Update on ISO 10993

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Past and Future Changes

What Has Changed?

ISO 10993-1:2018

- Released August 2018
- Significant Changes to Table A.1
  - Moved to informative Annex
  - Six new columns
    - Physical and/or chemical information
    - Material mediated pyrogenicity
    - Chronic toxicity
    - Carcinogenicity
    - Reproductive/developmental toxicity
    - Degradation

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Meet the New Standard: Table A.1 from ISO 10993-1

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		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		

Its All About Risk

What Has Changed?

Annex B cannibalized ISO TR 15499:2016

- TR 15499:2016 has been "withdrawn". Now proper risk evaluation details are contained within the standard.

Transitory contact, nanomaterials, and absorbable materials added

ISO 18562 referenced

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ISO 18562

Biocompatibility evaluation of breathing gas pathways in healthcare applications

ISO 18562-1: Evaluation and testing within a risk management process	**ISO 18562-2**: Test for emissions of particulate matter	**ISO 18562-3**: Tests for emissions of volatile organic compounds (VOCs)	**ISO 18562-4**: Tests for leachables in condensate
RISK EVALUATION	PARTICULATES	VOCs	CONDENSATE

Why the Changes

Place emphasis on a “Risk Based Approach’ instead of checkbox approach

- Emphasis on “Competent Individuals”

To create a thoughtful and planned approach

- Biological Evaluation Plan (BEP)
- Biological Evaluation Report (BER)

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Where are With Regulatory Bodies Acceptance?

Released in Aug 2018

EN and FR versions released in Nov 2018

Added to FDA consensus list Jan 2019

Except table A.1 in Annex A

No consensus in EU

State of the art?

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Where are With Regulatory Bodies Acceptance?

Besides the ISO Standard, Specific regulatory requirements can also affect the decision.

FDA Guidance 2016:

Perform Big Three, Chemistry, hemocompatibility, and implantation

EU (MDD or MDR): EU prefers analytical over animal approach but will be heavily dependent on reviewer.

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The Future?

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Cytotoxicity 10993-5

MEM vs. MTT/XTT vs. Neutral Red vs. Colony Forming Test

- Round robin being developed to understand differences between tests and labs
- More guidance on failures and investigation approaches

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Irritation and Sensitization 10993-10 (23)

