U.S. FOOD & DRUG ADMINISTRATION

2016 CDRH Biocompatibility Guidance

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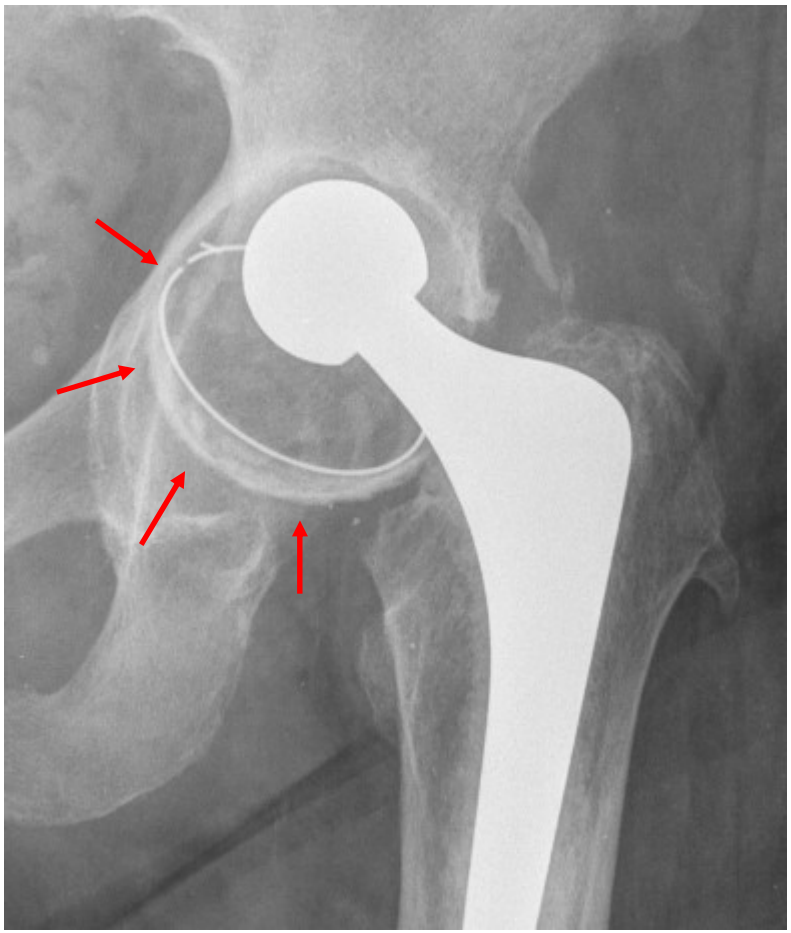
Why is Biocompatibility Important? (Industry and Patient)



- DEVICE: Acetabular Cup
- Change in external surface treatment can leave behind residuals
- Increased inflammation (a biocompatibility concern) can result in aseptic loosening/need for revision surgery

http://www.cardiffhipandknee.com/hip/hip-revisions/

Learning Objectives

- Review CDRH's 2016 Biocompatibility Guidance
- Learn some key definitions
- Learn when/how biocompatibility is considered
- Discuss risk-based approach
- Learn the difference between endpoint assessments vs. testing
- Review the chemistry information
- Discuss color additive information

CDRH's 2016 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: June 16, 2016

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

As of September 14, 2016, this document supersedes Blue Book Memorandum #G95-1 "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing,'" dated May 1, 1995.

For questions regarding this document, contact Jennifer Goode, 301-796-6374, jennifer.goode@fda.hhs.gov.

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

CDRH's 2016 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. Focus: 2009 version of ISO 10993-1 standard

How to use risk management to:

1) Address biocompatibility, and

2) Leverage existing testing, if possible

Instead of: What biocompatibility testing is needed?

CDRH's 2016 Biocompatibility Guidance (cont.)

Final Guidance (Outline):

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
VII. Chemical Assessments
VIII. Labeling Devices as "-Free"

CDRH's 2016 Biocompatibility Guidance (cont.)

Final Guidance (Key Attachments):

Att A: Evaluation Endpoints for Consideration *

Att B: Device Master Files for Biocompatibility Evaluations

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 *

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

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 direct or indirect contacting components (or could be)

When Biocompatibility is Considered

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

<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.

How Biocompatibility is Considered

- For all submission types: PMA, HDE, IDE, 510(k), and De Novo requests
- To determine potential for 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

Risk Based Approach (for Biocompatibility)

- Per 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 support no new biocompatibility concerns.

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 new and leveraged devices are described; and
3. Information is provided to explain why differences aren't expected to impact biocompatibility.

Endpoint Assessment vs. Testing

Annex A
(informative)

Biological evaluation tests

Table A.1 is a framework for the development of an assessment program and is not a checklist (see Clause 6). For particular medical devices, different sets of tests may be necessary, including either more or less testing than is indicated in the Table A.1. In addition to the framework set out in Table A.1, the following should be considered based 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							
nature of body contact (see 5.2)		contact duration (see 5.3) A – limited (u 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
Category	Contact									
Surface device		A	X [a]	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	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

[a] 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.

Contains Nonbinding Recommendations

Attachment A: Evaluation Endpoints for Consideration

The following is a framework for the development of a biocompatibility evaluation and is not a checklist for testing. For particular medical devices, different biological endpoints may require evaluation, including either additional or fewer endpoints than indicated. If it is unclear in which category a device falls, we recommend consulting device-specific guidances or contacting the appropriate review division for more information.[63] 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														
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																
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).

Endpoint Assessment vs. Testing

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

O = CDRH also asks for these.

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

Use:

- Existing data,
- Additional endpoint-specific testing, or
- Rationale for why endpoint doesn't require additional assessment.

(JLGoode OSMA Spring 2018)

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 table

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 table

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)
  - e.g., sterile, if applicable
- If not FFF, document any differences:
  - Attachment F (example documentation language) may be helpful

Sample Preparation (cont.)

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: June 16, 2016

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

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,

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

Biocompatibility Testing

- Cytotoxicity (Section VI, A)
- Sensitization (Section VI, B)
- Hemocompatibility (Section VI, C)
- Pyrogenicity (Section VI, D)
- Implantation (Section VI, E)
- Genotoxicity (Section VI, F)
- Carcinogenicity (Section VI, G)
- Reproductive & Development Toxicity (Section VI, H)
- Degradation Assessments (Section VI, I)

Chemistry Information

May be needed for:

- "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 unknowns, if TI cannot be derived

Color Additives

OSMA Biocomp Q3:

If a proposed 510(k) device contains color additives which are not CFR listed, what information is needed to support use of the color additives?

FDA Comment:

- See FDA's February 12, 2016 webinar (slides, audio presentation and transcript – includes 1 hour Q&A)

https://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm484421.htm

Resources

- CDRH's 2016 Biocompatibility Guidance:

  www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm348890.pdf

- Biocompatibility standards such as ISO 10993-1, and how CDRH uses them:

  www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

Questions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Analytical Evaluation Threshold (AET)

The analytical threshold at or above which a chemist should begin to identify and quantify a particular extractable/leachable and report it for potential toxicological risk assessment.