BREAK

Biocompatibility Guidance

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Jennifer L. Goode, BS, Biomedical Engineer is currently on detail to the Office of Device Evaluation at FDA where she is currently the Biocompatibility Program Advisor. Ms. Goode has been a premarket reviewer for over 24 years, with experience reviewing devices and combination products for surgical and interventional treatment of the peripheral vasculature, as well as cardiac monitoring, pacing, neurology and obstetrics and gynecology devices. For the past ten years, Ms. Goode has served as an FDA liaison to several ISO Working Groups responsible for the development of international standards for the biocompatibility evaluation of medical devices, including ISO 10993-1 and ISO 10993-4. Since 2008, Ms. Goode has been one of two Office of Device Evaluation representatives to the Biocompatibility Standards Task Group (STG) at the Center for Devices and Radiologic Health. This Biocompatibility STG is responsible for coordinating FDA input to, and scientific review and recognition of all biocompatibility standards used by CDRH.

2016 CDRH Biocompatibility Guidance

OSMA Spring Educational Meeting
Arlington, VA
Thursday, April 19, 2018

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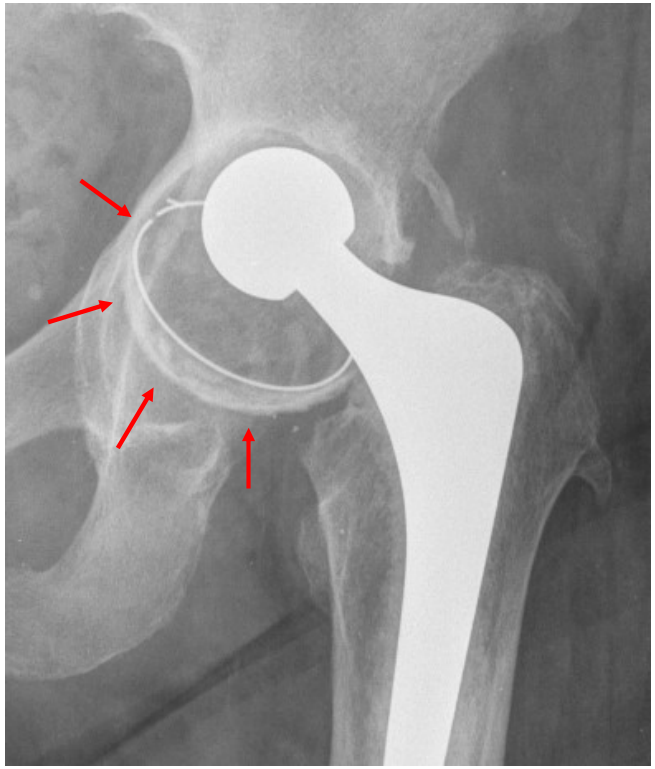
Why is Biocompatibility Important? (Industry and Patient)



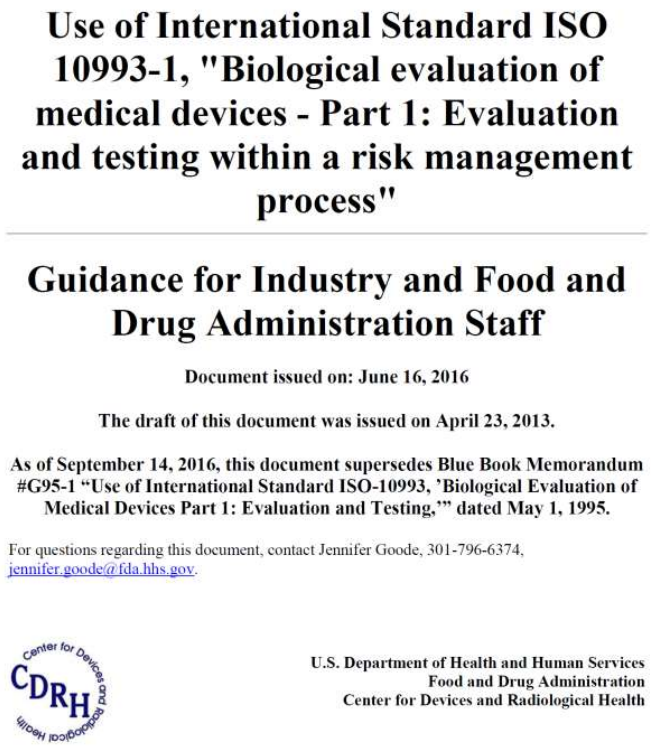
- DEVICE: Acetabular Cup
- Change in external surface treatment can leave behind residuals
- Increased inflammation (a biocompatibility concern) can result in aseptic loosening/need for revision surgery

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** (≤ 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			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.

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	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	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)													
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	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	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)													
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

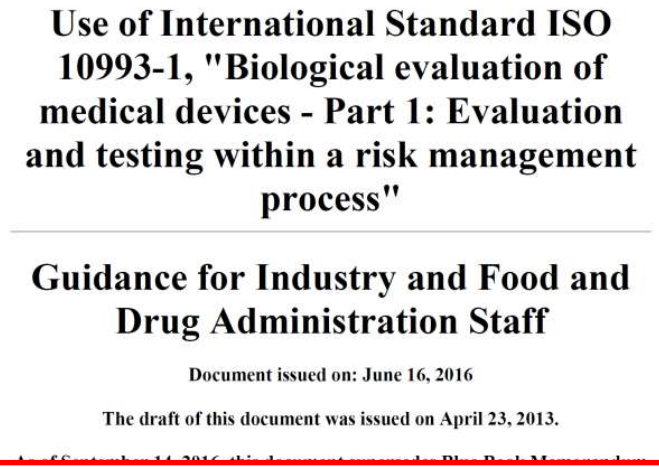
What Else is in the Guidance

- 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


FDA
U.S. FOOD & DRUG
ADMINISTRATION

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.