Separation of irritation and sensitization

- Sensitization stays as part 10 but irritation becomes part 23

Main irritaiton method is moved to in vitro

- Using Reconstructed Human Epidermis (RHE) tissues

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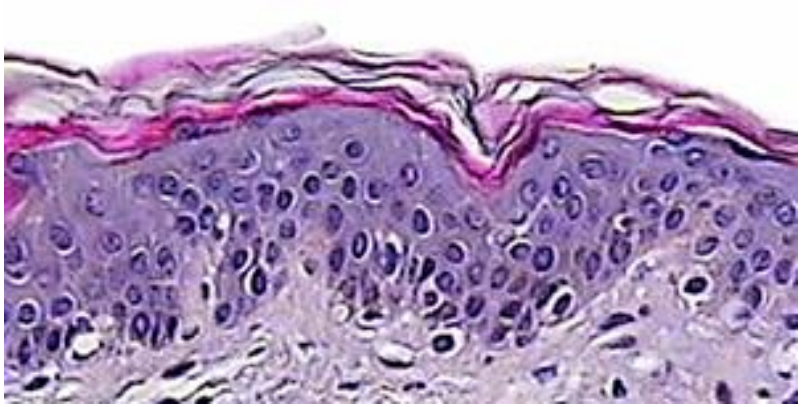
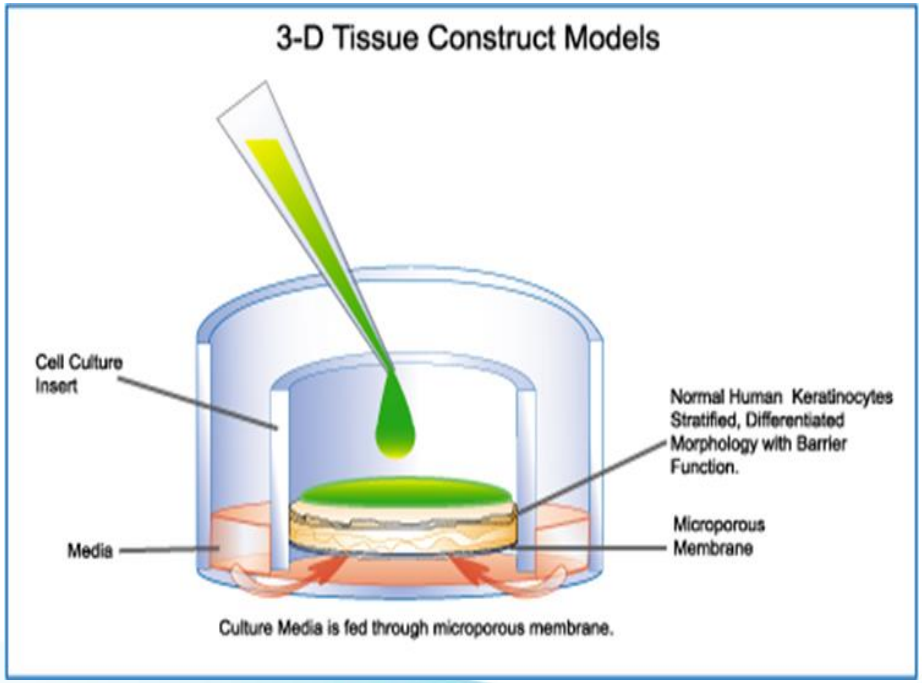
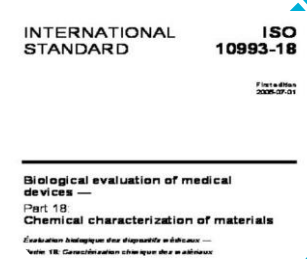
In Vivo Alternatives: Irritation

In Vitro Irritation





Chemical Characterization 10993-18


INTERNATIONAL STANDARD

ISO 10993-18

Biological evaluation of medical devices —
Part 18:
Chemical characterization of materials

ISO 10993-18 (2005): 17 pages


ISO/TC 194/SC N

Date: 2017-03-09

ISO/CD 10993-18:2017(E)

ISO/TC 194/SC /WG 14

Secretariat: DIN

Biological evaluation of medical devices — Part 18: Chemical characterization of materials

Warning

DIS 10993-18 (2019): 79 pages

- Major revision of the whole concept of chemical characterization
  - Broader definition of chemical characterization
  - Introduction of the concept of Analytical Evaluation Threshold (AET)
  - Definition of extractable testing
  - Definition of leachable testing
  - Clarification on the extraction procedures and analytical techniques to be used during chemical testing

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Chemical Characterization 10993-18

- The whole procedure is described on at the beginning of FDIS ISO 10993-18 (2019)

