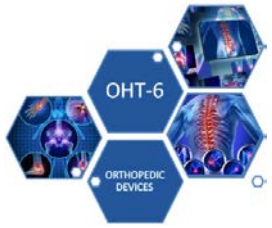


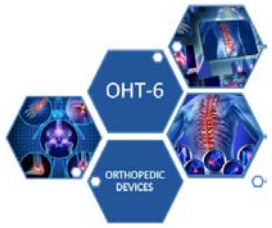
U.S. FOOD & DRUG ADMINISTRATION

Biocompatibility of Orthopedic Devices

Aprajita Garg, PhD
Lead Reviewer, Stereotaxic, Bone Growth Stimulators, and Facture Fixation Devices Team
DHT6C: Division of Restorative, Repair and Trauma Devices

Anne Talley, PhD
Lead Reviewer, Extracolumnar Spinal Devices Team
DHT6B: Division of Spinal Devices

OHT6: Office of Orthopedic Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health



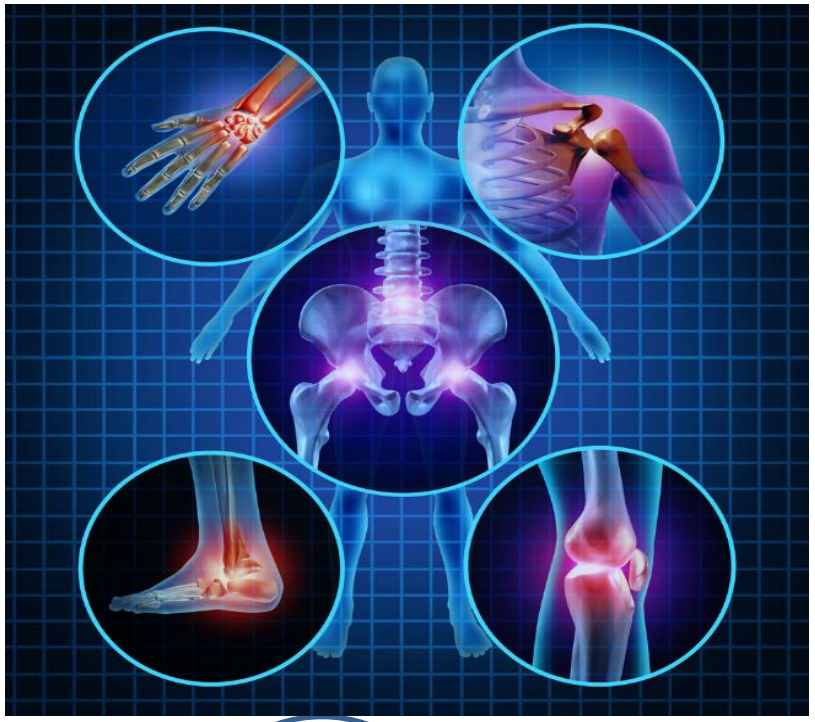
Outline

- Orthopedic Implants and Instruments – Recommended Biocompatibility Endpoints

- Biocompatibility Assessment
  - Approach I: Risk Assessment of the Final Finished Subject Device
  - Approach II: Risk Assessment of the Manufacturing Process
  - Approach III: Analytical Testing and Biological Testing
  - Approach IV: Biological Testing

- Additional Considerations for Complex Devices

Biocompatibility Assessment of Orthopedic Medical Devices



Per ISO 10993-1:2018 and CDRH's 2016 Biocompatibility Guidance, Attachment A: https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf

Contact type

Contact duration

Tissue /Bone

- A- limited (≤ 24h)
- B - prolonged (≥ 24h to 30 d)
- C – Long term (>30 d)

Endpoints of biological evaluation														
Physical and/or chemical informa-tion	Cyto toxi city		Irrita tion or intra cuta neous reac tivity	Ma-terial media ted pyro geni city[a]	Acute syste mic toxi city[b]	Sub acu te toxi city[b]	Sub chro nic toxi city[b]	Chr onic toxi city[b]	Impla nta tion ef-fects-[b,c]	Hem oco mpa tibil ity	Gen otox ici-ty[d]	Car cin oge nic ity[d]	Repro duc-tive/ develop mental toxici-ty[d,e]	Deg rada tion[f]
X	E	E	E	E	E									
X	E	E	E	E	E	E	E	E	E		E	E		

