Applying the New ISO 10993

(Risk-based Approach to Biocompatibility)

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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.

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CHANGE

The Years of Change in Biocompatibility

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

International Organization for Standardization

Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process

EU Medical Device Regulation

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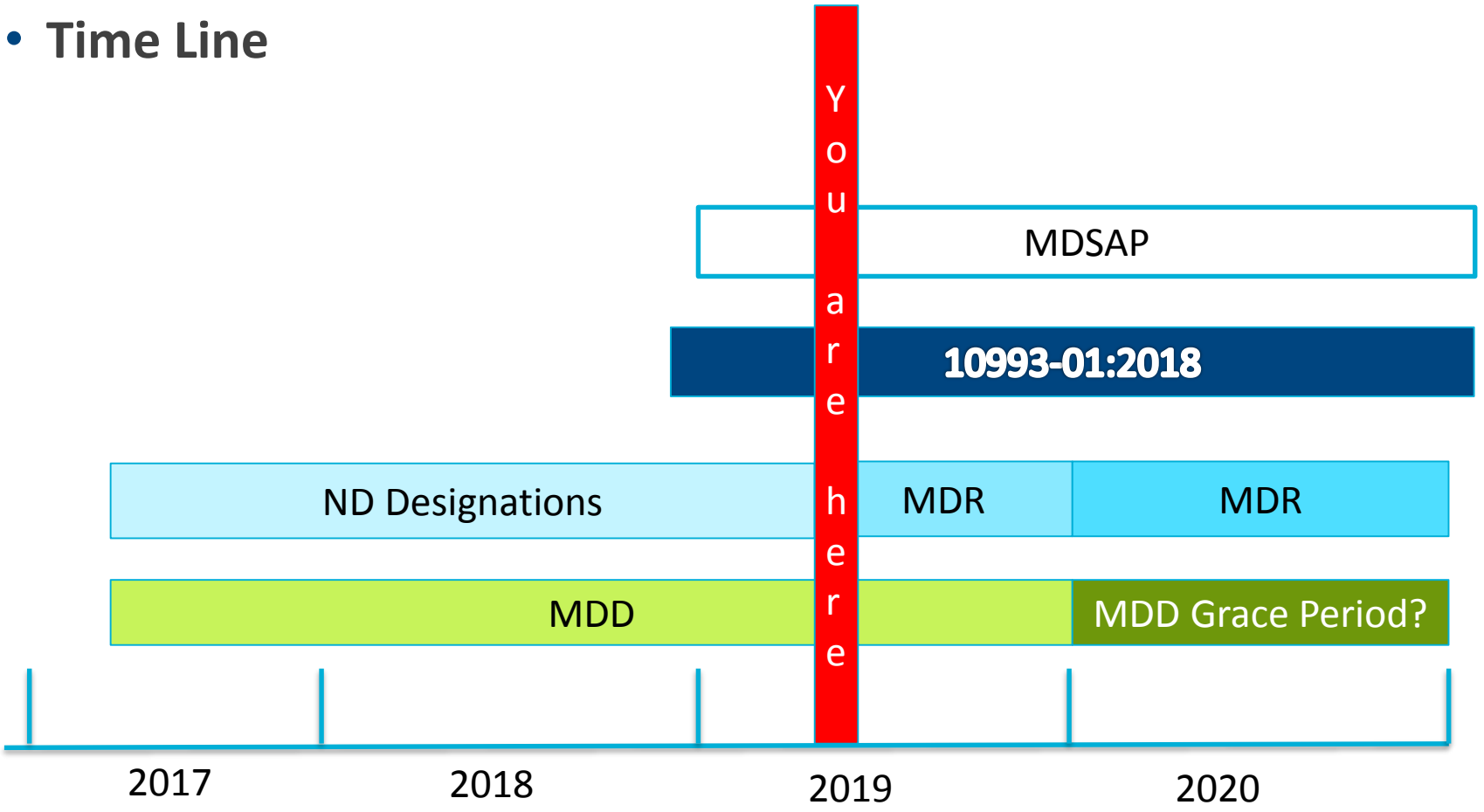
The MDR Countdown!

- **Time Line**



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Then Everything Changed….

More Governance

More Clinical Data

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Now the Clock is Ticking

- Are we going to be ready?

MedTech Europe

Our industry is prepared to submit product files to comply with the new Medical Device Regulation (MDR). However, we cannot do so. The new regulatory system is not ready to function. The deadline for the system to be fully operational is not 26 May 2020, the date of MDR application as the Commission continues to suggest. The deadline for the system to be ready for our industry to comply is now.

Re: Open letter on the implementation and readiness status of the new Medical Device Regulation 745/2017 (MDR)

Dear Vice-President Katainen,

I am writing to you regarding an issue of absolute urgency for patient care across Europe and for the internal market at large. The medical device industry in Europe confirms that without immediate action by the European Commission, the new regulatory system will not be ready on time to ensure continued access of patients and healthcare systems to life-saving and life-transforming devices.

Our industry is prepared to submit product files to comply with the new Medical Device Regulation (MDR). However, we cannot do so. The new regulatory system is not ready to function. The deadline for the system to be fully operational is not 26 May 2020, the date of MDR application as the Commission continues to suggest. The deadline for the system to be ready for our industry to comply is now.