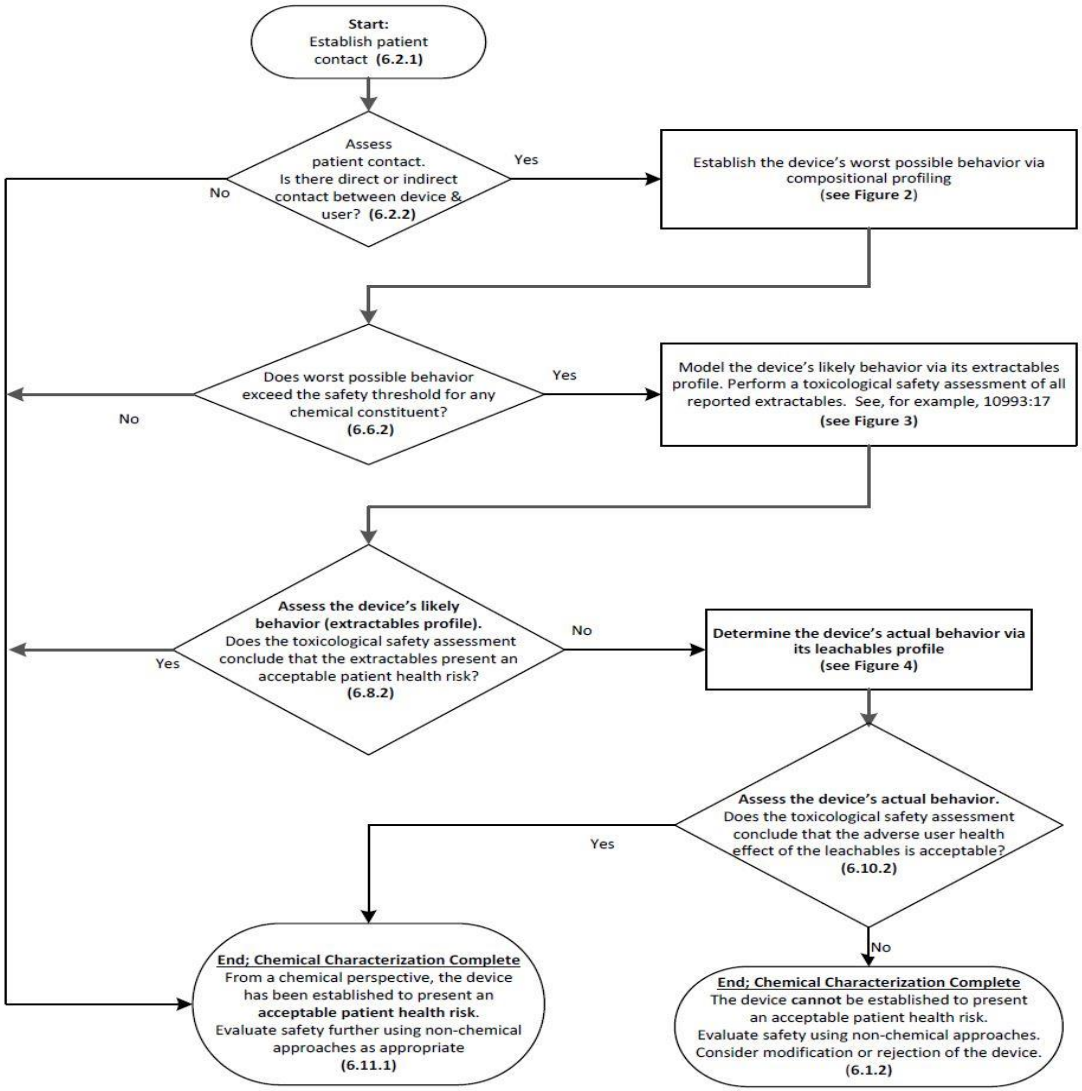

Figure 1 — General chemical characterization process

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Applying These Changes

Standards for Presentation

ISO 10993 Suite

Standards that cover all testing under "Biological evaluation of medical devices"

US FDA guidance document

"Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'" issued June 16, 2016.

Past Approach

Device contact

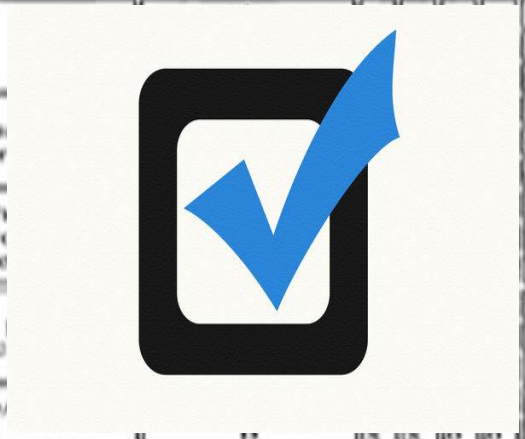
Contact time

Perform tests

510(k) Memorandum - #G95-1 Table 1

Initial Evaluation Tests for Consideration

Device Categories			Biological Effect											
Body Contact (see 4.1)		Contact duration (see 4.2) A-limited (24h) B-prolonged (24h to 30 days) C-permanent (>30days)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Acute Systemic Toxicity (oral)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Hemocompatibility		
Surface devices	Skin	A										
		B										
		C										
	Mucosal membrane	A										
		B										
		C										
	Breached or compromised surface	A										
		B										
		C										
External communicating devices	Blood (indirect)	A										
		B										
		C										
	Tissue/bone/dentin communicating*	A										
		B										
		C										
	Circulating blood	A										
		B										
		C										
Implant devices	Tissue/bone	A										
		B										
		C										
	Blood	A										
		B										
		C										