Biocompatibility of Orthopedic Devices

Aprajita Garg, Ph.D
Microbiologist
Joint Fixation Devices Branch 2
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Aprajita Garg, Ph.D.

Aprajita Garg is a reviewer in the Joints and Fixation Devices Branch II since October 2016. She provides Biocompatibility and Sterility consulting reviews for premarket submissions. Prior to joining FDA, she conducted post-doctoral research at the Yale School of Medicine. She earned her Ph.D. in Cell Biology and Molecular Genetics from the University of Maryland at College Park in 2012.

Biocompatibility of Orthopedic Devices

OSMA Spring Educational Meeting
The Key Bridge Marriott · Arlington Virginia
Thursday, April 19th, 2018

Aprajita Garg, PhD
Biocompatibility Reviewer
Joints and Fracture Fixation Branch II/Office of Device Evaluation
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Outline

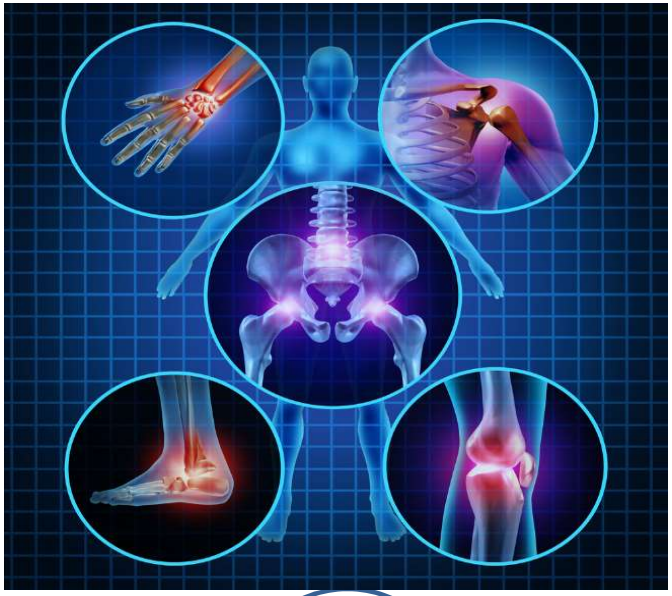
- Orthopedic Implants and Instruments – Recommended Biocompatibility Endpoints

- Biocompatibility Assessment
  - Approach 1: Risk Assessment of the Final Finished Subject Device
  - Approach 2: Risk Assessment of the Manufacturing Process
  - Approach 3: Material Characterization
  - Approach 4: Common Questions with Biocompatibility Testing

- Additional Considerations for Complex Devices

- OSMA Biocompatibility Questions: 1, 2

Biocompatibility Assessment of Orthopedic Medical Devices



Per CDRH's 2016 Biocompatibility Guidance, Attachment A: https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf

Contact type

Tissue /Bone

Contact duration

	Biological effect												
	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 (≤ 24h)	X	X	X	0	0								
B - prolonged (≥ 24h to 30 d)	X	X	X	X	0	X	X	X					
C - permanent (>30 d)	X	X	X	X	0	X	X	X		0	0		

Biocompatibility Assessment Approach I: Risk Assessment of the Final Finished Subject Device

CDRH's 2016 Biocompatibility Guidance: Attachment F-Based Justification for 510(k) submissions

- Permanent Implants (>30 d) ✓
- Instruments with Limited Contact (≤ 24h) ✓

Risk Assessment: Attachment F-Based Justification

Can the following comparison to previously marketed device be made: "The **[polymer/metal/ceramic/composite name] [component name]** of the medical device in its final finished form is **identical** to the **[component name]** of the **[name]** (legally US-marketed device)in formulation, processing, sterilization, and geometry, and no other chemicals have been added (e.g., plasticizers, fillers, additives, cleaning agents, mold release agents)." (per CDRH's 2016 Biocomp Guidance, Attachment F "Example Documentation Language")

- Consider if the referenced device has similar design, indications, type, and duration of contact. **Please refer to Attachment D of CDRH's 2016 Biocomp Guidance for a detailed flow chart for comparison criterion**

Risk Assessment: Attachment F-Based Justification (cont.)

The language is important. The use of term "similar" instead of "identical" is acceptable if differences in manufacturing process are described and biocompatibility risks associated with the differences are assessed and mitigated

EXAMPLE 1:*"The proposed XXXX1 implants in their final finished form are <u>similar</u> to the XXXX2 in processing, sterilization, and geometry and no other chemical agents have been added."*

XXXX1 and XXXX2 are from the same manufacturer

Additional risk assessment provided for why biocompatibility isn't impacted by differences

Risk Assessment: Attachment F-Based Justification (cont.)

The manufacturing process of the subject device is stated identical to a predicate, however the predicate does not belong to the same manufacturer

EXAMPLE 2: *"The XXXX System design, intend use and materials are same as predicate device YYYY, material composition are same. Biological safety evaluation for the XXXX System is not needed because it is identical device with YYYY system in terms of all aspects."*

XXXX and YYYY are from different manufacturers. This justification is not acceptable. Biocompatibility assessment is needed.

