Developing Biocompatibility for Medical Devices

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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.
MDR	Regulation (EU) 2017/45 of the European Parliament and of the Council of 5 April 2017 on Medical Devices

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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; Subacute or Subchronic Toxicity; Genotoxicity; Implantation; Hemocompatibility
Surface devices	Skin	A	
		B	
		C	
	Mucosal membrane	A	O
		B	X X O
		C	
	Breached or compromised surface	A	O
		B	X X O
		C	
External communicating devices	Blood (indirect)	A	O
		B	X X O X
		C	
	Tissue/bone/dentin communicating	A	O X X
		B	X X O O X X
		C	X X O O X X
	Circulating blood	A	X X X X O O
		B	X X X X O O O X
		C	X X X X X X O X
Implant devices	Tissue/bone	A	X X X O
		B	X X O O O X X
		C	X X O O O X X
	Blood	A	X X X X
		B	X X X X O X X X
		C	X X X X X X X

Past Approach

- Didn't understand
  - Materials
  - Testing

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

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		B	
		C	
	Mucosal membrane	A	O
		B	X X O
		C	
	Breached or compromised surface	A	O O
		B	X X O
		C	
External communicating devices	Blood (indirect)	A	
		B	O
		C	X X O X
	Tissue/bone/dentin communicating*	A	
		B	X X O O O X X
		C	X X O O O X X
	Circulating blood	A	X X X X O O
		B	X X X X O O O X
		C	X X X X X X O X
Implant devices	Tissue/bone	A	X X X O
		B	X X O O O X X
		C	X X O O O X X
	Blood	A	X X X X
		B	X X X X O X X X
		C	X X X X X X X X

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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."**

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Incorporating Risk

What is **Risk**?

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

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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
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														
Nature of body contact		Contact duration															
		A – limited (≤24 h)	Physical		ation	Irrita tion or	Ma- terial	Acute	Sub	Sub	Chr	Impla nta	Hem	Gen	Car	Repro duc-	

X means prerequisite information needed for a risk assessment.

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 not toxicological 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.

(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.

Table A.1: Biocompatibility Evaluation Endpoints

Medical device categorization by			Biological effect												
Nature of Body Contact		Contact Duration													
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity#	Degradation@
Surface device	Intact skin	A	X	X	X										
		B	X	X	X										
		C	X	X	X										
	Mucosal membrane	A	X	X	X										
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O			
	Breached or compromised surface	A	X	X	X	O	O								
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O	O		
External communicating device	Blood path, indirect	A	X	X	X	X	O				X				
		B	X	X	X	X	O	O			X				
		C	X	X	O	X	O	X	X	O	X	O	O		

Material Evaluation

[63] Device categorization information can be obtained informally via email, or as a part of ODE's Pre-Submission process. Refer to FDA's guidance document "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff - Guidance for Industry and FDA Staff" (February 18, 2014).

Nature of Body Contact		Contact Duration	Cytotoxicity	Sensitization	ion or Intracutaneous Reactivity	Acute Systemic Toxicity	terial-Mediated Pyrogenicity	bacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	uctive/Developmental Toxicity#	Degradation@
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent													
Implant device	Blood	A	X	X	X	X	O		O	X	X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		

X = ISO 10993-1: 2009 recommended endpoints for consideration

O = Additional FDA recommended endpoints for consideration

X = ISO 10993-1:2009 recommended endpoints for consideration*

O = Additional FDA recommended endpoints for consideration*

Note * All X's and O's should be addressed in the biological safety evaluation, either through the use of existing data, additional endpoint-specific testing, or a rationale for why the endpoint does not require additional assessment.

Note ~ Tissue includes tissue fluids and subcutaneous spaces

Note ^ For all devices used in extracorporeal circuits

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

Note @ Degradation information should be provided for any devices, device components, or materials remaining in contact with tissue that are intended to degrade.

Biological Safety Evaluation

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Device Description and Categorization

What is the device?

Picture

How does it contact the body?

- Be exact
- Is the contact incidental?