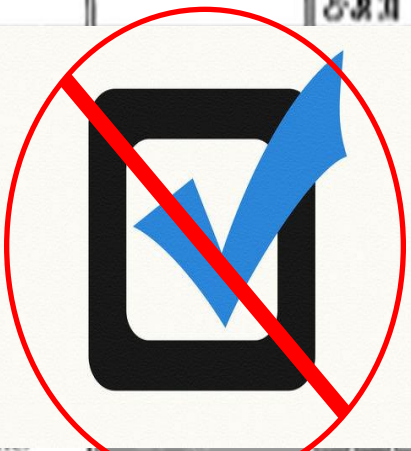
Past Approach

- Didn't understand
  - Materials
  - Testing

510(k) Memorandum - #G95-1 Table 1

Initial Evaluation Tests for Consideration

Device Categories			Contact duration (see 4.2) A=limited (24h) B=prolonged (24h to 30 days) C=permanent (>30days)	Biological Effect
Body Contact (see 4.1)				
Surface devices	Skin			
	Mucos membr			
	Breach compr surfac			
External communicating devices	Blood indirec			
	Tissue/ dentin communicating*			
	Circulating blood			
Implant devices	Tissue/ bone			
	Blood			



Medical device categorization by					
Nature of Body Contact		Contact Duration			
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) (> 30 d)	Physical and/or chemical information	Cytotoxicity	Sensitization
Surface device	Intact skin	A	X [g]	E [h]	E
		B	X	E	E
		C	X	E	E
	Mucosal membrane	A	X	E	E
		B	X	E	E
		C	X	E	E
	Breached or compromised surface	A	X	E	E
		B	X	E	E
		C	X	E	E
External communicating device	Blood path, indirect	A	X	E	E
		B	X	E	E
		C	X	E	E
	Tissue/bone/dentin [i]	A	X	E	E
		B	X	E	E
		C	X	E	E
	Circulating blood	A	X	E	E
		B	X	E	E
		C	X	E	E

ISO 10993 and RISK

ISO 10993 is intended as a guidance to determine the potential biological risks arising from the use of medical devices.

Meaning, what is the risk of my materials and processes to the patient?

ISO 10993-1: Biological evaluation of medical devices – Part 1: Evaluation and testing within a **risk** management process

Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"

Section III. Risk Management for Biocompatibility Evaluations

"Such a process should generally begin with assessment of the device, including the **material components**, the **manufacturing processes**, the **clinical use of the device**…" Considering this information, the **potential risks from a biocompatibility perspective** should be identified. Considering the potential biological impact, a plan should be developed … **either by biocompatibility testing or other evaluations that appropriately address the risks.**