Additional risk assessment provided to include a letter from the third party contract manufacturer confirming identical manufacturing of XXXX and YYYY devices

Biocompatibility Assessment Approach II: Risk Assessment of the Manufacturing Process

Risk Assessment: Manufacturing Process

- Permanent Implants (>30 d) ✔
- Instruments with Limited Contact (≤ 24h) ✔

Sufficient detail on the manufacturing process such as:

- Raw materials (including reference to a materials standard, specification of material grade, and/or identification of the supplier of the raw material)
- Manufacturing process/methods (including the sterilization process)
- Manufacturing aids (i.e., agents, additives, excipients).

➢ Leverage any available known biocompatibility information about the manufacturing process and chemicals used

Risk Assessment: Manufacturing Process (cont.)

EXAMPLE 3: Insufficient justification based on manufacturing process if:

- Manufacturing process and related chemicals provided, but relevant biocompatibility endpoints are not addressed

- ***Please address each of the recommended biocompatibility endpoints in accordance with the duration of contact***

Polishing	1.Cytotoxicity 2.Sensitization 3.Irritation or Intracutaneous reactivity 4.Acute systemic toxicity 5.Material -mediated pyrogenicity 6.Subacute/subchronic toxicity 7.Genotoxicity 8.Implantation 9.Chronic toxicity 10.Carcinogenicity 11.Bacterial endotoxins(BET)/LAL	① Polishing is complete mechanical process, there is no chemicals used and polishing solution is used, which is water soluble and washed off at final cleaning process ② HL 7 Haftfett is the polishing media used ,which is water solvable and washed off at final cleaning process so no residuals are introduced to affect the biocompatibility of the device ③ Bacterial endotoxins(BET)/LAL test was conducted and endotoxin limit is less than 20EU/device ④ No residuals are introduced to effect the biocompatibility of the device form the Polishing manufacturing process	1.Polishing media MSDS*(Attachment E.2)* 2.Cleaning process validation report*(Attachment D)* 3.BET/LAL test report*(Attachment A.1, A.2, A.3&A.4)*

Risk Assessment: Manufacturing Process (cont.)

EXAMPLE 4: Insufficient justification based on manufacturing process if:

Manufacturing chemicals associated with processing steps aren't described

Milling	1.Cytotoxicity 2.Sensitization 3.Irritation or Intracutaneous reactivity 4.Acute systemic toxicity 5.Material -mediated pyrogenicity 6.Subacute/subchronic toxicity 7.Genotoxicity 8.Implantation 9.Chronic toxicity 10.Carcinogenicity 11.Bacterial endotoxins(BET)/LAL	① Milling is complete mechanical process ,there is no chemicals used and washed off at final cleaning process ② Bacterial endotoxins(BET)/LAL test was conducted and endotoxin limit is less than 20EU/device ③ No residuals are introduced to effect the biocompatibility of the device form the Milling manufacturing process	1.Cleaning process validation report*(Attachment D)* 2.BET/LAL test report*(Attachment A.1, A.2, A.3&A.4)*

During the milling process, cutting oil AAAA, lubricant BBBB, and cleaning process solvent CCCC are used, and are common to milling of medical devices

Risk Assessment: Manufacturing Process (cont.)

EXAMPLE 5: Insufficient justification based on manufacturing process if:

Cleaning validation is provided as a justification for not conducting biocompatibility assessment

TABLE 1 - ACCEPTANCE CRITERIA REVIEW

#	Characteristic	Insp. Method	Acceptance Criteria
1	Quantification of extractable, gravimetric, ASTM F2459 (Non-polar Solvent, Methylene Chloride	Outside Lab	≥ 50% reduction from baseline ASTM F2459 (acceptance criteria maximum value of 100µg/g).
2	Quantification of extractable, gravimetric, ASTM F2459 (Polar Solvent, Water)	Outside Lab	≥ 50% reduction from baseline ASTM F2459 (acceptance criteria maximum value of 50µg/g).
3	Particulate testing per USP 788	Outside Lab	< 6000 for particles 10 to 25 micrometers per device volume (ml) for each sample tested.* < 600 for particles > 25 micrometers per device volume (ml) for each sample tested*
4	Total organic Carbon (TOC) per USP 643	Outside Lab	< 100 micrograms per device cc (ml) device volume, for each sample tested.*
5	Cytotoxicity - MEM Elution, 72 hours incubation, triplicate, L929 Cells, 24 hr. extraction. 3 samples, 1 test per sample per device	Outside Lab	≤ 2 per ISO 10993-5 (0-4 scale)
6	BIO220 -Bioburden testing	Outside Lab	Average of 5 test does not exceed 500 CFU

Limitations:

- Usually only water extract, residues of non-polar, semi-polar nature not examined
- Extraction most likely not exhaustive
- Limited analysis techniques
- Endpoints difficult to interpret with respect to medical device extractables/leachables that will be present over device use: Total organic carbon (TOC), Total hydrocarbon (THC). Individual extractable/leachable chemicals not assessed

Please conduct a biocompatibility assessment based on the manufacturing process as discussed earlier

Risk Assessment: Manufacturing Process (cont.)