Traditional RTA Checklist: Biocompatibility

G.	**Biocompatibility** *If an in vitro diagnostic (IVD) device, select "N/A." The criteria in this section will be omitted from the checklist if "N/A" is selected.*			☐	
	32. For a biocompatibility assessment of tissue-contacting components, submission includes: • Each relevant endpoint for the device (as identified in device-specific guidance, or Attachment A of the FDA guidance document entitled "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,'" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and), has been addressed. • For any testing performed, test protocol (including identification and description of test article including whether the test article is the device in its final finished form using the recommended approach in Attachment F of "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,'" methods, and pass/fail criteria), and analysis of results (including tables with data points and statistical analyses, where appropriate), as described in Attachment E of the guidance document entitled "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'" provided for each completed test. **OR** A statement that biocompatibility testing is not needed with a rationale that considers all relevant endpoints (e.g., materials and manufacturing/processing are identical to the predicate).	☐	☐		

Per FDA's "Refuse to Accept Policy for 510(k)s – Guidance for Industry and Food and Drug Administration Staff"

Draft Guidances: Safety and Performance Based Pathway

Orthopedic Non-Spinal Metallic Bone Screws and Washers – Performance Criteria for Safety and Performance Based Pathway

Draft Guidance for Industry and Food and Drug Administration Staff

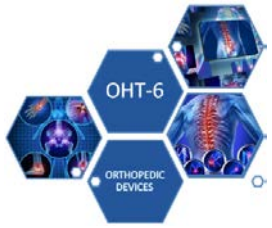
DRAFT GUIDANCE

&

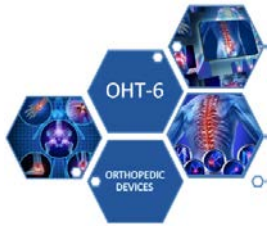
Spinal Plating Systems – Performance Criteria for Safety and Performance Based Pathway

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE



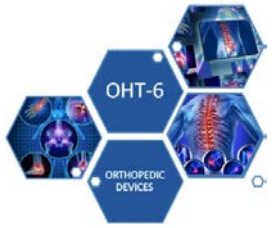
Biocompatibility Assessment Approach I: Risk Assessment of the Final Finished Subject Device



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

Accepted rationale - Subject device is identical to the predicate

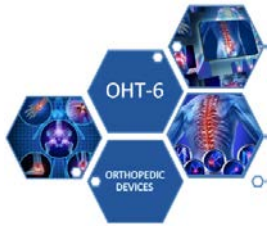
- Permanent/Long-Term(>30 d) ✔
- Instruments with Limited Contact (≤ 24h) ✔



Risk Assessment: Attachment F-Based Justification

Example Documentation Language - "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 Biocompatibility Guidance, Attachment F)**

- Consider how predicate device and subject device compare in terms of design, indication(s), type, and duration of contact. **Please refer to Attachment D of CDRH's 2016 Biocompatibility Guidance for a detailed flow chart for comparison criterion.**



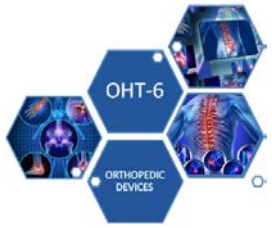
Risk Assessment: Attachment F-Based Justification (cont.)

The language is important. The use of term "similar"/"equivalent" 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 similar 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 should be provided for why biocompatibility is not impacted by differences (e.g. for a change in manufacturing process, a side by side comparison of manufacturing process, material type and amount is provided, with evaluation of risks from any new or increased chemical with respect to the recommended endpoints).



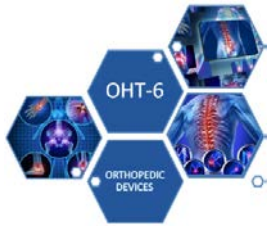
Risk Assessment: Attachment F-Based Justification (cont.)

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

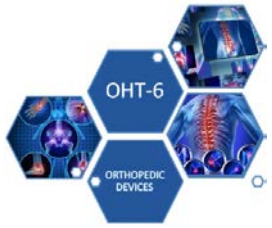
EXAMPLE 2: *"The XXXX System design, intend use and materials are same as predicate device YYYY, material composition are same. Biological safety evaluation for the XXXX System is not needed because it is identical device with YYYY system in terms of all aspects."*

XXXX and YYYY are from different manufacturers

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



Biocompatibility Assessment Approach II: Risk Assessment of the Manufacturing Process

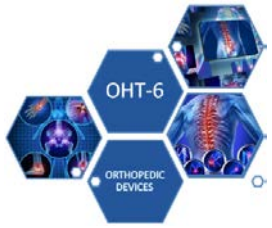


Risk Assessment: Manufacturing Process

- Permanent / Long-Term Implants (>30d) ✓
- 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)



Risk Assessment: Manufacturing Process (cont.)

- Leverage any available known biocompatibility information about the manufacturing process and chemicals used to address the recommended endpoint.

- Clinical data may not be leveraged to address biocompatibility endpoints. This is because clinical studies are generally not designed to collect the recommended endpoint specific information.