One of the critical concerns is the designation and capacity of Notified Bodies, which the European Commission and Member States are still assessing to the new rules. It is only after being designated that

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The Links

http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf

http://data.consilium.europa.eu/doc/document/ST-10728-2016-INIT/en/pdf

https://standards.aami.org/higherlogic/ws/public/download/11414/Public%20Review%20Draft%20CDV_2%2010993_1.pdf

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Is Your Backpack Too Full?

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Is biocompatibility really necessary?

"My device has been on the market for years…"

"We only use biocompatible materials…"

"Our materials are made according to ASTM standards…"

"We did some testing during the device R&D…"

"Our device is only used for 5 minutes…"

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Past Approach

"I don't have to understand the material's impact on the body."

"I don't have to understand the testing" (black box approach)

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Past Approach

Vs.

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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	X X X . . . . .
		B	X X X . . . . .
	Mucosal membrane		
	Breached or compromised surfaces		
External communicating devices	Blood path, indirect		 X
	Tissue/bone dentin communica		 X
	Circulating blood		 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 . . X X
		B	X X X X O X X X
		C	X X X X X X X X

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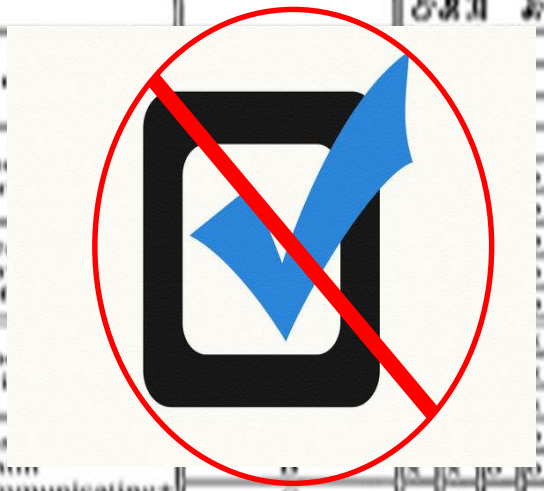
Past Approach

- Didn't understand
  - Materials
  - Testing

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	
		B	x x o o o x x o
		C	x x x x x x x o
	Breached or compromised surface	A	
		B	x x o o o x x o
		C	x x x x x x x o
External communicating devices	Blood path, indirect	A	
		B	x x o o o x x o
		C	x x x x x x x o
	Tissue/bone/dentin communicating*	A	
		B	x x o o o x x o
		C	x x o o o x x o
	Circulating blood	A	x x x x o[A] o[A] o[A] x
		B	x x x x o x o x
		C	x x x x x x o x
Implant devices	Tissue/bone	A	x x x o o o o o
		B	x x o o o x x o
		C	x x o o o x x o
	Blood	A	x x x x o o o 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 is all about 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

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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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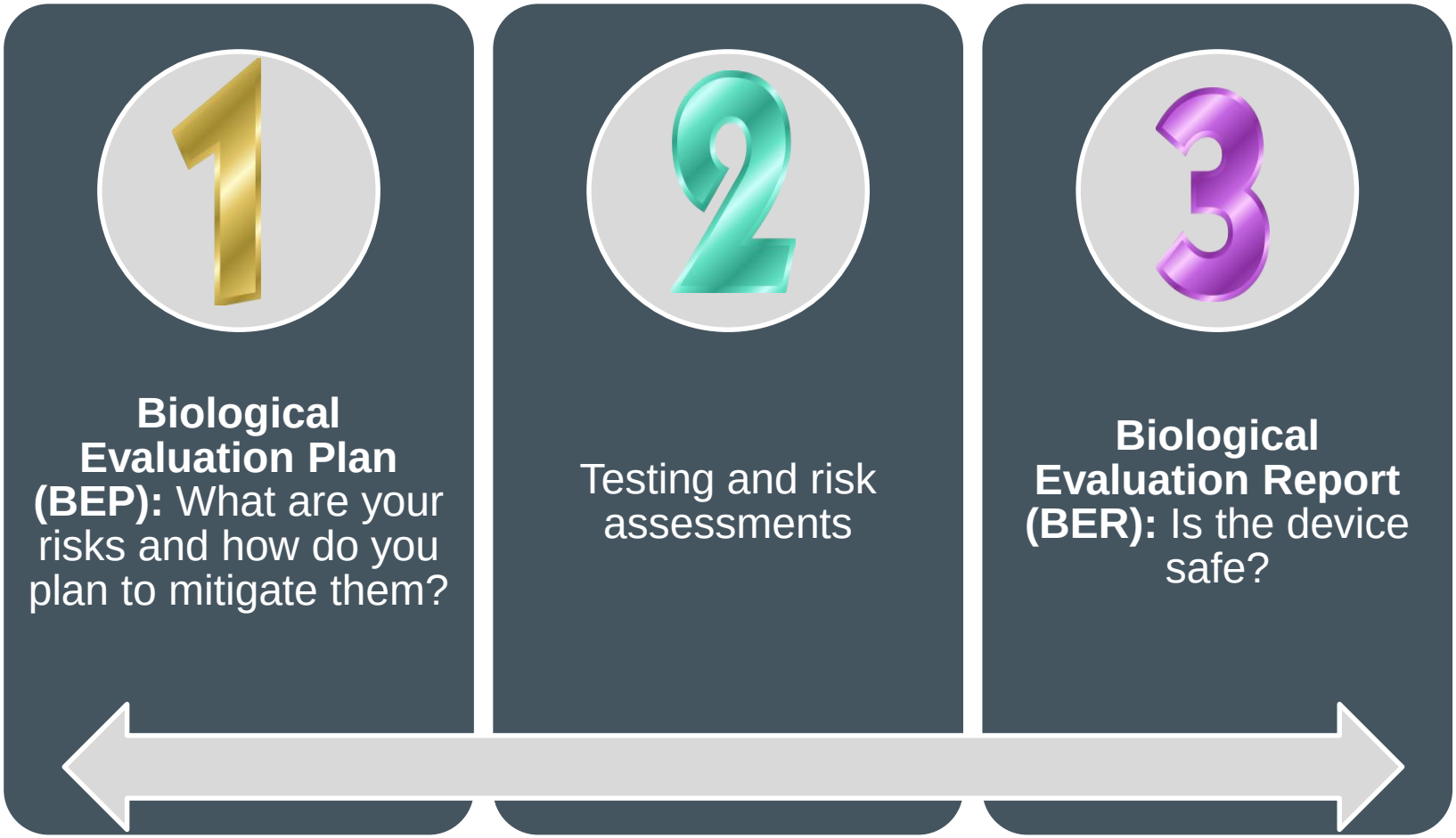
Biological Safety Evaluation