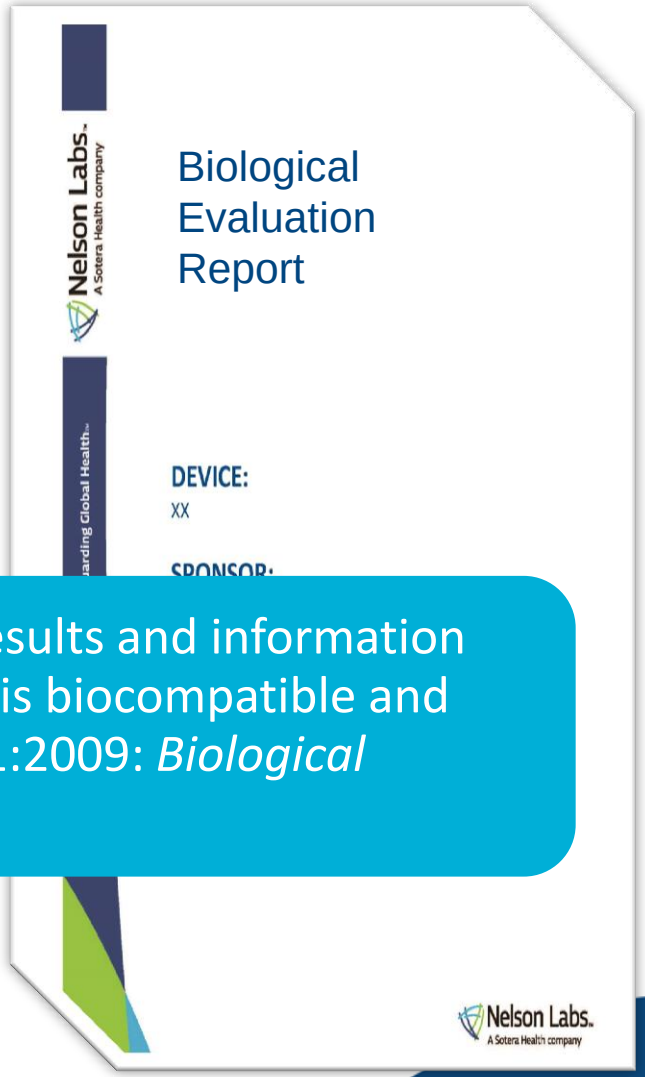
Incorporating Risk

What is **Risk**?

ISO 14971 Definition: Combination of the **probability of occurrence** of harm and the **severity of that harm.**

Biological Safety Evaluation

Biological Evaluation Report



CONCLUSION: "Based on the testing results and information summarized in this report, the DEVICE is biocompatible and meets the requirements of ISO10993-1:2009: *Biological evaluation of medical devices – Part 1*.

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What If I Fail a Test?

Confirm Procedure

Confirm Result

Eliminate Toxicity

Accept Toxicity

Label for Safety

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What If I Fail a Test?

Correct article tested?

Article made correctly?

Article properly cleaned, labeled and stored?

Protocol followed?

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What If I Fail a Test?

Do the repeat tests have the same result?

Physical / Chemical Profile

Published Literature

Lot history

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What If I Fail a Test?

Change test procedure?

Reformulate test article?

Reconfigure test article?

Replace material with another?

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What If I Fail a Test?