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Body Contact

Indirect contact

- medical device or component through which a fluid or gas passes, prior to the fluid or gas coming into physical contact with body tissue (in this case the medical device or medical device component itself does not physically contact body tissue)

Transitory contact

- *medical device* or medical device component that has a very brief duration of contact with body tissue

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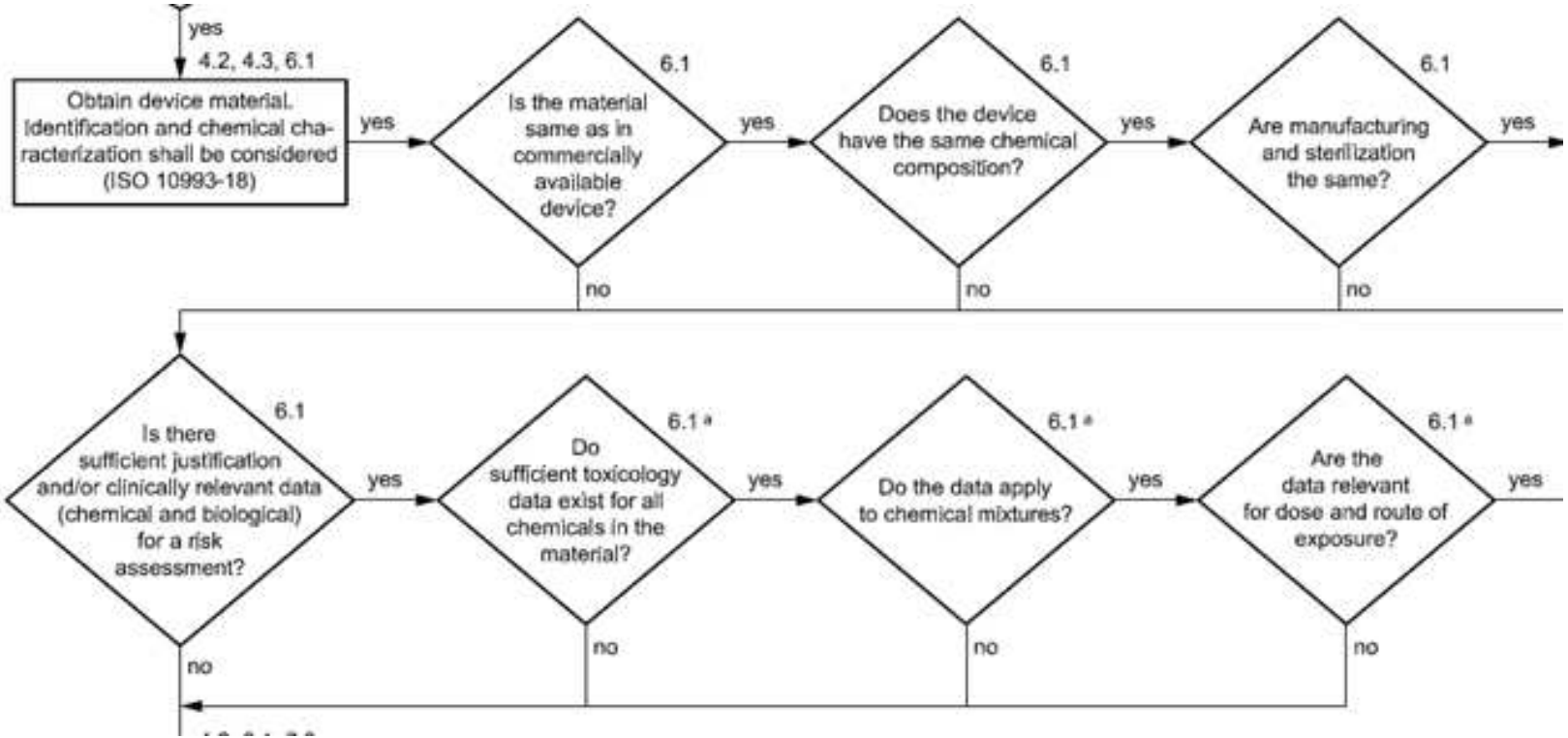
Biological Evaluation Plan (BEP)

Identify Risks by identifying what we already know



Material Characterization

Supplier information

ISO 10993 compliance		USP Class VI		
What tests?	Applicable?	Irritation	Acute Systemic Tox	Implant (7 day)

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Material Characterization

"The extent of chemical characterization required should reflect the **nature** and **duration** of the clinical exposure…"

ISO 10993-18

Limited contact: identify materials and processing; use biocompatibility testing to support safety.

