Biocompatibility of Orthopedic Devices

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Outline

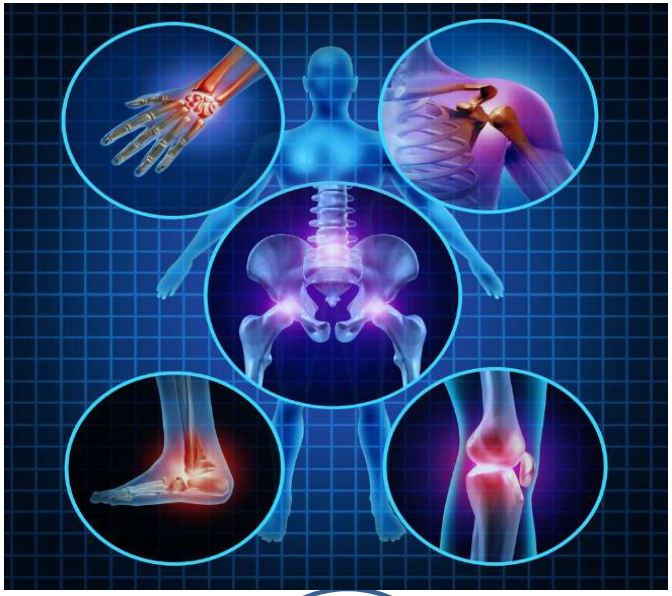
- Orthopedic Implants and Instruments – Recommended Biocompatibility Endpoints

- 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

- ? 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!