U.S. FOOD & DRUG ADMINISTRATION

Biocompatibility Basics

FDA Small Business Regulatory Education for Industry (REdI) Annual Conference

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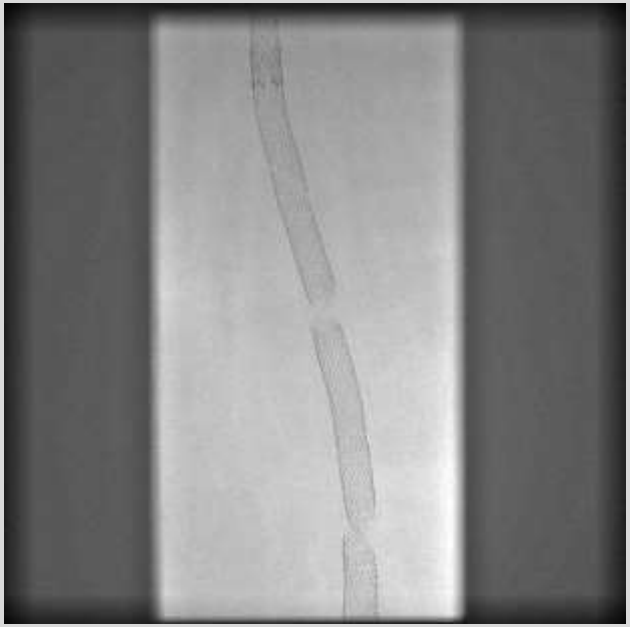
Why is Biocompatibility Important?



EXAMPLE: Nitinol stents

- Mechanical fragments – can result in downstream emboli
- Leaching chemicals – can result in other adverse biological events due to known chemical-specific toxicities

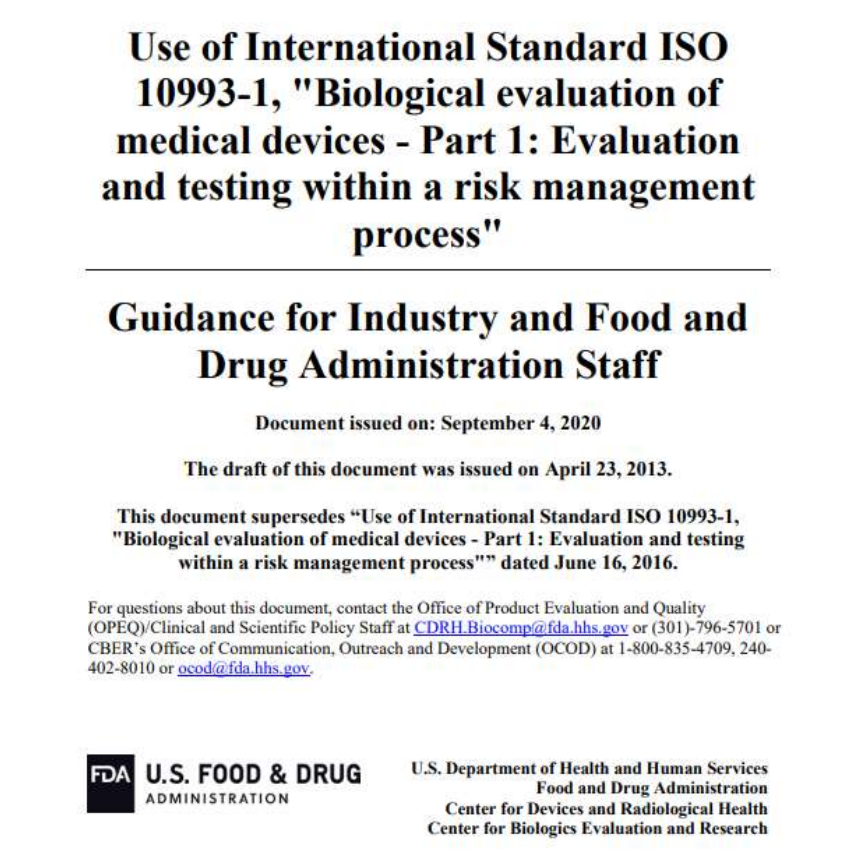
www.angiologist.com/vascular-intervention/stent-fracture-in-the-lower-extremities/

Learning Objectives

- Review FDA's Biocompatibility Guidance
- Define key terminology
- Explain when and how biocompatibility is considered
- Discuss risk-based approach
- Identify the difference between endpoint assessments and testing
- Review chemistry information

FDA'S BIOCOMPATIBILITY GUIDANCE

FDA's Biocompatibility Guidance



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

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 4, 2020

The draft of this document was issued on April 23, 2013.