Label for safety

Check competitive material in use

Risk assessment

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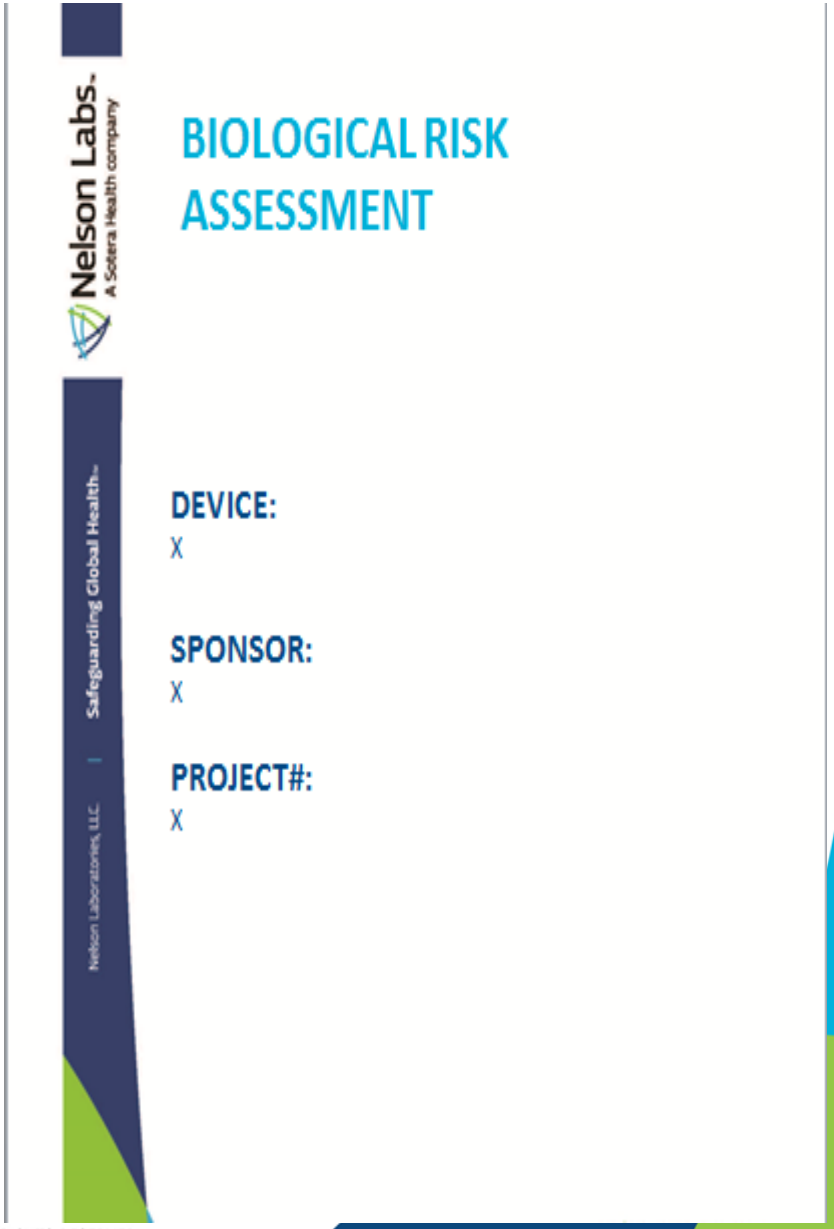
Offerings

- Biological Risk Assessment
  - Material change
  - Failed test
  - Location change
  - Process change
  - Specific requests by a regulatory body



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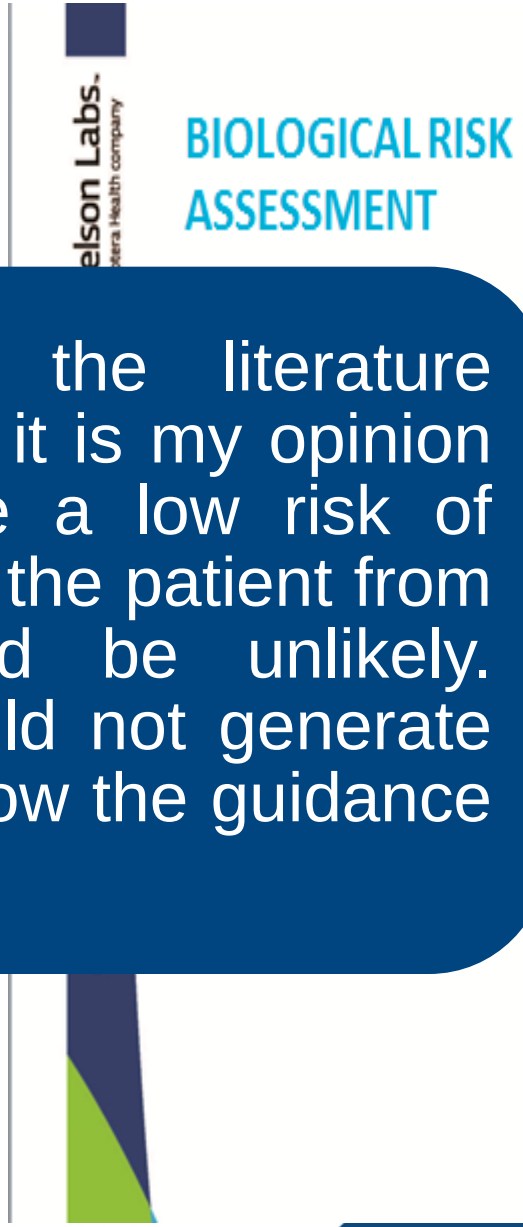
Offerings

- Biological Risk Assessment
  - Material change



CONCLUSION: Based on the literature review of compound/material, it is my opinion that the change would pose a low risk of toxicity and adverse effects to the patient from this material change would be unlikely. Additional animal testing would not generate useful data and would not follow the guidance in ISO 10993 part 2.