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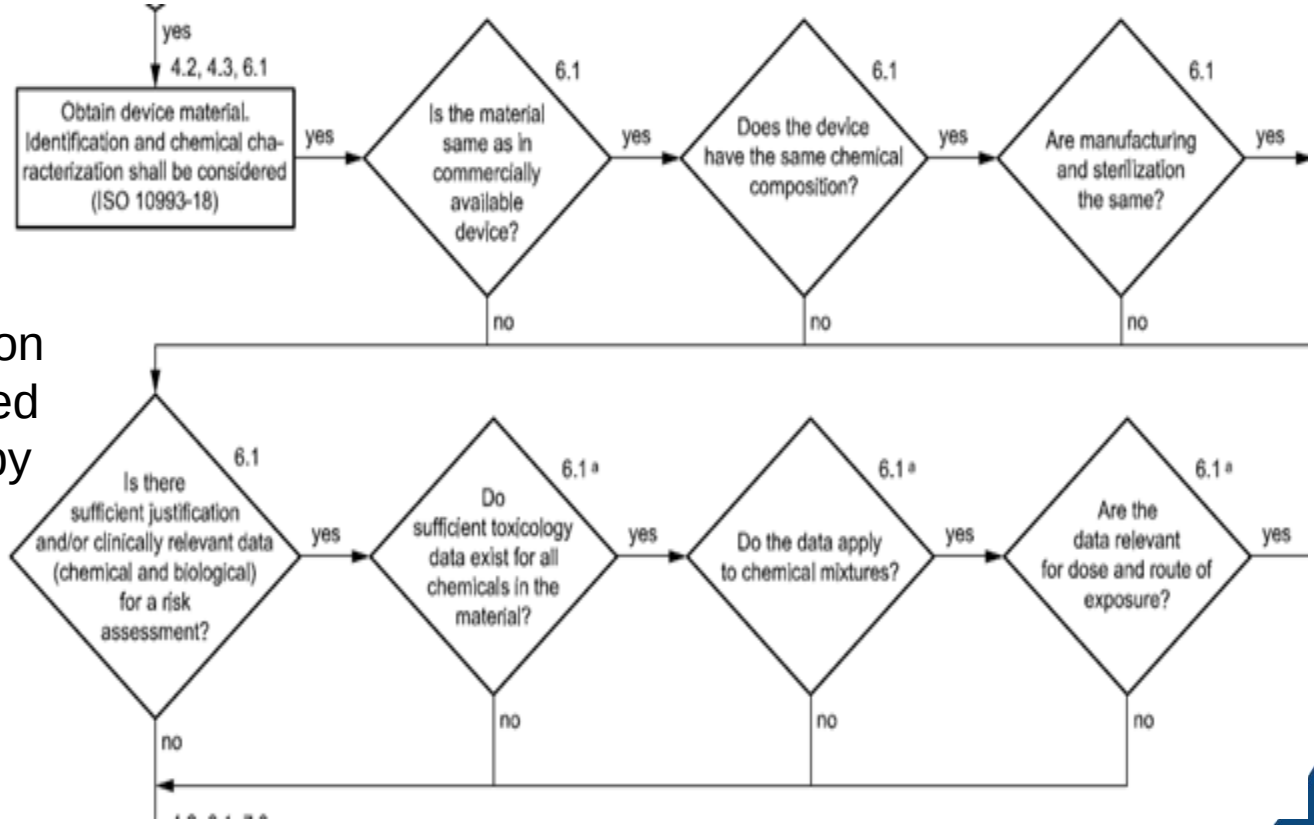
Biological Evaluation Plan (BEP)

- Identify Risks
  - Use Figure 1 in ISO 10993-1



The biological evaluation shall be planned, carried out, and documented by knowledgeable and experienced professionals.