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

For questions about this document, contact the Office of Product Evaluation and Quality (OPEQ)/Clinical and Scientific Policy Staff at CDRH.Biocomp@fda.hhs.gov or (301)-796-5701 or CBER's Office of Communication, Outreach and Development (OCOD) at 1-800-835-4709, 240-402-8010 or ocod@fda.hhs.gov.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Issued: 2016

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www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and

Biocompatibility Guidance (cont.)

1. How FDA uses ISO 10993-1 “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.”
2. Common biocompatibility testing issues in submissions to the US FDA.
3. Change in focus: 2009 and 2018 revisions of ISO 10993-1

How to use risk management to:

1) Address biocompatibility, and

2) Leverage existing testing, if possible

Instead of: What biocompatibility testing is needed?

Biocompatibility Guidance (cont.)

<u>Guidance Outline:</u>

I. Introduction

II. Scope

III. Risk Management for Biocompatibility Evaluations *

IV. ISO 10993 – Part 1 and the FDA Modified Matrix

V. General Biocompatibility Testing Considerations

VI. Test-Specific Considerations *

Biocompatibility Guidance (cont.)

<u>Guidance Outline (cont.):</u>

VII. Chemical Assessments *

VIII. Labeling Devices as “-Free” *

<u>Key Attachments</u>

Att A: Evaluation Endpoints for Consideration *

Att B: Device Master Files for Biocompatibility Evaluations

Biocompatibility Guidance (cont.)

Key Attachments (cont.):

Att C: Summary Biocompatibility Documentation

Att D: Biocompatibility Evaluation Flow Chart

Att E: Contents of a Test Report

Att F: Component and Device Documentation Examples *

Att G: Glossary *

BIOCOMPATIBILITY GUIDANCE: KEY TERMINOLOGY

Key Definitions

- **Biocompatibility:** ability of a device material to perform with an appropriate host response in a specific situation
- **Direct contact:** term used for a device or device component that comes into physical contact with body tissue
- **Indirect contact:** … device or device 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 device or device component itself does not physically contact body tissue)

Key Definitions (cont.)

- **Final finished form (FFF):** term used for a device or device component that includes all manufacturing processes for the “to be marketed” device including packaging and sterilization, if applicable
- **Novel material:** material that has not previously been used in any legally US-marketed medical device
- **Sponsor:** manufacturer, submitter or applicant

+ 15 more definitions

BIOCOMPATIBILITY GUIDANCE: CONSIDERATIONS

When Biocompatibility is Considered

- As a critical part of FDA's determination of safety and effectiveness for:
  - **New devices:** if medical device materials come into direct or indirect contact with the human body
  - **Modified devices:** if changes are to tissue contacting components (or could be)

When Biocompatibility is Considered

<u>EXAMPLE – Modified Device</u>:
New internal component added (no body contact).
Heat applied to join to another component w/ body contact.
Heat could change chemistry, so biocompatibility should be evaluated.

FDA Biocompatibility Guidance (Section I, page 5)

How Biocompatibility is Considered

- For all submission types: PMA, HDE, IDE, 510(k), and *de novo* requests
- To determine the potential for an unacceptable adverse biological response
- Biocompatibility standards can be used to facilitate information submission to FDA:
  - ISO 10993-1 and related 10993 series of standards
  - ASTM, ICH, OECD and USP biocompatibility standards

BIOCOMPATIBILITY GUIDANCE: RISK BASED APPROACH

Risk Based Approach

ISO 10993-1, includes consideration of:

- Device design, material components and manufacturing processes
- Clinical use of the device including the intended anatomical location
- Frequency and duration of exposure
- Potential risks from a biocompatibility perspective
- Information available to address identified risks
- Information needed to address any remaining knowledge gaps, such as new biocompatibility testing or other evaluations that appropriately address risks

Risk Based Approach (cont.)

New biocompatibility testing may **not** be needed if:

1. The device is made of materials that:
   - Have been well characterized chemically and physically in the published literature
   - Have a long history of safe use
2. Materials and manufacturing information is provided to demonstrate that no new biocompatibility concerns exist.

Risk Based Approach (cont.)

Leverage of previous biocompatibility info if:

1. Previous device use is in a similar part of the body for a similar timeframe;
2. Differences in materials or manufacturing between the new and leveraged devices are described; and
3. Information is provided to explain why differences aren't expected to impact biocompatibility.

BIOCOMPATIBILITY GUIDANCE: ENDPOINT ASSESSMENT VS. TESTING

Endpoint Assessment versus Testing

ISO 10993-1:2009

FDA Biocomp Guidance

Annex A
(informative)

Biological evaluation tests

...velopment of an assessment program and is not a checklist ... devices, different sets of tests may be necessary, including either ... the Table A.1. In addition to the framework set out in Table A.1, ... ed 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							
Category	nature of body contact (see 5.2) Contact	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	Hemocompatibility
Surface device		A	X*	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	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.