Prolonged contact: Use biocompatibility testing to support safety. Maybe chemical characterization if materials are new.

Permanent contact : Perform chemical characterization testing with a toxicological risk assessment.

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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															
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	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		
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		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		

Chemical Characterization

ISO 10993-18: Chemical characterization of materials

- Gathering of data through testing for VOCs, SVOCs, NVOCs, and metals

ISO 10993-17: Toxicological Risk Assessment of E&L data

- Assessment of chemistry results, correlating them to a patient dose per device
- Calculation of **Tolerable Intake**, **Tolerable Exposure** and **Margins of Safety**

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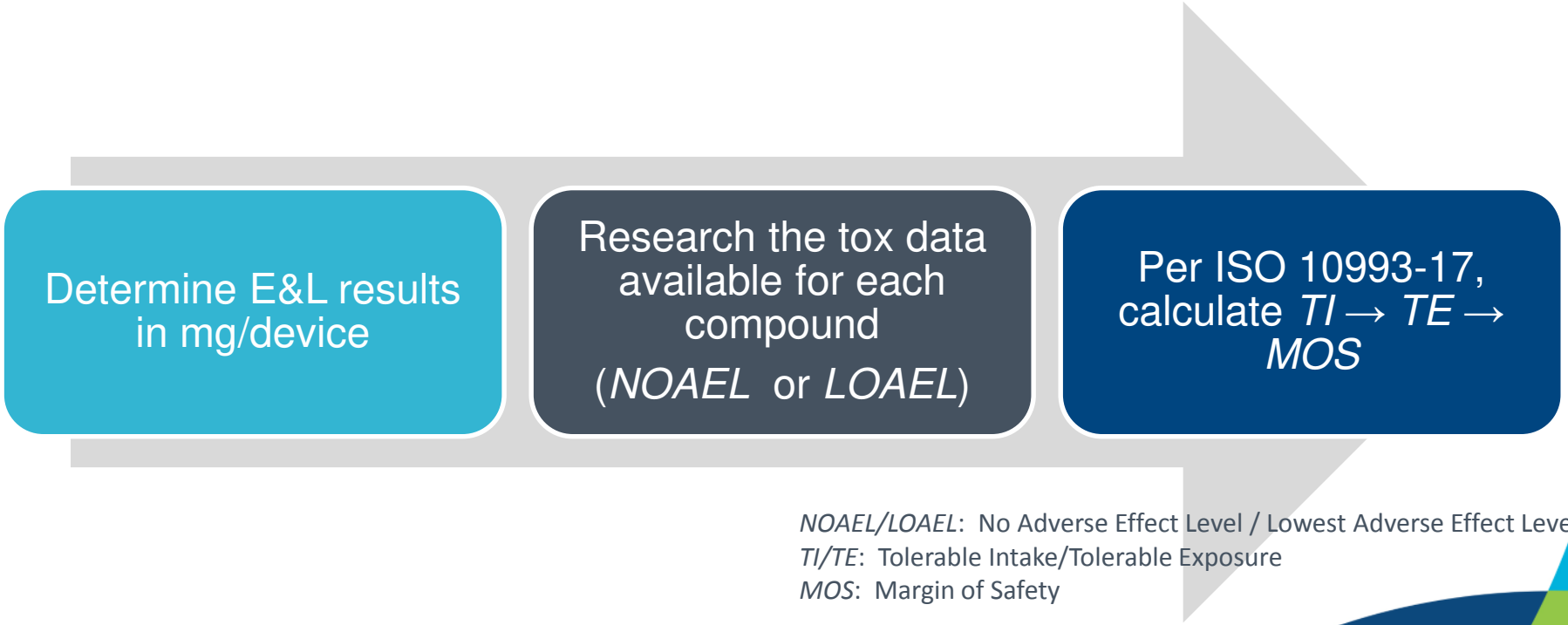
Toxicological Risk Assessment