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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		

[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 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@
Category	Contact														
	Tissue+/bone/ dentin	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Circulating blood	A	X	X	X	X	O		O^		X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		
Implant device	Tissue+/bone	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	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*

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

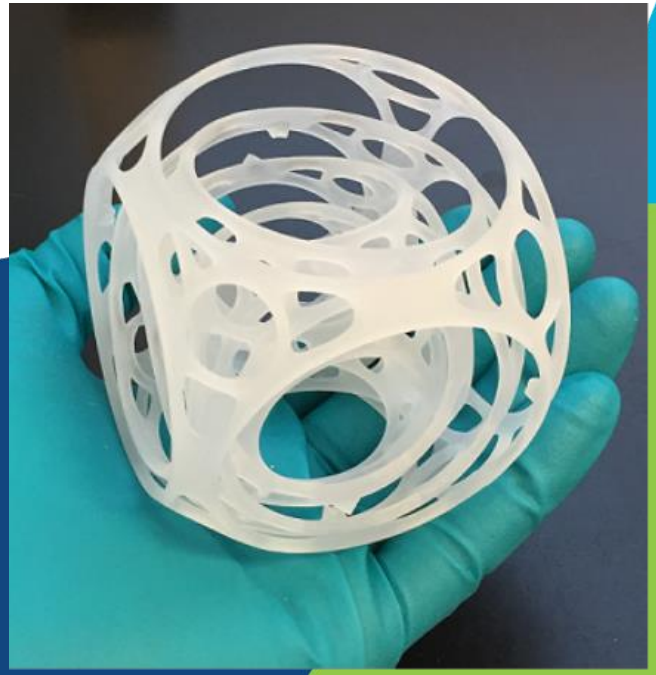
Note # Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, devices with relevant target populations (e.g., pregnant women), and/or devices where there is the probability for local presence of device materials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

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

Medical device categorization by			Endpoints of biological e							
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]
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	
		C	X	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	
		C	X	E	E	E	E	E	E	E
Externally communicating medical device	Blood path, indirect	A	X	E	E	E	E	E		
		B	X	E	E	E	E	E	E	
		C	X	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	
		C	X	E	E	E	E	E	E	E
	Circulating blood	A	X	E	E	E	E	E		
		B	X	E	E	E	E	E	E	
		C	X	E	E	E	E	E	E	E

Material Evaluation



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What Are The Challenges?

Understand your product

Understand changes to your product through its lifecycle

Understand the impact of leachables substances within your product

Can you predict clinical safety from only a few tests conducted on the product

Remember: risks may change over the life of the product

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Understand the Product

Materials

- New materials
- Leveraged materials
- Material interactions?
- Combination products

Geometry

Patient Contact

Failure Modes

(additional exposure?)

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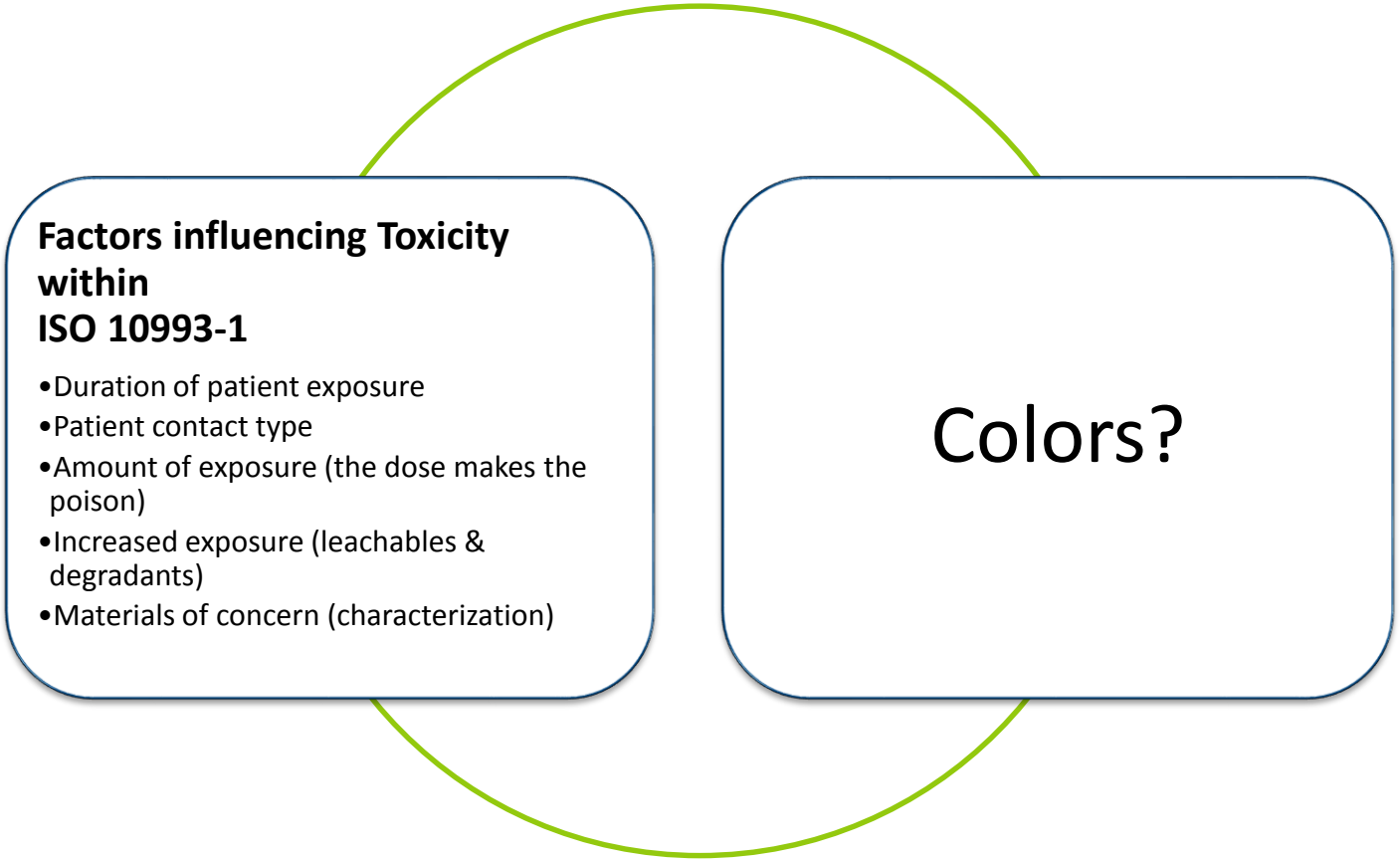
Toxicological Safety Assessment