© 2009 Association for the Advancement of Medical Instrumentation ■ ANSI/AAMI/ISO 10993-1:2009

Contains Nonbinding Recommendations

Attachment A: Evaluation Endpoints for Consideration

The following is a framework for the development of a biocom... checklist for testing. For particular medical devices, different ... evaluation, including either additional or fewer endpoints than ... category a device falls, we recommend consulting device-specific guidances or contacting the appropriate review division for more information.[43] For example, FDA has historically considered devices used to drain fluids (such as Foley catheters) as externally communicating devices rather than as surface devices contacting mucosal membranes.

Table A.1: Biocompatibility Evaluation Endpoints

Medical device categorization by			Biological effect												
Category	Nature of Body Contact: 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#	Biodegradation#
Surface device	Intact skin	A	X	X	X										
		B	X	X	X										
		C	X	X	X										
	Mucosal membrane	A	X	X											
		B	X	X		O	O	O		O					
		C	X	X		[illegible]	[illegible]	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		

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).

Endpoint Assessment vs. Testing (cont.)

ISO 10993-1:2018

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

Medical device categorization by: Nature of body contact		Contact duration	Physical and/or chemical information	Cytotoxicity		Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[a]	Subacute toxicity[a]	Subchronic toxicity[a]	Chronic toxicity[a]	Implantation effects[b]	Hemocompatibility	Genotoxicity[c]	Carcinogenicity[c]	Reproductive/developmental toxicity[c]	Degradation[d]
		A – limited (≤24 h)	X[e]	E[h]	E	E											
Surface medical device	Intact skin	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	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[i]			
		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		
Implant medical device	Tissue/bone[f]	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 tested/ 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.

FDA Biocomp Guidance

Contains Nonbinding Recommendations

Attachment A: Evaluation Endpoints for Consideration

The following is a framework for the develo
checklist for testing. For particular medical
evaluation, including either additional or fe
category a device falls, we recommend cons
appropriate review division for more information.[43] For example, FDA has historically considered devices used to drain fluids (such as Foley catheters) as externally communicating devices rather than as surface devices contacting mucosal membranes.

Table A.1: Biocompatibility Evaluation Endpoints

Medical device categorization by: Category	Nature of Body Contact: Contact	Contact Duration	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#
		A – limited (<24 h)	X	X	X										
Surface device	Intact skin	B – prolonged (>24 h to 30 d)	X	X	X										
		C – permanent (> 30 d)	X	X	X										
	Mucosal membrane	A	X	X											
		B	X	X		O	O	O		O					
		C	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		

[43] 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).

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Endpoint Assessment vs. Testing (cont.)

X = ISO 10993-1:2009 asks for these.

O = CDRH also asks for these (and some, but not all are included in the 2018 revision of 10993-1).

Address all X's and O's in the biological safety evaluation. Use:

- Existing data,
- Additional endpoint-specific testing, or
- Rationale for why the endpoint does not require additional assessment.

Endpoint Assessment vs. Testing (cont.)

- **Relevance:** All endpoints identified by an “X” or “O” in Attachment A may not be relevant for all devices in a particular category
- **Novel materials/manufacturing processes:** Additional evaluations beyond those recommended in Attachment A may be needed
- **Multiple types of exposure:** Include information to address each exposure category.

Endpoint Assessment vs. Testing (cont.)

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@
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		

*portion of FDA Table A.1

Endpoint Assessment vs. Testing (cont.)

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@
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		

*portion of FDA Table A.1

KNOWLEDGE CHECK:
ENDPOINT ASSESSMENT VS. TESTING

Knowledge Check #1

What can I use to determine which endpoints to include in my biocompatibility evaluation?

1. ISO 10993-1:2018, Annex A, Table A.1
2. FDA's Biocompatibility Guidance, including Attachment A, Table A.1
3. Either one (they are both the same)

Knowledge Check #1

What can I use to determine which endpoints to include in my biocompatibility evaluation?

1. ISO 10993-1:2018, Annex A, Table A.1
2. FDA's Biocompatibility Guidance, including Attachment A, Table A.1
3. Either one (they are both the same)

Knowledge Check #1

What can I use to determine which endpoints to include in my biocompatibility evaluation?

1. ISO 10993-1:2018, Annex A, Table A.1
2. FDA's Biocompatibility Guidance, including Attachment A, Table A.1
3. Either one (they are both the same)

Knowledge Check #2

I always need to conduct some kind of test to address the endpoints in Table A.1 of FDA's Biocompatibility Guidance, Attachment A.