EXAMPLE 6 (Metal-Based Devices): For justification based on manufacturing process that can help mitigate biocompatibility risks, please consider <u>all</u> of the following:

i. Raw material used in accordance with an FDA-recognized material standard

ii. Manufacturing process includes *passivation / electropolishing** to reduce surface residue levels on the device

iii. Manufacturing process includes a relevant cleaning process* if a manufacturing aid is used that could adversely impact device biocompatibility

*(in accordance to FDA recognized consensus standard such as F-86)

✓ ***The biocompatibility risk from chemicals used prior to passivation / electropolishing can be mitigated***

However, downstream chemicals (i.e., post-passivation / electropolishing) could also impact biocompatibility

Risk Assessment: Manufacturing Process (cont.)

EXAMPLE 7 (Polymer-based devices, e.g., PEEK): For justification based on manufacturing process to help mitigate biocompatibility risks, please consider <u>both</u> of the following:

i. Raw material used in accordance with an FDA Master File that has information for raw material biocompatibility and manufacturing recommendations

ii. Manufacturing process described to confirm no manufacturing chemicals used during manufacture (e.g., all machining done without the use of cutting fluids/lubricants/cleansers other than water)

✔ ***The biocompatibility risk from manufacturing process can be mitigated***

❓ ***Material standards for polymers may not be supportive of biocompatibility***

Risk Assessment: Manufacturing Process (cont.)

EXAMPLE 8: Acceptable justification based on manufacturing process help mitigate biocompatibility risks:

- ✓ A letter from a third party contract manufacturer stating identical raw material and manufacturing for subject device and predicate/reference device (including predicate device trade name/510(k) number)

The biocompatibility risk for the raw material and manufacturing process can be mitigated

Biocompatibility Assessment - Approach III: Material Characterization

Material Characterization*: Test Article

Final finished device

or

If **"representative" test articles** are used:

- Same manufacturing and sterilization
- Same ratio of materials as device in its final finished form (FFF)
- Same chemical, physical and surface properties
- Information describing why differences won't impact biocompatibility (e.g., extraction information and surface characterization)

*** Typically conducted for biocompatibility assessment of Permanent Implants**

Material Characterization*: Extraction

Extraction conditions:

- ✔ Exhaustive
- ? Other approaches may be acceptable with justification; may depend on material (e.g., metal)

Extraction vehicles:

- ✔ Polar, non-polar, and semi-polar

Extraction ratio:

- ✔ Guided by Analytical Evaluation Threshold (AET)

***Typically conducted for biocompatibility assessment of Permanent Implants**

Material Characterization*: Analysis

Techniques include:

✔ Volatile, non-volatile, and inorganic residue analysis

❓ Missing non-volatile residue analysis

Residue information presented as:

✔ Residue per device

❓ Residue presented per surface area or per volume of extract only

Limit of Detection (LOD) and Limit of Quantitation (LOQ):

✔ Adequate to address the systemic toxicity endpoints in toxicological risk assessment

***Typically conducted for biocompatibility assessment of Permanent implant**

Material Characterization*: Endpoint Assessment

✔ Each identified residue assessed through toxicological risk assessment (TRA) for all relevant biocompatibility endpoints

Endpoints that can be assessed with TRA:

✔ Acute systemic toxicity, Subacute/Subchronic systemic toxicity, Chronic toxicity, Genotoxicity, Carcinogenicity

❓ Cytotoxicity, Irritation, Sensitization, Material Mediated Pyrogenicity: if chemical-specific data are available

❓ Implantation: chemistry and surface properties can impact biological response

***Typically conducted for biocompatibility assessment of Permanent implant**

Biocompatibility Assessment - Approach IV: Biocompatibility Testing

Biocompatibility Testing: Common Questions

FDA

❓ Test article clarification

Extraction ratio:

✔ Ratio determined based on the surface area of the device

❓ Ratio determined based on mass, if justified

Extraction conditions:

✔ 50°C / 72h, 70°C / 24h (Implants, except cytotoxicity)

✔ 37°C / 72h (Implant cytotoxicity)

✔ 37°C / 24h (Instruments)

❓ Need for positive control for sensitization testing

❓ LAL testing in lieu of material-mediated pyrogenicity testing

Biocompatibility Testing: Common Questions (cont.)

Implantation:

- ? Missing early implantation endpoint
- ? Missing representative histological images

Genotoxicity:

- ✓ Bacterial reverse mutation assay, and *in vitro* mammalian genotoxicity assay (e.g., mouse lymphoma)
- ? *Less sensitive in vivo tests do not replace in vitro assays (requested as supplemental tests for novel materials)*

Carcinogenicity:

- ? Missing explanation for why carcinogenicity is not a concern (FDA does not usually request testing for this endpoint)

Complex Devices:
Additional Considerations

Complex Devices: Additional Considerations*

***In situ* polymerizing/absorbable devices**

- Device degradation studies
- Additional implantation endpoints
- Biological evaluation over time: some combination of biological testing, analytical chemistry, theoretical discussion may depend on type of material and indication
- Biocompatibility testing: justification for sample preparation/non-standard testing conditions

Devices with wear particle generation concerns (type/volume)

- Biological response resulting from wear particles (implantation study)

➢ ***A Pre-submission is recommended to discuss biocompatibility assessment approach***

* Common FDA/Industry discussion points (other issues may also apply)

Complex Devices: Additional Considerations* (cont.)