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)*

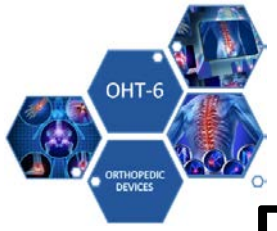
Risk Assessment: Manufacturing Process (cont.)

EXAMPLE 4: Insufficient justification based on manufacturing process if:

Manufacturing chemicals associated with processing steps are not 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. Risk assessment for each endpoint is included.



Risk Assessment: Manufacturing Process (cont.)

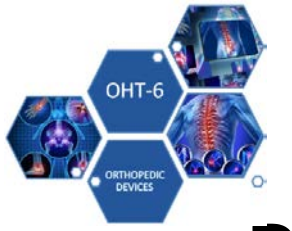
EXAMPLE 5: Insufficient justification based on manufacturing process if:

Cleaning validation in accordance to ISO 19227:2018, is provided as a ***stand alone*** justification for not conducting biocompatibility assessment.

Limitations of *only* cleaning validation based biocompatibility assessment:

- Rarely includes analysis of polar, mid polar and non polar extracts
- Unclear if the extraction is exhaustive
- Limited analysis techniques
- Endpoints difficult to interpret with respect to medical device extractables/leachables: Total organic carbon (TOC), Total hydrocarbon (THC)
- Individual extractable/leachable chemicals not assessed

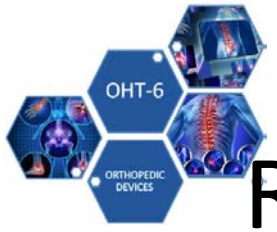
Please conduct a biocompatibility assessment based on the manufacturing process as discussed previously.



Risk Assessment: Manufacturing Process (cont.)

Cleaning validation test reports may be requested on a case by case basis as part of risk assessment approach for biocompatibility assessment. For example,

- Implants/instruments with complex geometry; biocompatibility justification is includes passivation
- Device manufactured by additive manufacturing approach
- A cleaning aid is used post passivation



Risk Assessment: Manufacturing Process (cont.)

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

i. Raw material used in accordance with an FDA-recognized material standard and has history of use;

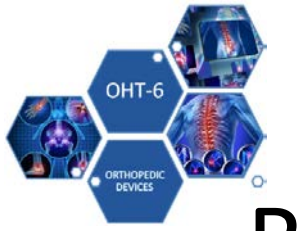
ii. Manufacturing process includes *passivation* / electropolishing*/anodization II or III* to reduce surface residue levels on the device; and

iii. Manufacturing process includes an adequate cleaning process, if a manufacturing aid is used that could adversely impact device biocompatibility

*(in accordance to FDA recognized consensus standard such as ASTM F86)

✔ The biocompatibility risk from chemicals used prior to passivation / electropolishing can be mitigated.

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



Risk Assessment: Manufacturing Process (cont.)

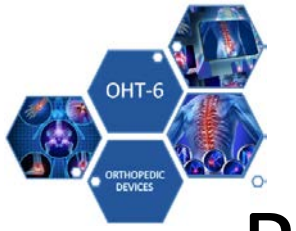
EXAMPLE 7 (Polymer-based devices, e.g., PEEK): For justification based on manufacturing process to help mitigate biocompatibility risks, please consider <u>both</u> of the following:

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

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)

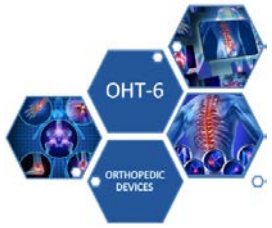
✔ The biocompatibility risk from manufacturing process can be mitigated.

? Material standards for polymers may not be supportive of biocompatibility.



Risk Assessment: Manufacturing Process (cont.)

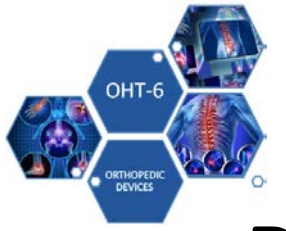
- **Use of animal derived material:** If an animal derived material is used as a device component or during the device manufacturing process, please refer to the recent 2019 FDA guidance, "Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices)": https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-containing-materials-derived-animal-sources-except-vitro-diagnostic-devices. We recommend that future submissions include sufficient information to address the specific considerations described in this guidance.



Risk Assessment: Manufacturing Process (cont.)

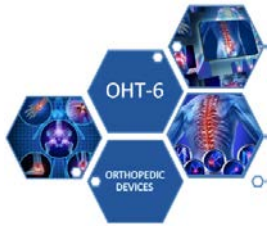
- **Packaging:** Packaging component in immediate contact to device should be assessed.

- **Sterilization process:** Biocompatibility assessment for final finished device. If manufacturing rationale is used to address biocompatibility, evaluate the effect of sterilization on the material and manufacturing chemicals.
  For example, if Polymer MAF used steam sterilized test article **while** subject device is Ethylene oxide (EO) or Hydrogen peroxide (H_2O_2) sterilized. Assess the effect of EO/ H_2O_2 on raw material, manufacturing material, device surface characteristics.