1. True
2. False
3. It depends

Knowledge Check #2

I always need to conduct some kind of test to address the endpoints in Table A.1 of FDA's Biocompatibility Guidance, Attachment A.

1. True
2. False
3. It depends

Knowledge Check #2

I always need to conduct some kind of test to address the endpoints in Table A.1 of FDA's Biocompatibility Guidance, Attachment A.

1. True
2. False
3. It depends

BIOCOMPATIBILITY GUIDANCE: OTHER TOPICS

What Else is in the Guidance

- Sample preparation for biocompatibility testing
- Testing considerations for various types of endpoints (e.g., cytotoxicity)
- Use of literature for some endpoints (e.g., carcinogenicity, reproductive and developmental toxicity)
- Common issues where FDA asks questions (if not addressed in a submission)

Sample Preparation

- Use device in its final, finished form (FFF), for example, sterile, if applicable.
- If not FFF, document any differences:
  - Attachment F (example documentation language) may be helpful

Sample Preparation (cont.)

Comparison to test article: The test article is identical to the medical device in its final finished form in formulation, processing, sterilization, and geometry and no other chemicals have been added (e.g., plasticizers, fillers, additives, cleaning agents, mold release agents).

Comparison to previously marketed device: The medical device in its final finished form is identical to **[name]** (previously marketed device) in formulation, processing, sterilization,

FDA Biocompatibility Guidance (Attachment F, page 63)

Sample Preparation (cont.)

- ISO 10993-12: more details on sample preparation (e.g., surface area/extract volume);
- Extraction studies: polar (like saline) and non-polar (like oil) solvents;
- Simulation of extractables and leachables representative of clinical use conditions;
- Extract separately:
  - Limited vs. prolonged vs. permanent components.
  - New materials: assess separately from other material components.

Test-Specific Considerations

VI.A. Cytotoxicity

VI.B. Sensitization

VI.C. Hemocompatibility

VI.D. Pyrogenicity

VI.E. Implantation

VI.F. Genotoxicity

VI.G. Carcinogenicity

VI.H. Reproductive & Development Toxicity

VI.I. Degradation Assessments

Considerations for “-Free” Labeling

- Current methods may not be able to detect an allergen or toxic compound at very low levels that could still produce an adverse effect in a highly sensitive individual.
- Labeling statements that wouldn’t require testing:
  - “Not made with [MATERIAL NAME]” (device + package)
  - “[COMPONENT] not made with [MATERIAL NAME]”

BIOCOMPATIBILITY GUIDANCE: CHEMISTRY INFORMATION

Chemistry Information

- “Long history of safe use” rationales
- Unexpected biocompatibility test findings
- Devices made from materials intended to change (e.g., in situ polymerizing or absorbable materials)
- Devices made from chemicals with known toxicities (e.g., carcinogenicity), where new biocompatibility testing is rarely conducted
- New chemicals used to modify material formulations or device manufacturing processes
- Devices made from novel materials

Chemistry Information (cont.)

- Descriptive info can include:
  - Chemical identity
  - Composition, formula/formula weight, structural information, and manufacturing and purity information
  - Amount by weight percent and total amount (e.g., ug)
  - Identity of other devices marketed in the US where the chemical entity has been used previously
- Possible chemistry information sources:
  - Material/component supplier (MAF, Attachment B)
  - Extractables/Leachables testing

Chemistry Information (cont.)

- Exposure assessments:
  - Chemicals and related impurities that may be available over time
  - Consideration of repeat device use
  - Extractables/leachables modeling or studies to optimize estimation of exposure during clinical use
- Safety assessments:
  - Known data from toxicology literature or material supplier
  - Derived Tolerable Intake (TI) or Threshold of Toxicological Concern (TTC) for chemicals where a TI cannot be derived.

BIOCOMPATIBILITY GUIDANCE: SUMMARY

Summary

- Consider FDA's Biocompatibility Guidance and its risk-based approach when preparing your submission
- Understand the difference between endpoint assessments versus testing
- Chemistry information can be important to your submission

Resources

Resource	URL
Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process	www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and
ISO 10993-1	ISO 10993-1 “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
Device Advice: Biocompatibility Assessment Resource Center	www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/biocompatibility-assessment-resource-center
CDRH Learn- Specialty Technical Topics • Final Guidance on "Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process • Color Additives	www.fda.gov/training-and-continuing-education/cdrh-learn#collapseFive
CDRH Recognized Consensus Standards • Specialty Task Group Area: Biocompatibility	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

Questions