NOAEL/LOAEL: No Adverse Effect Level / Lowest Adverse Effect Level
TI/TE: Tolerable Intake/Tolerable Exposure
MOS: Margin of Safety

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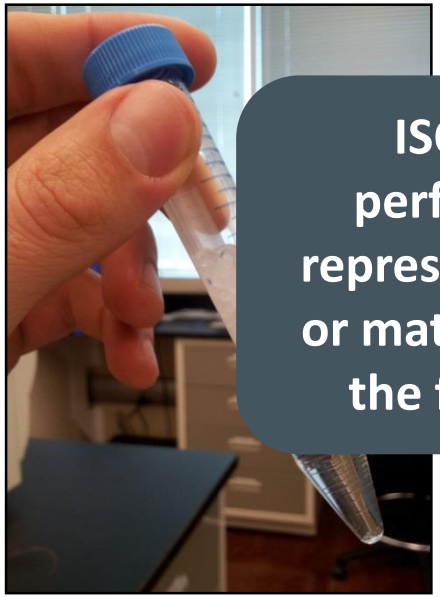
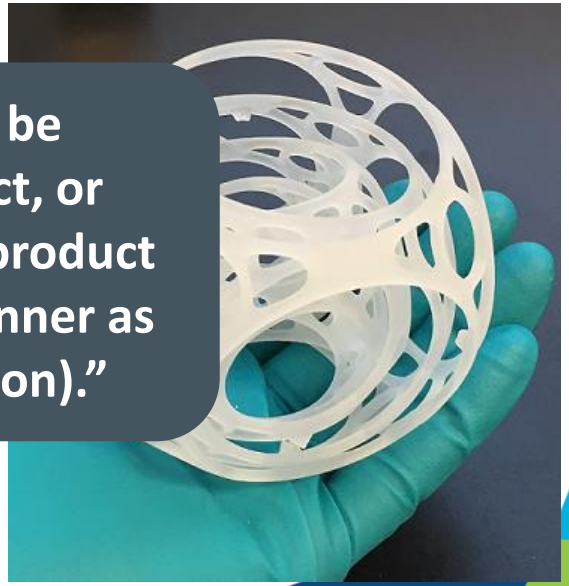
Biological Evaluation Plan (BEP)

Test Sample Selection



Raw Material

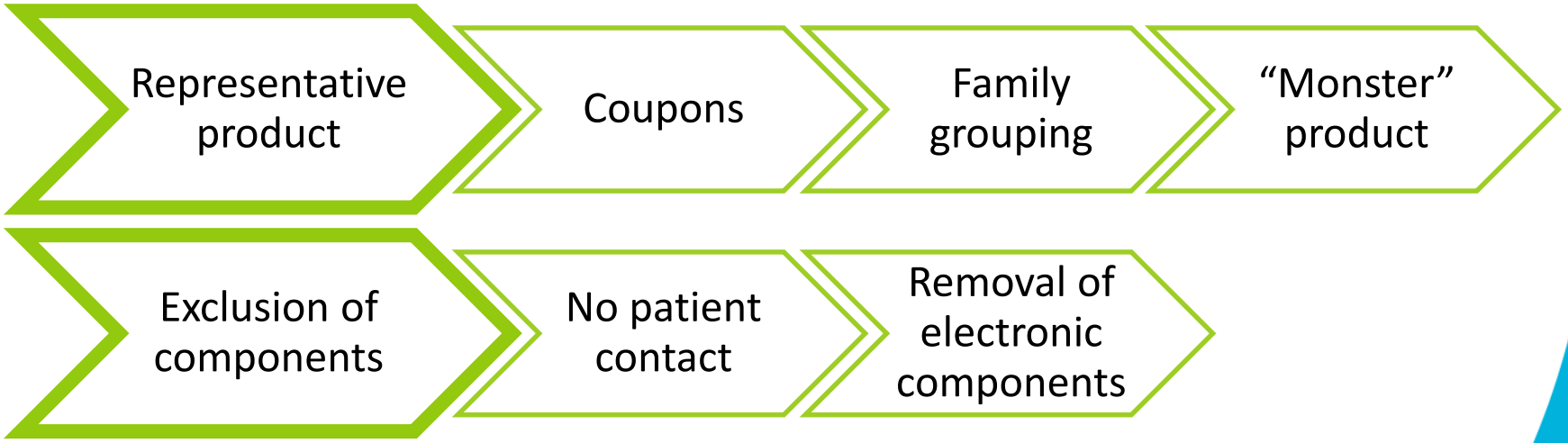
ISO 10993-1, 6.3.1 a) "Testing shall be performed on the sterile final product, or representative samples from the final product or materials processed in the same manner as the final product (including sterilization)."