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Material or Chemical Characterization?

This is the first step of the ISO 10993 Biocompatibility process.

"In the selection of materials to be used in device manufacture, the first consideration shall be fitness for purpose with regard to characteristics and properties of the material, which include chemical, toxicological, physical, electrical, morphological and mechanical properties." ISO 10993-1

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Material Characterization

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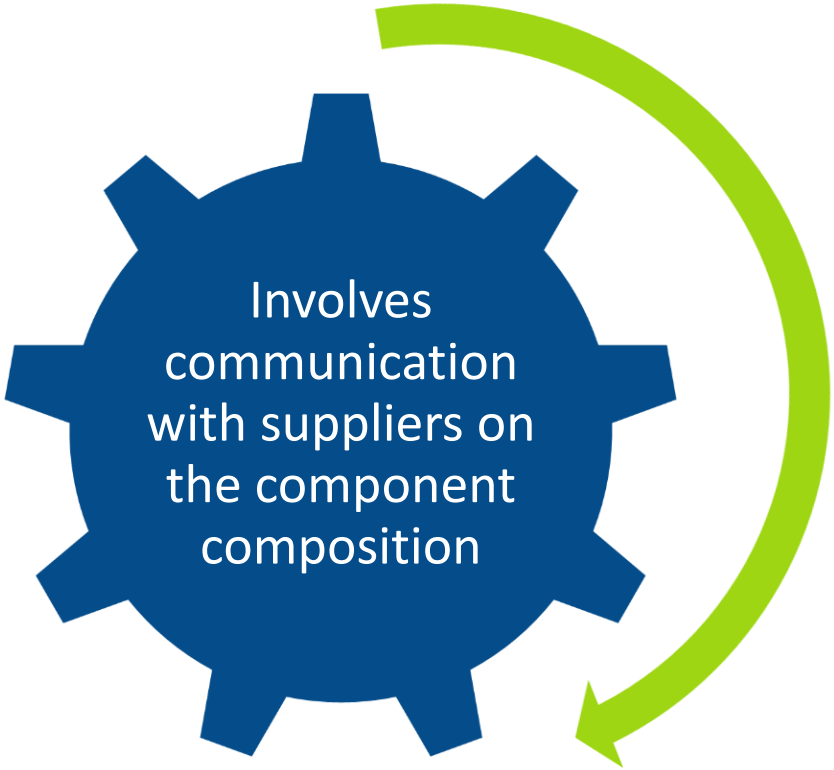
Material Characterization



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Material Characterization

Medical Device Manufacturers need to have **solid relationships with suppliers** and ensure full disclosure of materials through:

Manufacturing agreements	Composition disclosures	Processing aide and residual chemical disclosure	Material Safety Data Sheets (MSDS)	Device Master File Information availability to the regulatory authorities