Antimicrobial-containing devices

- Antimicrobial elution profile (bound/eluting antimicrobial)
- Combination product review assessment (for antimicrobial drugs)

Devices with nanofeatures

- Nanoparticles can potentially interfere with standard biocompatibility assessments
- Information may be requested to support claims regarding “nanofeatures” (e.g., surface)

➢ ***A Pre-submission is recommended to discuss biocompatibility assessment approach***

* Common FDA/Industry discussion points (other issues may also apply)

OSMA Biocomp Question 1:

For new a 510(k) which includes a device with a new material (new for FDA), there is no predicate cleared with FDA. However there are biocompatibility tests for the material itself and this testing shows that the material itself is biocompatible according to ISO 10993 and CDRH's 2016 Biocomp Guidance. Is biocompatibility testing needed for the final product? Or is it sufficient to evaluate the manufacturing steps, e.g., do chemical analysis with a toxicological risk assessment?

FDA Comments:

- For truly novel materials, endpoints beyond those identified in ISO 10993-1 may be needed. (See "novel" in CDRH's 2016 Biocomp Guidance.)
- Processing of new materials may result in different extractables and or surface properties that could impact the biological response.
- Often for new materials, biological testing alone or in conjunction with chemical characterization is recommended unless otherwise justified (e.g., data from the literature to demonstrate that processing is unlikely to impact chemistry or surface properties).

OSMA Biocomp Question 2:

For a new 510(k) with components made from medical grade stainless steel (according to recognized standards like ISO7153-1), do the stainless steel components need to be tested for biocompatibility? Or is it sufficient to:

(1) State that the material itself is biocompatible, and

(2) Conduct a chemical analysis with a toxicological risk assessment to evaluate concerns with the manufacturing aids?

Are there any biocompatibility tests which cannot be covered with a risk assessment (e.g. material-mediated pyrogenicity)?

FDA Comments:

- For stainless steel devices/components, a description of the manufacturing materials with a literature review to address toxicity potential may be sufficient. Analytical extractables testing with a traditional toxicological risk assessment often is not needed.
- The presence of a passivation process during manufacturing can address biocompatibility risk for surface residues from chemicals used prior to the passivation process.

Thank You

Questions!

Endotoxin Update

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Division of Reproductive, Gastro-Renal and Urological Devices
FDA

Elizabeth Gonzalez, Ph.D.

Dr. Elizabeth Gonzalez received her Ph.D. in Cellular Biology and Molecular Genetics from the University of Maryland. She did her postdoctoral work on reprocessing reusable medical devices at the FDA. Currently she is a Microbiology Reviewer in the Division of Reproductive, Gastro-Renal, and Urological Devices at FDA. She is FDA's primary representative to AAMI's Working Group 8, Microbiological Methods.

Endotoxin Update

OSMA Spring Educational Meeting
The Key Bridge Marriott · Arlington Virginia
Thursday, April 19th, 2018

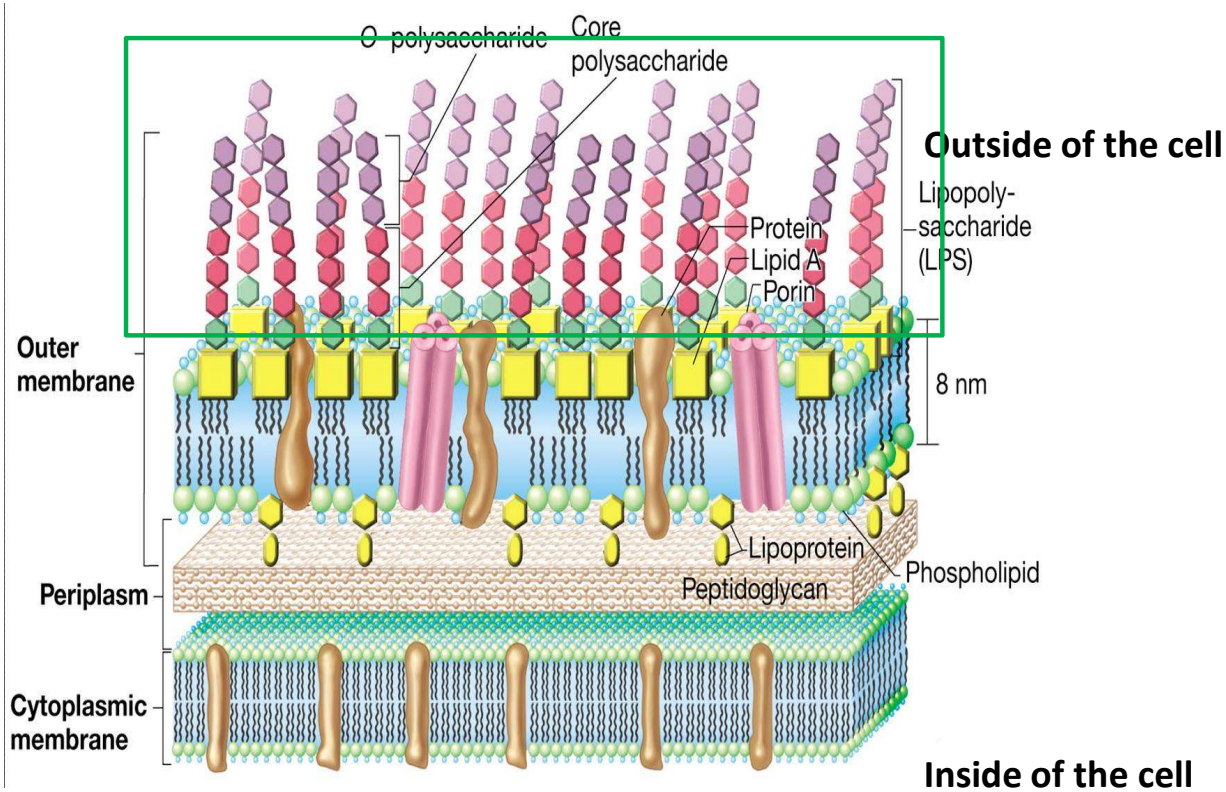
Elizabeth Gonzalez, PhD
Microbiologist
Office of Device Evaluation
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Outline