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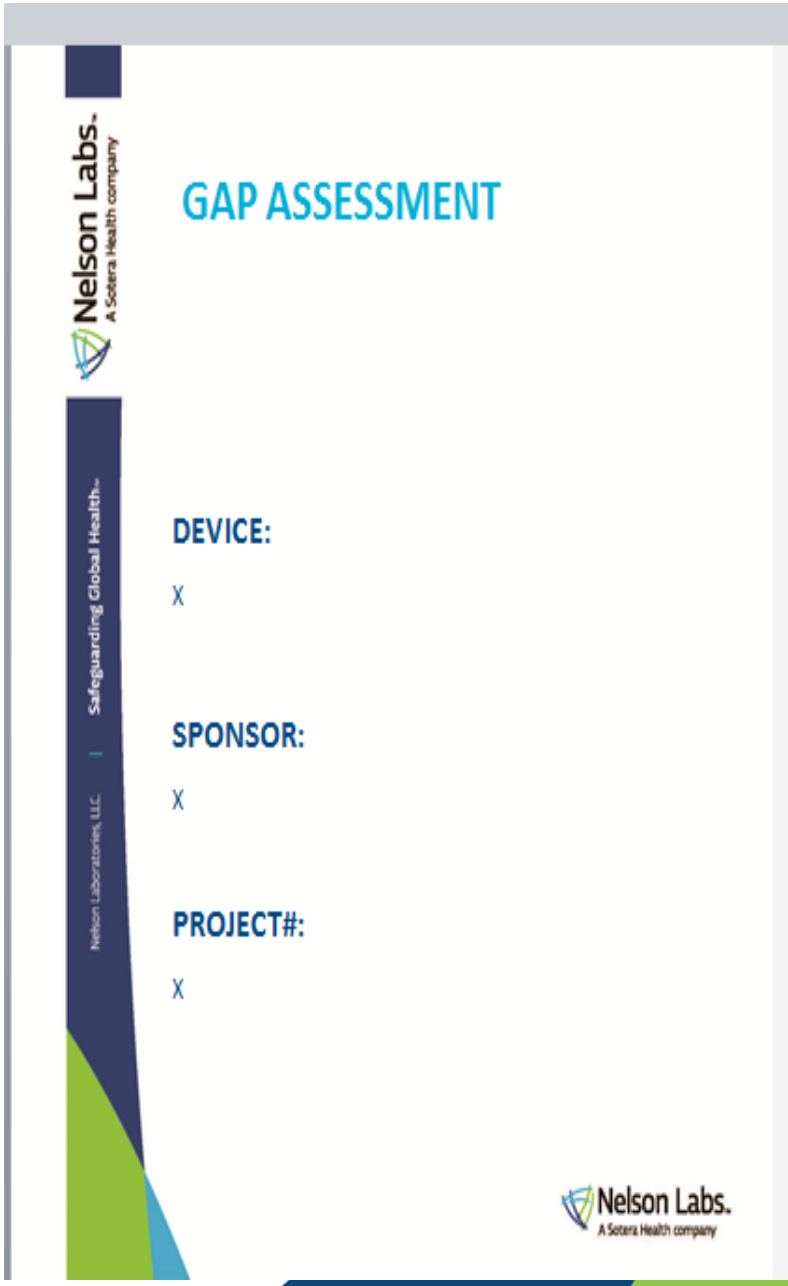
Offerings

- Gap Analysis
- **Purpose**
  - The purpose of this report is to perform a gap analysis between the completed testing on the device and the current testing requirements. This gap analysis will uncover any testing that may need to be performed to meet the current standards.