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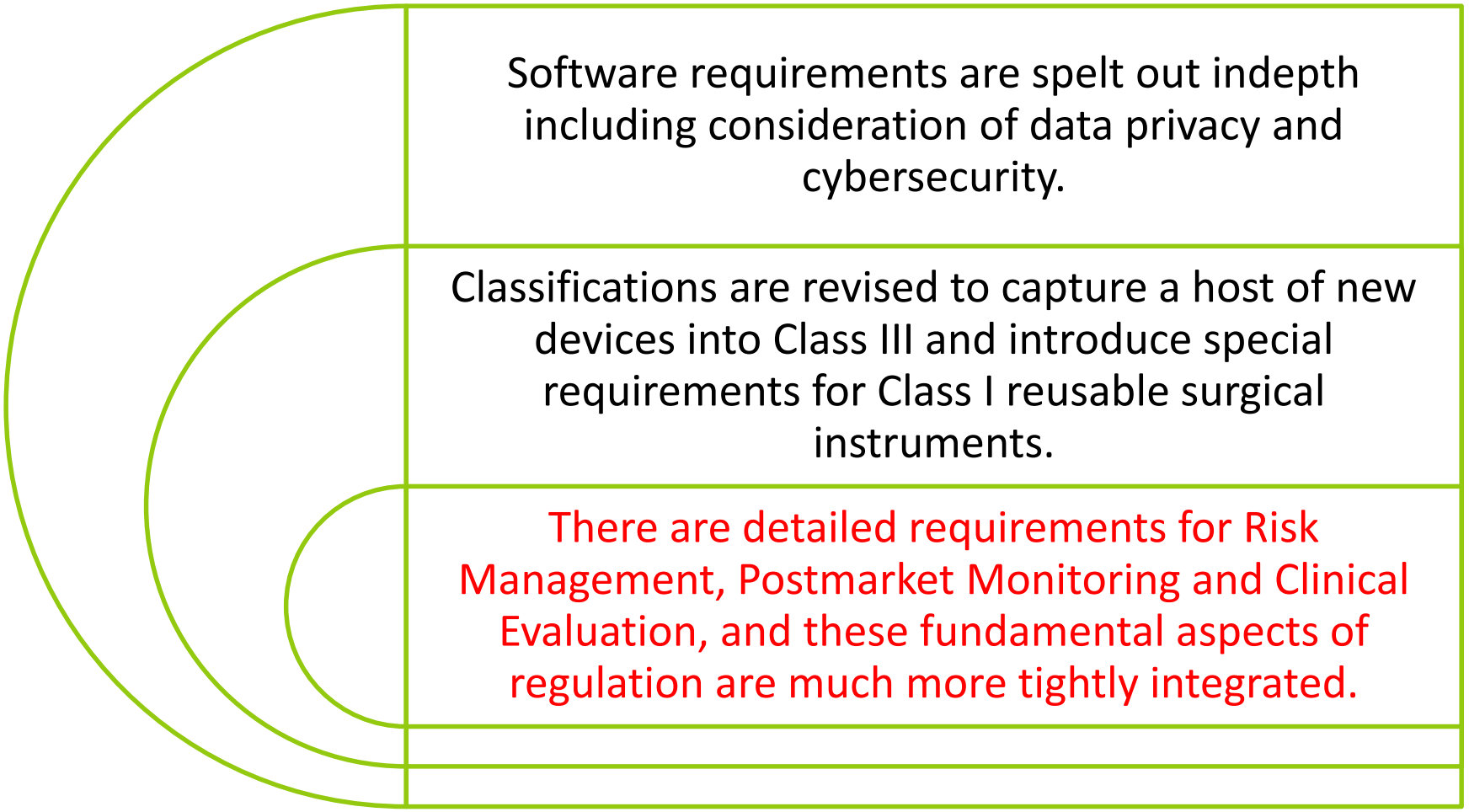
New Directives

What's New?

- Framework is the same….but the new regulations introduce a considerably more prescriptive requirements in almost every area.
- The 14 Essential Requirements are replaced with 23 General Safety and Performance Requirements with much more detail.



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There are new requirements around single use devices and their reprocessing.

Custom devices which are mass produced will no longer be exempted from conformity assessment.

Notified Bodies are no longer contracting partners that allow for collaboration with the medical device industry, including enforcement tasks and extended authorities (e.g. unannounced inspections).

Phase 3: Biological Evaluation Report

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Biological Evaluation Report

Attachment C: Summary Biocompatibility Documentation

The example table (Table C.1) is provided to illustrate one possible approach to documentation of the biocompatibility information included or referenced in a submission; other approaches are acceptable. Manufacturers are encouraged to use an approach that works for their specific purposes, taking into account the considerations discussed in this guidance document. Note that these are generalized examples to demonstrate documentation and do not necessarily account for every possible consideration.

Table C.1 - Example Table of Summary Biocompatibility Evaluation Information for a Device Submission

Biological endpoint	Location of new test reports provided in submission	Location of test reports leveraged from previous submission	Supporting data from literature	Citation	Test article	Rationale for why additional information isn't needed
Cytotoxicity	Implant: L929 testing (V2, App A-1, pdf p.x/200) Implantation accessory: L929 testing (V3, App B-1, pdf p. x/300)	Implant: [DEVICE NAME] (K# V2, App X-1, pdf p.x/200) Implantation accessory: [DEVICE NAME] (K# V3, App X-1, pdf p.x/300)	n/a	n/a	Identical - see documentation (per Attachment F) V1, pdf p.x/100	Testing conducted on final, sterilized device (implant tested separately from implantation accessory)
Genotoxicity	Implant: chemical characterization (V2, App A-2, pdf p. x/200)	n/a	Test name (e.g., chromosomal aberration): doses with effects and/or doses without effects	Author, Title, Journal, date, volume, and pages	Slight differences between test article and final, sterilized device – see comparison information: V1, pdf p.x/100	Genotoxicity tests are hazard identification tests. Chemical characterization data can be used to confirm that chemicals which elute from the device are not genotoxic per literature.