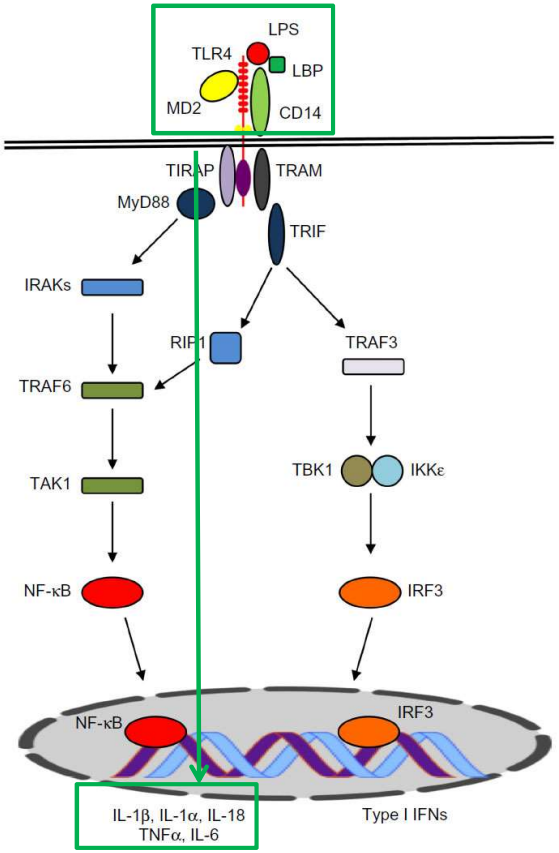
- What are pyrogens?
- Endotoxin testing
- Specific Questions

What are pyrogens?

- Substance that cause a fever response
- Bacteria-sourced pyrogens
  - Encompass a variety of bacteria components
  - Strongest elicitor is bacterial endotoxin
- The *Limulus* amoebocyte lysate assay (LAL) is the most sensitive and specific test for LPS


O-polysaccharide
Core polysaccharide
Outside of the cell
Lipopoly-saccharide (LPS)
Protein
Lipid A
Porin
Outer membrane
8 nm
Lipoprotein
Phospholipid
Peptidoglycan
Periplasm
Cytoplasmic membrane
Inside of the cell