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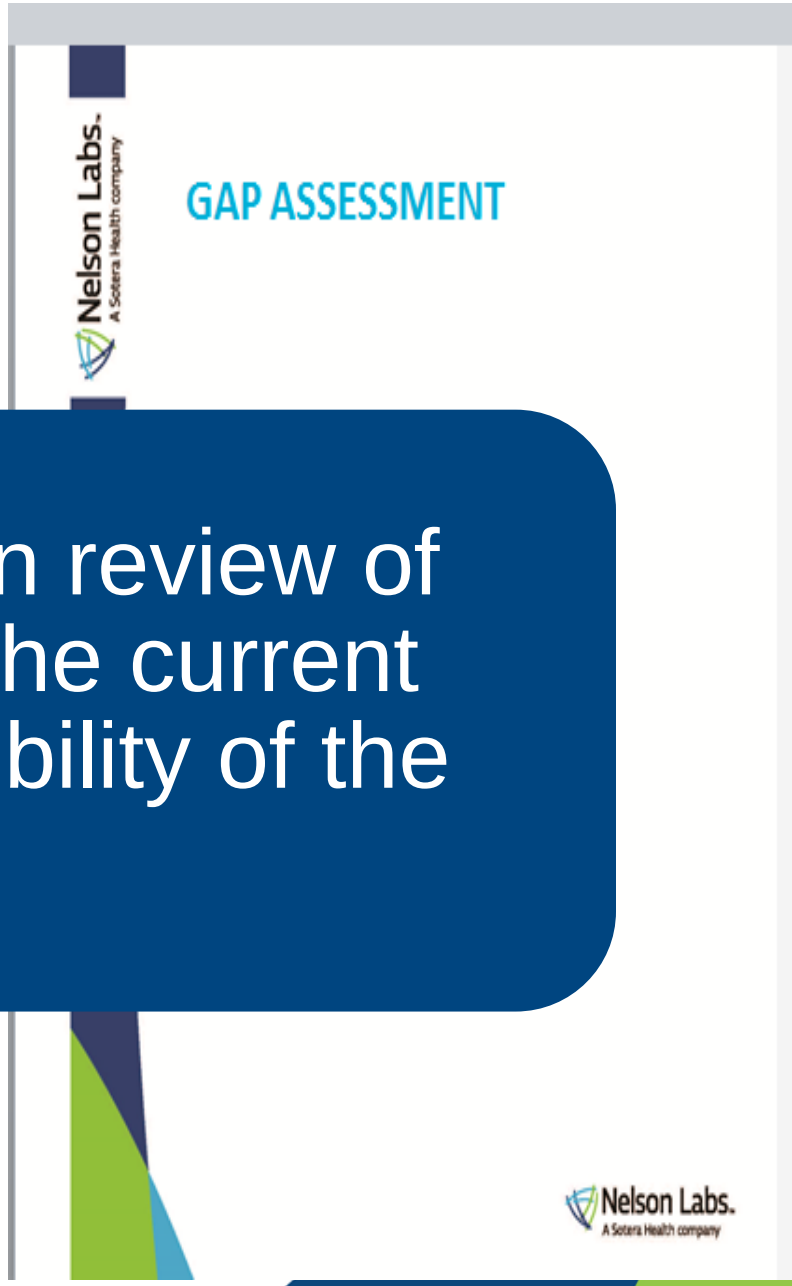
Offerings

- Gap Analysis
- **Purpose**
  - The purpose of this report is to perform a



CONCLUSION: Based on review of the tests performed and the current standards the biocompatibility of the device is well supported.

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More Information

Irritation and sensitization *in vitro* developments	• Sensitization working on bringing laboratories together to collaborate on a procedure.
"How Chemical Characterization Can Supplement & Support Biocompatibility Testing"	• Authors - Sarah Campbell, Thor Rollins, Audrey Turley http://directory.qmed.com/download-this-whitepaper-to-examine-the-various-file060395.html
FDA Guidance Document on ISO 10993-1	• http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf • Effective September 14, 2016

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THANK YOU!

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