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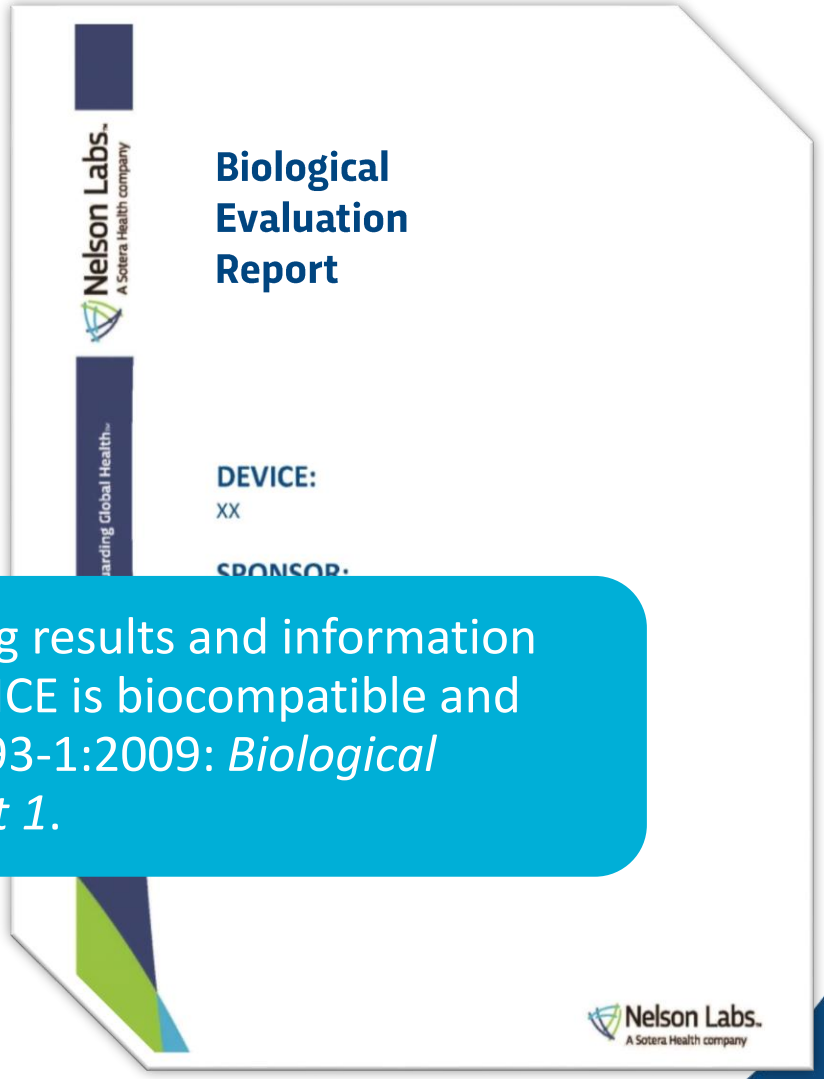
Biological Evaluation Report

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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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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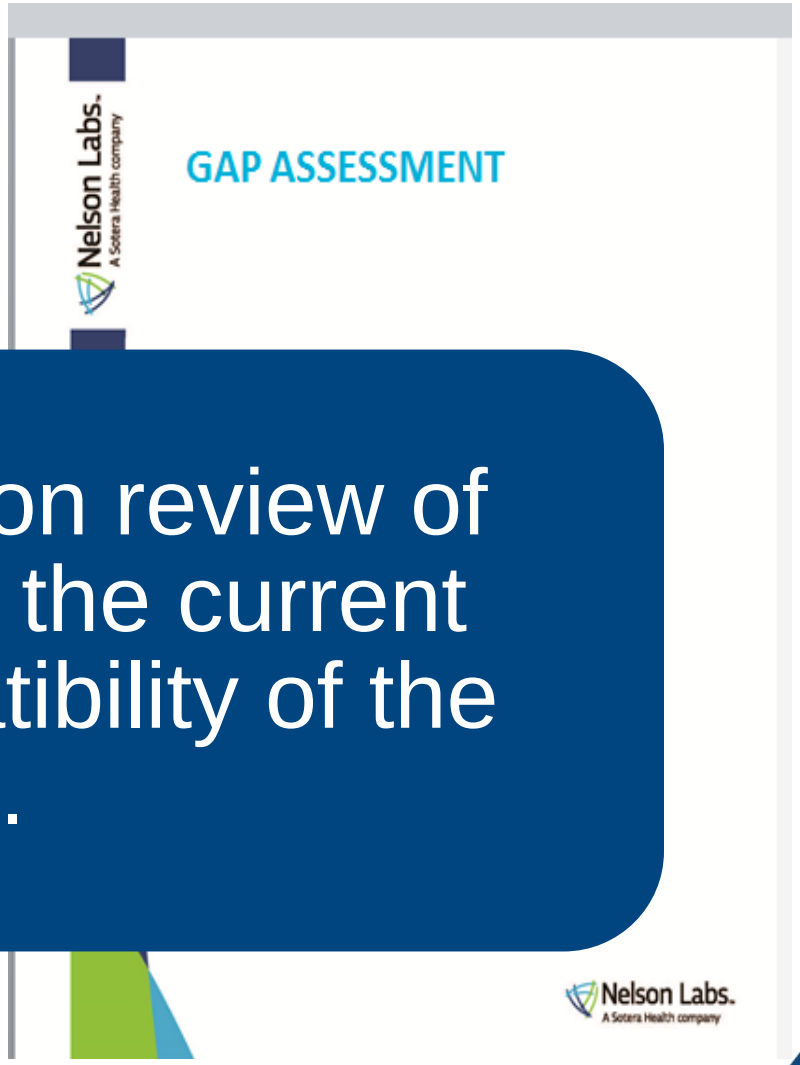
Offerings

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



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

Case Study: A Family of Orthopedic Devices

Set of Devices:

- 4 different plate sizes
- 5 different screw sizes
- Each screw comes in two colors
- Each plate available in cpTi or 316SS
- Each plate and screw equivalently available from 2 suppliers

- 36 line items to be considered
- 80 different possible patient contacting configurations

Step 1: Understand Endpoints Required for Evaluation

Table A.1 *(continued)*

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]
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		