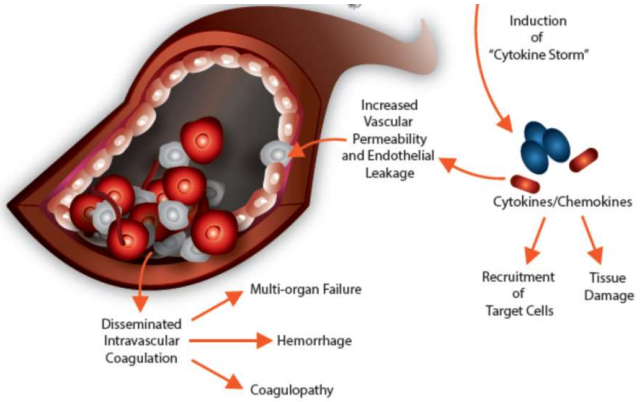
Molecular Mechanisms

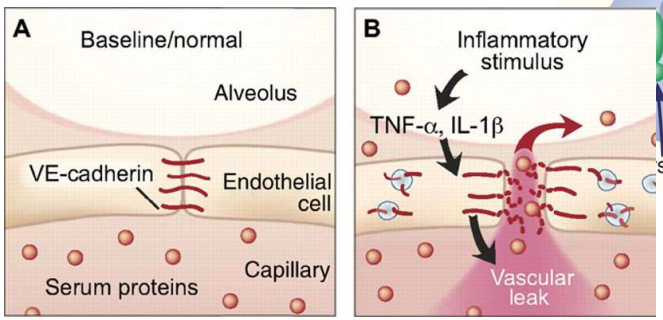


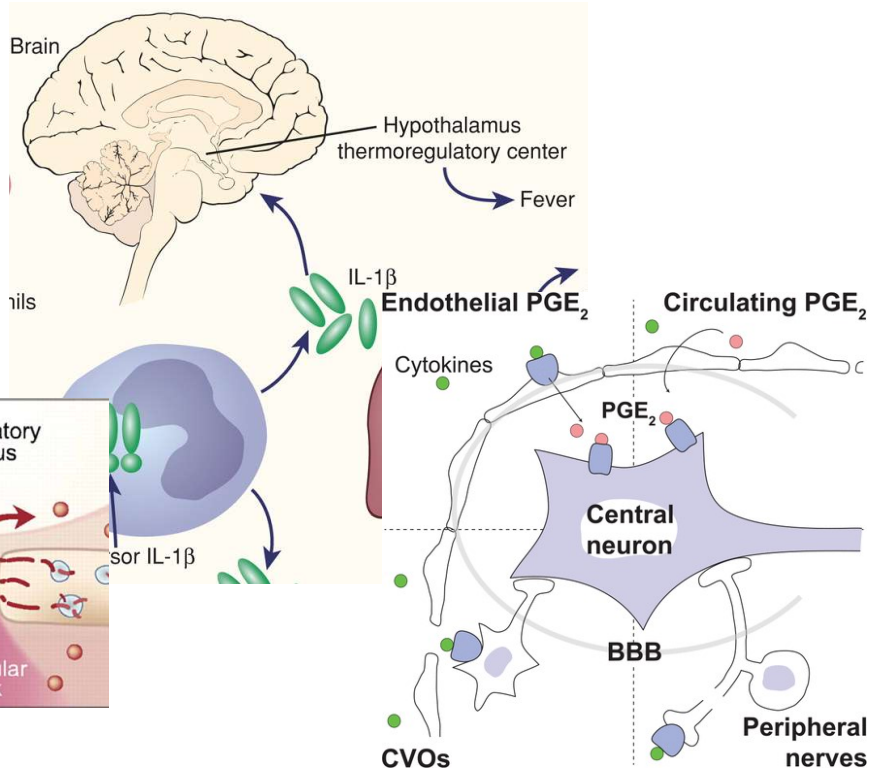
Binding of LPS to receptors on the membrane of human cells leads to cytokine production.

Molecular Mechanisms

- Inflammatory Cytokines
  - Fever
  - Attracts white blood cells (chemokines)
  - Vascular Leakage







Why are they relevant to implanted orthopedic devices?

- Local response
  - Aseptic loosening leads to >40,000 joint revisions/year in US
  - Endotoxin leads to cytokine release, inflammation, and bone resorption
  - Animal studies have demonstrated that endotoxin contamination on implants inhibit osseointegration and decrease the force required to pull the implant out
- Systemic response
  - Less likely due to indirect contact through lymphatic system
  - More serious consequences – shock, organ failure

Greenfield M, Bi Y, Ragab A, Goldberg V, Nalepka J, Seabold J. 2004 Does endotoxin contribute to aseptic loosening of orthopedic implants? J Biomed Mat Res. 72B: 179–185.

Bonsignore L, Anderson J, Lee Z, Goldberg V, Greenfield E. 2013 Adherent lipopolysaccharide inhibits the osseointegration of orthopedic implants by impairing osteoblast differentiation. Bone. 52(1): 93–101.

Why is batch testing recommended?

- Contamination can be sourced to:
  - Raw materials
  - Manufacturing equipment and processes
  - Personnel and handling
- No recommendations in recognized standards on how to perform pyrogen removal validation
- Therefore, the default recommendation is that every batch is tested

Alternatives to Batch Testing

As long as it is confirmed that the specified endotoxin limits are met at the time of 510(k) clearance, we will not be individually assessing alternatives to batch testing for adequacy during the premarket review, since this largely falls under QSR and manufacturing process controls.

2016 FDA 510(k) Sterility Guidance

The sponsor should provide the information outlined below:

a. a description of the method used to make the determination that the device meets pyrogen limit specifications (e.g., bacterial endotoxins test (BET), also known as the *Limulus* amebocyte lysate (LAL) test);

b. a statement confirming that endotoxin testing will be conducted on every batch or if not, information regarding the sampling plan used for in-process testing and/or finished product release, as recommended in the FDA guidance, Pyrogen and Endotoxins Testing: Questions and Answers" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM310098.pdf);

c. identification of the chosen testing limit; and

d. an explanation supporting the selected endotoxin limit.

Current Advisory

- You have provided an alternative to batch testing plan to monitor endotoxin levels on your device in further production. Please note the following advisory comments. We recommend that you consider, and maintain on file, the following about your alternative plan:
  - Explicit description as to how adequate safeguards are incorporated to ensure that non-conforming product does not reach patients (e.g., a timeline that enables recovery of product from inventory or distribution if monitoring systems detect failures).
  - How your plan is based on adequate historical data from earlier batch testing (as relevant). (The Agency recommends beginning with maximum coverage and adjusting sampling plans as confidence increases in the prevention of endotoxins in manufacturing processes.)
  - Identification of endotoxin limiting or reduction steps, and subsequent potential endotoxin contributing steps.
  - Sufficient documentation showing qualification and control over manufacturing processes, including component materials, manufacturing materials (e.g., water quality) and processes (e.g., passivation method specifications), environment and manufacturing lines to assure that endotoxin levels are within specifications. These may include (per AAMI ST72, section B.10):
    - Heat: 250-300°C for 30-120min (note: injection molding is often not sufficient)
    - Acid or base hydrolysis (e.g., passivation with nitric acid (see ASTM A967))
    - Oxidation (may lyse cells) – (e.g., anodization; may not sufficiently reduce pyrogens)
    - Water quality and specifications (e.g., distillation, reverse osmosis, for adequate time)
- Regardless of the method used to ensure endotoxin levels are within specifications, the effectiveness of the process should be supported by literature, and/or adequate validation.
  - Inclusion of an alternative sampling plan, for use if a failure occurs.

OSMA Endotoxin Q1: Out of Specification

Question: As an alternative for batch testing, a method has been proposed to use process control procedures. This includes the assessment of out of specification measurements.

One of the previous questions from FDA was how to contain and address product manufactured in a process with an out of specification point. A total recall of released product could negatively impact patients due to lack of device availability.

We would contend that an out of specification measurement can and will happen in any process. If this happens and the firm has procedures to address this situation, will this be sufficient for continued processing if documented and justified?

