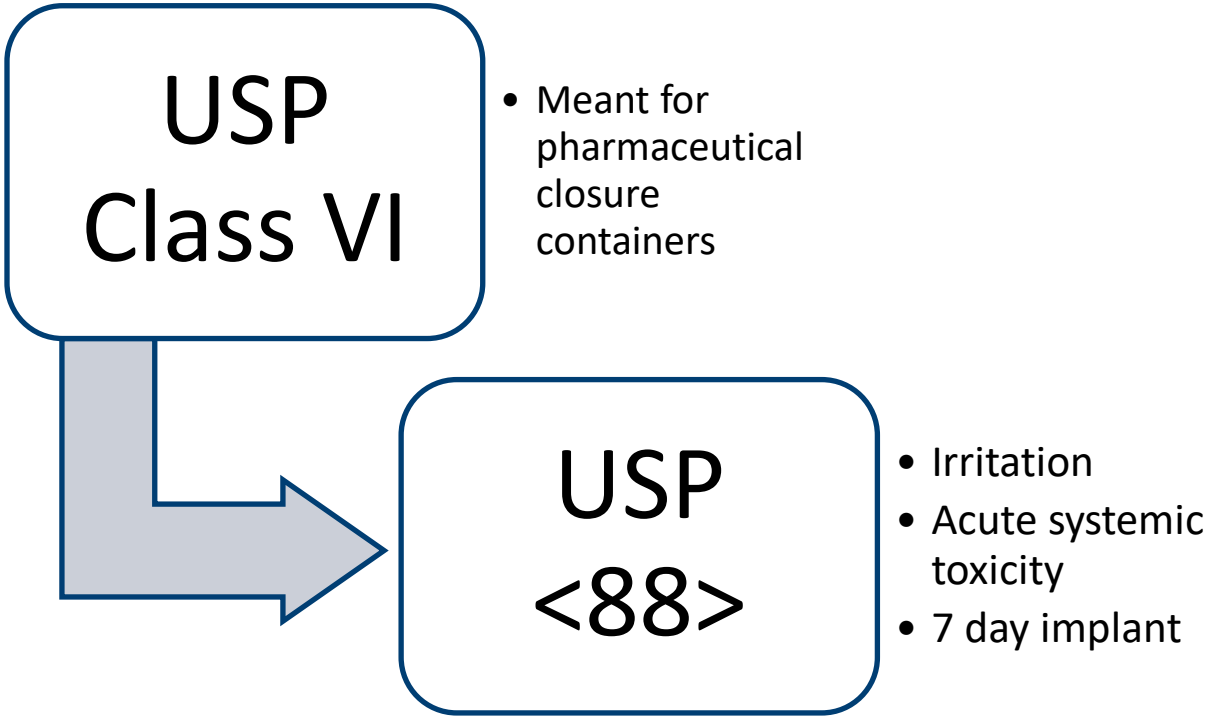
Supplier Information



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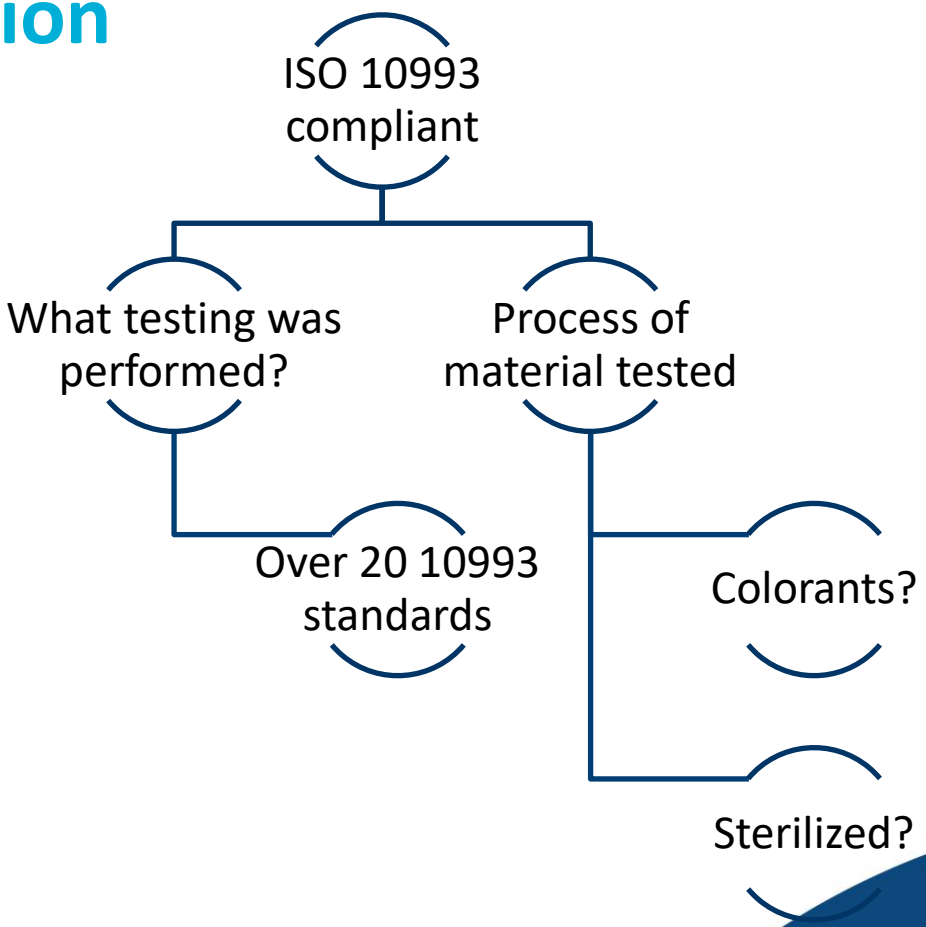
Supplier Information



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		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

Cytotoxicity

Sample requirements

- MEM Elution: 120 cm^2 or 4 g
- Agar Overlay: 500 mm^2 or 1g

TAT

- 4 days for preliminary data, 6 days for final report

Usual problems

- Latex, Natural Rubber, Silver, Copper, Dark Inks, Short Curing Times.

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Cytotoxicity: MEM Elution

GRADE	REACTIVITY	DESCRIPTION
0	None	• Discrete intracytoplasmic granules, no cell lysis.
1	Slight	• Not more than 20% of the cells are rounded, loosely attached, and without intracytoplasmic granules; occasional lysed cells are present.
2	Mild	• Not more than 50% of the cells are rounded and devoid of intra cytoplasmic granules; no extensive cell lysis and empty areas between cells.
3	Moderate	• Not more than 70% of the cells are rounded and/or lysed.
4	Severe	• Nearly complete destruction.

Pass

Fail

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Irritation

Intracutaneous Reactivity

3 Rabbits

- 10 injections each: 5 right (test) and 5 left (control)

DATA

- Subjective, Qualitative data

TAT

- 4-5 weeks

Sample Req.

- 240 cm^2 or 8 g, min. two samples

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Irritation

Injection	Extracts on 5 sites on right (test) and 5 other sites on left (control)
Observation	Sites are observed for 24, 48, and 72 hours post injection and given an irritation score (0-4) or erythema and oedema.
Data Interpretation	After the 72 hours, all the scores are added then divided by 15 (3 time points X 5 injection sites); then the scores from the rabbits will be added and divided by 3
Results	The test article is considered a non-irritant if the difference between the test article and control mean score is **1.0 or less**

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Introduction to *in vitro* irritation

Uses Reconstructed Human Epidermis (RhE)