Finished Device

Biological Evaluation Plan (BEP)

Test Sample Selection



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Biological Evaluation Plan (BEP)

Test Sample Preparation

Extraction Time and Temperature
per ISO 10993-12

- 37°C for 24 hours
- 37°C for 72 hours
- 50°C for 72 hours
- 70°C for 24 hours
- 121°C for 1 hours

Cytotoxicity (72 hrs for implants)

All other biocompatibility testing

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Biological Evaluation Plan (BEP)

Test Selection

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	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		

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Table A.1 *(continued)*

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

Biological Evaluation Plan

Carcinogens, Mutagens and Reproductive Toxic Substances (CMR)

Per Section 10.4.2 of the MDR states “Justification regarding the presence of CMR and/or endocrine-disrupting substances in a concentration above 0.1 % weight by weight (w/w)” in the device is required. Per the MDR, the justification should be based on:

- analysis and estimation of potential,
- analysis of possible alternatives, or
- argument for current design

Biological Evaluation Report

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Biological Evaluation Report

Review materials of final finished device	• Address material/processing changes
Review Tests performed – highlighting test set up and conclusion	• Temperature and time of extraction • Solvents used • Results
Address any failures	• Perform risk assessment

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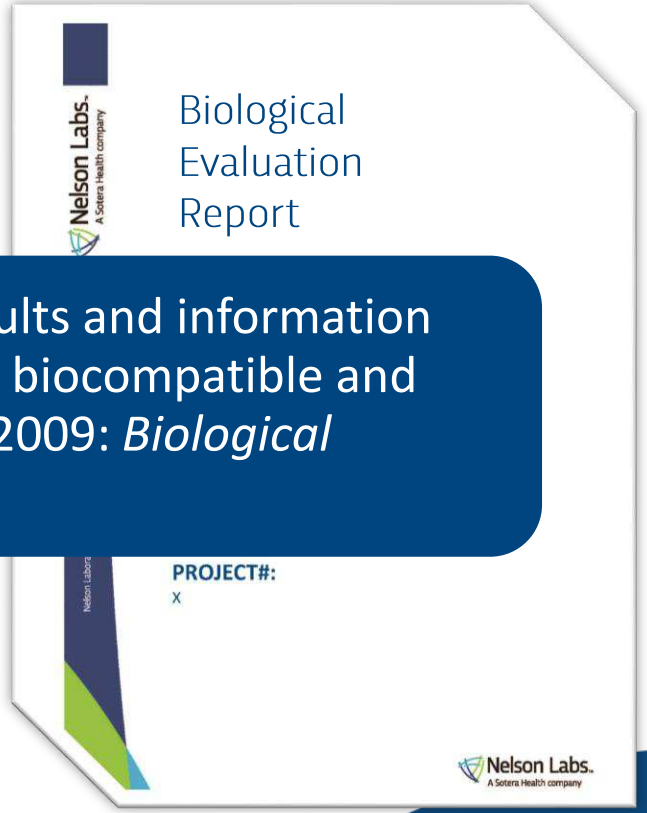
Biological Evaluation Report

TABLE OF CONTENTS

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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Highlights

- Perform an initial risk assessment (BEP)
- Clarify approach to Material Characterization
- Summary Report (BER) with conclusion regarding biocompatibility

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