Response: FDA agrees that the sponsor should have a plan for dealing with out of specification results and that the response should be risk-based and not limited to recall.

OSMA Endotoxin Q2: Testing Per Package

Question: Can it be confirmed that, as is now stated in the new ST72 standard, that the testing required is on product contained in a single package and not the full systems for large implant products?

Response: The endotoxin limit is being applied to a sterile barrier system

OSMA Endotoxin Q3: Inclusion Criteria

Question: Are accessories to the surgical procedure included in those recommended for endotoxin testing according to ST72? For example jigs, blades, pointers, trials, etc. Materials usually found in a loaner tool set.

Response:

- Surgical accessory devices do not remain in the body following the procedure
- Endotoxin testing is therefore not needed for these devices

OSMA Endotoxin Q4: Testing Endpoint

Question: Since any surgical implantation results in local inflammation, the risk of inflammation is known for this effect and is well studied. Is it acceptable that for orthopedic implants, localized inflammation should be listed as a known risk but not one associated with endotoxin if below a tested limit?

Response: FDA agrees that if the device meets FDA-recognized endotoxin limits (typically 20 EU/device*) this is sufficient to address the concern regarding endotoxin-mediated inflammation

* Could be lower if the device is in contact with cerebrospinal fluid or is an ophthalmic device

OSMA Endotoxin Q5: Inclusion Criteria

Question: Are temporary implants (e.g., mandible extractors, external fixation pins) able to be removed from endotoxin testing if resulting risk assessments conclude endotoxin is not a risk?

Response:

- FDA does not believe that the time an implant is in contact with the patient should be the deciding factor for whether or not the device should be non-pyrogenic.
- A pyrogenic response could be caused either by a contaminated device in contact with the patient for 24 hours or by one that is in contact for 30 days.
- A risk based assessment could be used to determine that an alternative to batch testing may be appropriate.

OSMA Endotoxin Q6: Testing Final Finished Device

Question: For products such as bone cement where there is a powder and liquid component but each cannot be tested individually, these are currently mixed with sterile non-pyrogenic water made into testable coupons and tested as per the standard for releasing lots. Is this an acceptable practice?

Response:

- FDA recommends that the LAL testing be performed on the final finished device, which should include the same components, mixing, and handling that would be used in the final product.
- In the case of the bone cement, creating testable coupons allows the final form of the device to be tested for endotoxin.

Questions?

LUNCH
(*networking session*)

OSMA

ORTHOPEDIC INSTRUMENT ACCESSORIES

Classification Challenges

Multiple Classifications for Same Instrument

Most are Class I as per published classification

Have been "upclassified" by FDA (Class II and III) through premarket review due to association with implant system

Instruments considered Class I exempt for many years until FDA began to communicate policy that instruments were accessories to implant system- i.e., "parent device"- and, therefore, took on the classification of the higher class implant system

- No formal guidance on submission requirements
- Inconsistent reviewer direction
- Does not address legacy instruments of the same type introduced to market at an earlier time point
- Introduces complexity for manufacturers in tracking multiple classifications for same instrument through internal PLM systems

Post-market Impact

Classifications also drive post-market requirements, which do not reflect relative risk of instrument vs. implant

- Example- Changes to design, manufacturing process or site of manufacture of a Class III instrument (e.g., broach used with Class III hip system), will require a PMA supplement

MDR Reporting/Recalls

- Using implant product code can cause confusion as to what devices are the subject of recalls or MDR reports
    - Some manufacturers have received queries from FDA asking for clarification due to use of implant product codes

UDI

Using implant product code causes mismatch with GMDN codes and descriptions

- Issue will magnify as UDI requirements are adopted by other Health Authorities

Class I reusable devices are not required to be direct part marked before September 2020

- UDI direct part marking compliance dates are September 2016 for Class III and September 2018 for Class II

OSMA Request

- With these complexities in mind, and with new classification/reclassification mechanisms afforded by FDARA, as well as the risk-based approach mandated by the 21st Century Cures Act, we ask FDA to consider appropriate reclassification action for the types of orthopedic instruments described above. **As these "device-specific" instruments have never been formally defined by FDA either through Guidance or Regulation, we respectfully request that FDA revert to its previous longstanding practice and treat all manual surgical instruments provided with Class II or Class III orthopedic implant systems as Class I (510(k)/PMA exempt) devices, in accordance with the already established Class I classification designations- i.e., *manual surgical instrument for general use 21 CFR § 878.4800 or orthopedic manual surgical instrument 21 CFR § 888.4540*, or other established Class I product codes. Alternatively, we request that FDA publish new classifications (with associated product code description(s)) for those instruments which FDA believes carry a higher risk, and, therefore, should be classified as Class II or III.**

Potential Paths Forward

- **Communicate revised FDA policy that new and currently marketed instruments can follow the classifications already defined by currently published regulations**
  - If necessary, appropriate risk-based rationales that are documented by manufacturers and subject to FDA review during QMS inspections could be compiled
- **Update FDA Accessories guidance** to reflect the revised policy (i.e., retrospective reclassification based on supporting internal documentation) or **publish new guidance that is specific to orthopedic instrument accessories**
- **Provide submission format and requirements for manufacturers to submit instrument reclassification requests *(not ideal pathway due to resource requirements and inefficiencies for both manufacturers and FDA)***
- **Other regulatory mechanisms** to address realignment of instrument classifications with currently published regulations? Mass updates to the GUDID database to align updated product codes/classifications?