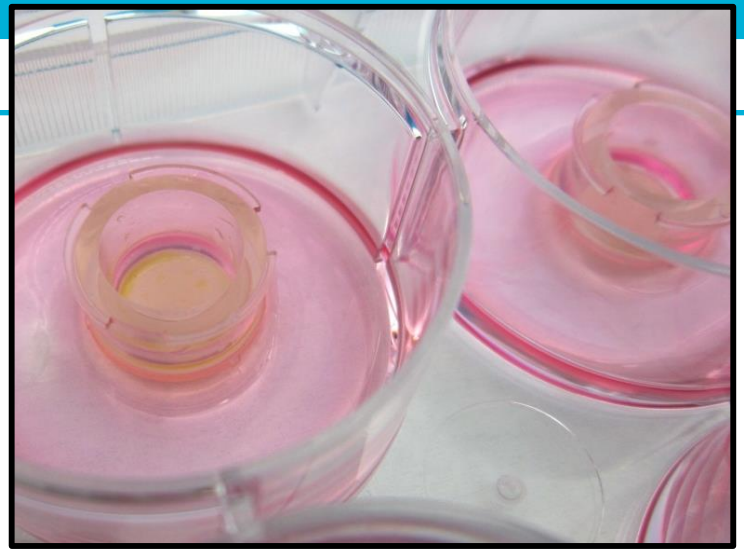

Photo by Daniel Olsen. ©Nelson Laboratories, LLC.

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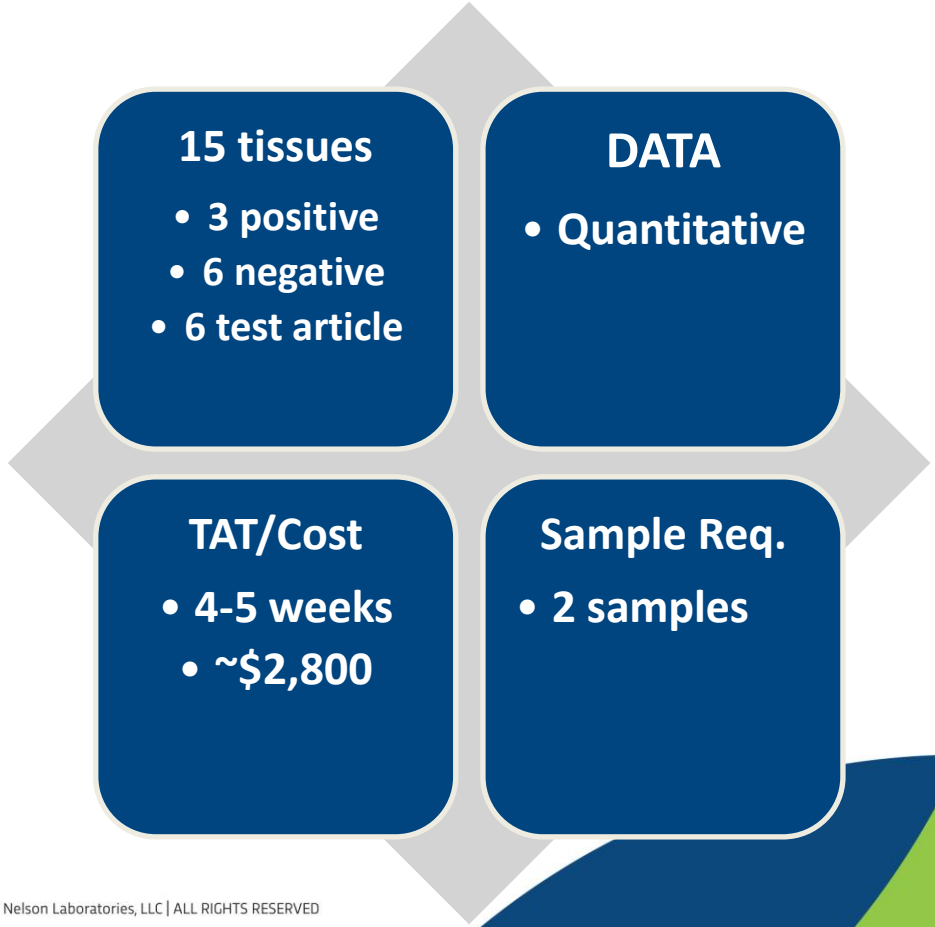
In Vitro Irritation