Step 2: Look at Options for Evaluations

Device with Permanent Contact
Tissue/bone

Required Endpoint for Evaluation:

- Cytotoxicity
- Sensitization
- Irritation
- Material Mediated Pyrogenicity
- Acute Systemic Tox
- Subacute/Subchronic Tox
- Chronic Tox
- Genotox
- Carcinogenicity
- Implantation

General Options to Address Risks:

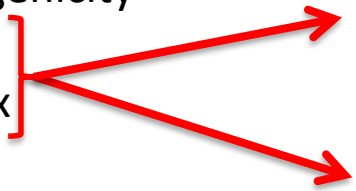
- Written evaluation addressing risk without testing
- Traditional biological tests
- Chemistry testing followed by written evaluation

Step 2: Look at Options for Evaluations

Device with Permanent Contact
Tissue/bone

Required Endpoint for Evaluation:

- Cytotoxicity
- Sensitization
- Irritation
- Material Mediated Pyrogenicity
- Acute Systemic Tox
- Subacute/Subchronic Tox
- Chronic Tox
- Genotox
- Carcinogenicity
- Implantation



General Options to Address Risks:

- Written evaluation addressing risk without testing
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Step 2: Look at Options for Evaluations

Device with Permanent Contact
Tissue/bone

Required Endpoint for Evaluation:

- Cytotoxicity
- Sensitization
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- Material Mediated Pyrogenicity
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Step 2: Look at Options for Evaluations

Device with Permanent Contact
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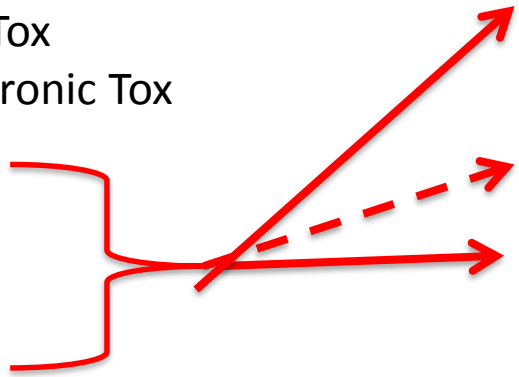

General Options to Address Risks:

- Written evaluation addressing risk without testing
- Traditional biological tests
- Chemistry testing followed by written evaluation

Step 2: Look at Options for Evaluations

Device with Permanent Contact
Tissue/bone

Required Endpoint for Evaluation:

- Cytotoxicity
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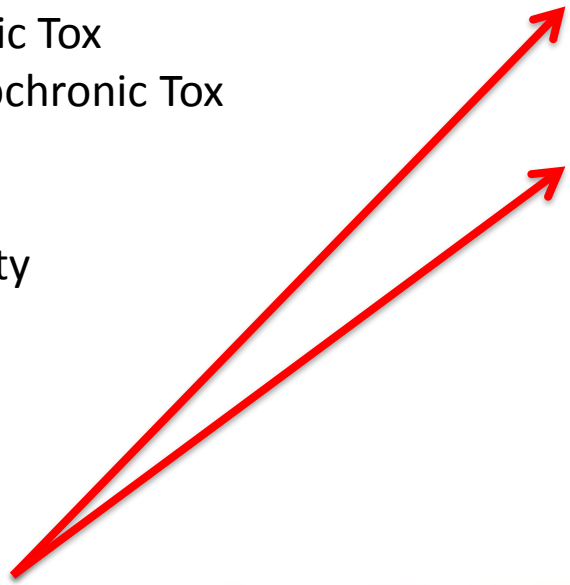

General Options to Address Risks:

- Written evaluation addressing risk without testing
- Traditional biological tests
- Chemistry testing followed by written evaluation

Step 2: Look at Options for Evaluations (no usable existing data)

Biological Endpoint to be Addressed	Course of Action	Reason
Cytoxocity	Biological Testing	Even though materials are common, residuals from manufacturing are unknown and could be concerning, no existing data to support endpoints
Sensitization		
Irritation		
Material Mediated Pyrogenicity		
Acute Systemic Toxicity	Chemistry Testing and Assessment	
Subacute/Subchronic Toxicity		
Genotox		
Chronic Toxicity		
Carcinogenicity		
Implantation	Biological Testing	

Step 2: Look at Options for Evaluations (lots of usable data)

Biological Endpoint to be Addressed	Course of Action	Reason
Cytoxocity	Biological Testing	Useful to screen for the unexpected
Sensitization	Written Assessment	Cleaning validation proves there are no residuals, material is well proven
Irritation		
Material Mediated Pyrogenicity	Biological Testing	Useful to screen for the unexpected
Acute Systemic Toxicity	Written Assessment	Cleaning validation proves there are no residuals at concentrations above a TTC
Subacute/Subchronic Toxicity		
Genotox		
Chronic Toxicity		
Carcinogenicity		

Step 3: Family Groupings

Set of Devices:

- 4 different plate sizes
- 5 different screw sizes
- Each screw comes in two colors
- Each plate available in cpTi or 316SS
- Each plate and screw equivalently available from 2 suppliers

- 36 line items to be considered
- 80 different possible patient contacting configurations

Family Groupings:

- Largest plate size
- Largest screw size*
- Test cpTi and 316SS separately
- Pool plates from different suppliers

- Colored screws can be considered equivalent if colored using anodization

- **One or two sets of parts can represent entire collection**

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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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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QUESTIONS?

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