Welcome to today's

FDA/CDRH Webinar

Thank you for your patience while we register all of today's participants.

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ODE Final Biocompatibility Guidance

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

Published: June 16, 2016

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Outline

- Goals for this guidance
- Guidance development history
- Guidance framework
- Key definitions
- When should biocompatibility be considered
- Risk-based focus for biocompatibility evaluation
- Focus on endpoint assessment instead of testing
- Endpoint assessment considerations
- Chemical assessment recommendations
- Considerations for labeling devices “-Free”

Goals for this Guidance

1. **To clarify how US FDA is currently using ISO 10993-1** ✓ **Draft**

2. **To address common biocompatibility testing issues in submissions to the US FDA** ✓ **Draft**

3. **To address changes in ISO 10993-1:2009**

   From: What biocompatibility testing is needed?

   To: ***How to use risk management to:***

   1) Address biocompatibility, and

   2) Leverage existing testing, if possible

Final: New focus

Guidance Development History

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

Draft Guidance Published: April 23, 2013
(Comments closed: July 22, 2013)

- 700+ comments received
- Document revised to be responsive to comments received

Final Guidance Published: June 16, 2016

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

Guidance Development History (cont.)

36 Groups/Individuals provided comments, including:

- 11 device companies
- 7 trade associations
- 4 drug companies
- 3 biocompatibility test labs
- 2 standards development organizations
- 2 consulting groups
- 1 academic institution

Guidance Development History (cont.)

Highlight of comments received on FDA's draft Biocompatibility Guidance:

- More emphasis on risk assessment ✓
- Additional considerations in lieu of biocompatibility testing ✓
- Inclusion of definitions for terminology ✓
- Testing considerations ✓
- Chemicals of concern ✓
- Tables and flow chart in attachments ✓

Guidance Framework

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”

*** New**

Guidance Framework: 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 *

* New

Guidance Framework: Changes from Draft

- Removed issues more appropriate for separate guidances due to level of detail needed:
  - Color additives
  - Biocompatibility of gas pathway devices

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; or
  - **Modified devices:** if changes are to any direct or indirect contacting components, or could affect another component that has tissue contact.

EXAMPLE – Modified Device:
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.

When Biocompatibility is Considered (cont.)

- 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

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 the identified risks; and
  - information needed to address any remaining knowledge gaps, such as new biocompatibility testing or other evaluations that appropriately address the risks.

Risk Based Approach (cont.)

- New biocompatibility testing may not be needed if:
  - The device is made of materials that:
    - Have been well characterized chemically and physically in the published literature; and
    - Have a long history of safe use;
  - Materials and manufacturing information is provided to demonstrate that no new biocompatibility concerns exist.

Risk Based Approach (cont.)

- It may be possible to leverage previously conducted biocompatibility information if:
  - The previously tested device has similar indications, type, and duration of contact;
  - An explicit statement is provided regarding any differences in materials or manufacturing between the new and leveraged devices under consideration; and
  - Information is provided to explain why differences aren't expected to impact biocompatibility.

Endpoint Assessment vs. Testing

- Attachment A:
  - Provides a framework for the development of a biocompatibility evaluation.
  - Is modified from ISO 10993-1, Annex A.
  - Is not a checklist for testing.

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

O = Additional FDA recommended endpoints for consideration

Address all X's and O's in the biological safety evaluation. Can use existing data, additional endpoint-specific testing, or a rationale for why the endpoint does not require additional assessment.

Endpoint Assessment vs. Testing (cont.)

- Biocompatibility evaluation:
  - All endpoints identified by an “X” or “O” in Attachment A may not be relevant for all devices in a particular category.
  - For novel materials or manufacturing processes, additional evaluations beyond those recommended in Attachment A may be needed.
  - Devices with multiple types of exposure should 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 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														
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 Considerations

- If it is determined that some testing is needed, the guidance identifies:
  - General testing considerations for sample preparation;
  - Specific testing considerations for various biocompatibility endpoints (e.g., cytotoxicity); and
  - Why literature is often used to assess specific endpoints (e.g., carcinogenicity, reproductive and developmental toxicity)
- Test-specific issues included where deficiencies are frequently identified in premarket submissions.

Endpoint Considerations: 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

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 ...

Endpoint Considerations: Sample Prep (cont.)

- ISO 10993-12: for sample amount selection (e.g., surface area/extract volume).
- Extraction studies using polar and non-polar 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.

Endpoint Considerations: Test Specific

- 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)

Chemical Assessment

- Additional chemistry information may be needed for:
  - Support of long history of safe use rationales;
  - Devices with unexpected biocompatibility test findings;
  - Devices manufactured from materials that intentionally change over time (e.g., in situ polymerizing or absorbable materials);
  - Some devices including chemicals with known toxicities (e.g., carcinogenicity), where new biologic testing is rarely conducted;
  - New chemicals used to modify material formulations or device manufacturing processes; and
  - Devices made from novel materials.

Chemical Assessment (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

Chemical Assessment (cont.)

- Exposure assessment to include:
  - Chemicals and related impurities that may be available over time;
  - Consideration of repeat device use; and
  - Extractables/leachables modeling or studies to optimize estimation of exposure during clinical use;
- Safety assessment for each chemical to consider:
  - Known data from toxicology literature or material supplier;
  - Derive Tolerable Intake (TI) or use Threshold of Toxicological Concern (TTC) for unknowns, if TI cannot be derived.

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]"

Questions?

General questions about this webinar?

Contact - Division of Industry and Consumer Education: DICE@fda.hhs.gov (800) 638-2041

Questions about this biocompatibility guidance?

Contact - Jennifer Goode: jennifer.goode@fda.hhs.gov

(301) 796-6374

Slide Presentation, Transcript and Webinar Recording will be available at: http://www.fda.gov/training/cdrhlearn

Under Heading: Specialty Technical Topics in the "Biocompatibility“ section

FDA Guidance Team Members

- **Absorbables & Implantation**: Molly Ghosh, Joseph Nielsen, Charles Durfor, Judith Davis, Tory Hampshire (retired)
- **Chemistry**: Brendan Casey, Irada Isayeva, Ji Guo, Jiwen Zheng
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- **Hemocompatibility**: Qijin Lu, Molly Ghosh, Rich Malinauskas, Judith Davis, Tory Hampshire (retired), Eleni Whatley
- **Sample Prep/Cytotox/Sensitization/Pyrogenicity**: Molly Ghosh, Joseph Nielsen, Vicki Hitchins
- **Reproductive/Developmental Tox**: Michael Bailey