***In vitro* irritation (RhE)**



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In Vitro Irritation

Extraction	**Polar and non-polar according to ISO 10993-12.**
Exposure	**Test article extract is topically applied to tissues. Incubated for 18-24 hrs.**
Cell Viability	**After exposure, tissues are rinsed and exposed to MTT. Then, tissues are rinsed again and extracted in IPA.**
Data Analysis	**The IPA extract is read on a spectrophotometer and results are compared to the negative control.**

MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

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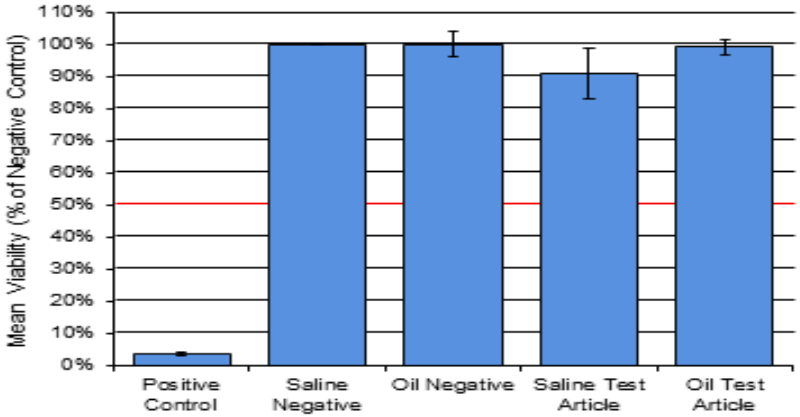
Data Analysis

Percent viability(%) = [$OD_{PC/TA}$/Mean OD_{NC}] x100

Results Summary

Sample	Optical Density		Percent Viability		Category
	Mean	St. Dev.	Mean	St. Dev.	
Positive Control	0.050	0.006	3.4%	0.4%	I
Saline Negative	1.503	0.003	100.0%	0.2%	NI
Oil Negative	1.605	0.066	100.0%	4.1%	NI
Saline Test Article	1.365	0.120	90.8%	8.0%	NI
Oil Test Article	1.590	0.037	99.1%	2.3%	NI



- **≤ 50%: Irritant (I), R38 GHS Category 2**
- **> 50%: Non-irritant (NI)**

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Sensitization

Test Method	Device Contact	TAT	Sample Amount	Data
Guinea Pig Maximization	Indirect	8-9 weeks	6 samples (120 cm^2 or 4 g each)	Qualitative
Local Lymph Node Assay (LLNA)	Indirect	4-6 weeks	6 samples (120 cm^2 or 4 g each)	Quantitative
Buehler	Direct	8-9 weeks	100, 1x1 inch patches	Qualitative

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Other considerations

Selling for cardiovascular devices?

Consider hemolysis testing

4 devices, ~$1,500 and 14 days

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Certificate of Biocompatibility

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Certificate of Material Biocompatibility

Material:

This statement of biocompatibility only applies to the XXXX. Any change or additional processing needs to be further assessed for impact to biocompatibility of the final finished product.

Specification of Test Article
The material was then sterilized by EO/Gamma/VHP/steam prior to testing.

Table 1. Tests Performed

Biological Effect	Assay Title	Testing Standard	Result
Cytotoxicity	MEM Elution	ISO 10993-5	
Sensitization	Magnusson-Kligman Maximization	ISO 10993-10	
Irritation	Intracutaneous Reactivity	ISO 10993-10	
Systemic Toxicity (acute)	Systemic Injection	ISO 10993-11	
Pyrogenicity	Material Mediated Pyrogen	ISO 10993-11	
Hemocompatibility	Hemolysis (indirect)	ISO 10993-4 and ASTM F756	
	Hemolysis (direct)	ISO 10993-4 and ASTM F756	

Conclusion

The XXXX as described was tested for the biological endpoints required by ISO 10993-1 as outlined in Table 1.

Any change to or additional processing needs to be further assessed for impact to biocompatibility of the final finished product. It is the responsibility of the manufacturer to assess the final finished device or product for its biocompatibility.

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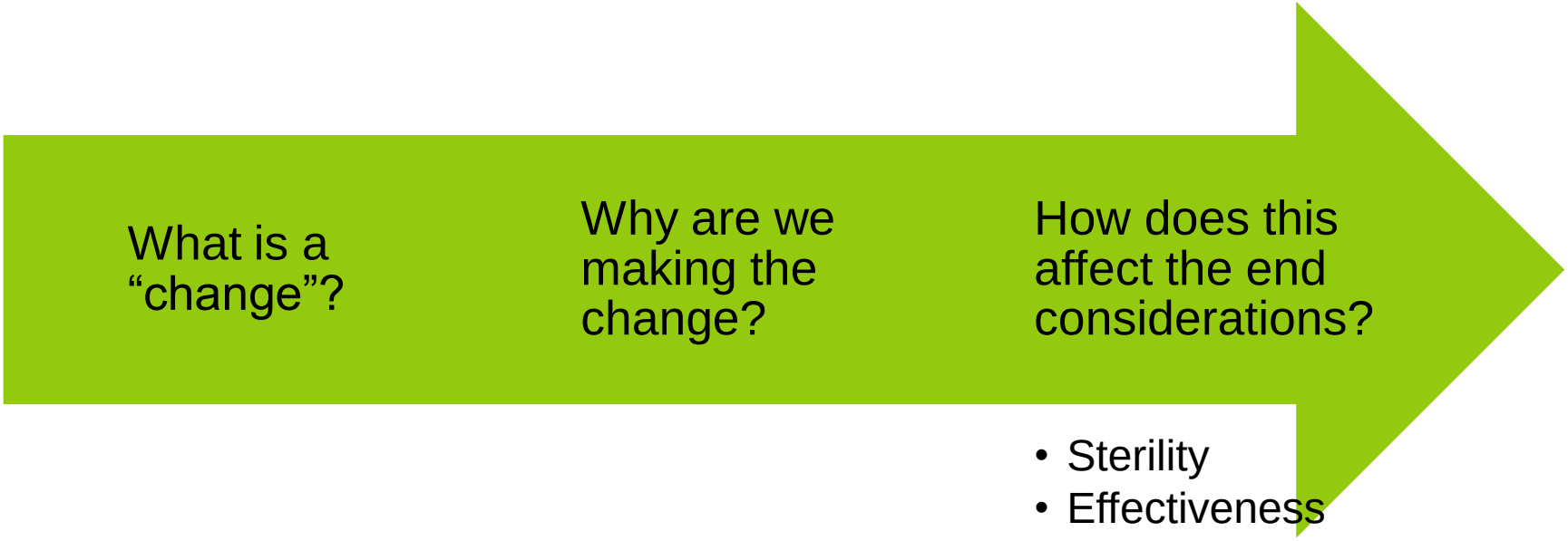
A Note on Changes



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A Note on Changes

A glass raw material is being tested for lot release and has years of passing cytotoxicity scores. Recently, one lot of material received a cytotoxicity score of “2”.

What are some possible causes of this outcome?

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Overview

ISO 10993-1: How this applies to raw materials	Gathering physical/chemical informtion is a requirement and starts with the raw materials
Medical Device Regulation: discuss regarding carcinogens, mutagens, and reproductive toxins (CMRs)	CMR Certificate is required for devices sold in the EU
Who is responsible for testing?	Final device manufacturer
What information and testing on raw materials is useful for medical device companies?	ISO 10993: cytotoxicity, sensitization, irritation and sometimes hemolysis

Where to go from here

More information on biocompatibility?	• https://www.nelsonlabs.com/find-a-test/medical-devices/biocompatibility-toxicology/
Interested in our offerings presented here?	• Email inquiries to consulting@nelsonlabs.com
More webinars on biocompatibility	• https://www.nelsonlabs.com/event-category/on-demand-webinars/

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