Risk Assessment: Manufacturing Process (cont.)

- Absorbable materials are sensitive to manufacturing process, difference in process temperature, purging may affect the device characteristics. Additionally, raw material may demonstrate variations in molecular weight, residual monomer content, crystallinity etc. Hence, use of manufacturing-based approach alone to support biocompatibility may be challenging.



Risk Assessment: Devices with Coatings

- ✔ MAF with biocompatibility assessment for all the relevant endpoints.
- ✔ A marketed device with identical base material/coating (specification per respective coating standard and guidance) may be leveraged with additional assessment on post coating process. Consider, how referenced device and subject device compare in terms of design, indications, type, and duration of contact.
- ? If new specifications are different/worst case, a complete biocompatibility assessment may be needed.
- ? Reference to coating standards alone is not adequate.

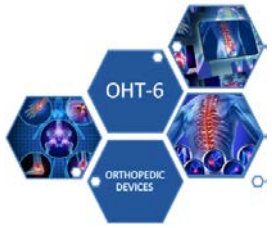
Review of Test Reports

The reason for including biocompatibility related test reports in a submission should be provided.

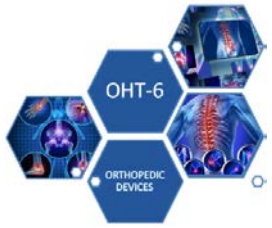
Example:

- ✔ Subject device has undergone change in raw material and/or manufacturing change compared to the predicate.

- ? If subject device is identical to the predicate as described in the Attachment F of the guidance – unclear why testing would be provided.



Biocompatibility Assessment - Approach III: Combination of Chemical Characterization (analytical testing) and Biological Testing



Considerations for Analytical Testing

- ISO 10993-18:2020 Biological evaluation of medical devices —Part 18: Chemical characterization of medical device materials within a risk management process ***Recent recognition (partial)***

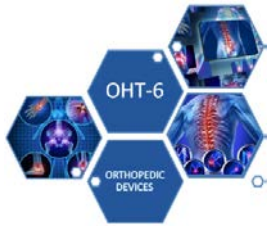
- ANSI AAMI ISO 10993-17:2002/(R)2012 Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances ***Partial recognition and *Undergoing major revision***

- ISO /TS 21726 First edition 2019-02- Biological evaluation of medical devices - Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents ***Relatively new standard***

➢ CDRH Scientific Perspective on Analytical Testing and Toxicological Risk Assessment for Medical Devices, Wednesday, May 22, 2019, available at https://www.toxicology.org/groups/ss/MDCPSS/docs/Webinar-SOT-MDCPSS-May22-2019-Slides-final.pdf

➢ Agency's 2016 Biocompatibility guidance Document Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"

✔ **A Q-submission may be considered for feedback on analytical testing protocol**



Analytical Testing Considerations

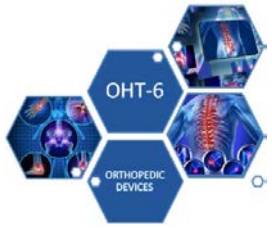
- ✔ Each identified residue assessed through toxicological risk assessment (TRA) for all relevant biocompatibility endpoints

- ✔ Endpoints that can be assessed with TRA:
  Acute systemic toxicity, Subacute/Subchronic systemic toxicity, Chronic toxicity, Genotoxicity, Carcinogenicity

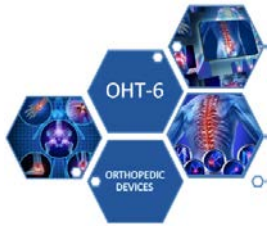
- ? Cytotoxicity, Irritation, Sensitization, Material Mediated Pyrogenicity: if chemical-specific data are available

- ? Implantation: surface properties, geometry may impact biological response

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



Biocompatibility Assessment - Approach IV: Biological Testing



Biological Testing Considerations

ISO 10993-1 Fifth edition 2018-08 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process

Agency's 2016 Biocompatibility guidance Document Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"

- ✓ Failure – A justification for why the failure is not clinically relevant. Root cause analysis

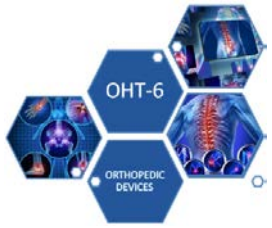
- ✓ Test article and extract related observations – Evaluate color, cloudiness, particles in the extract, and corrosion, discoloration, or any other change in test article. For such observations, a justification may be acceptable based on clinical relevance and/or a labeling update

The Special 510(k) Program- Guidance for Industry and and Food and Drug Administration Staff, September 13, 2019

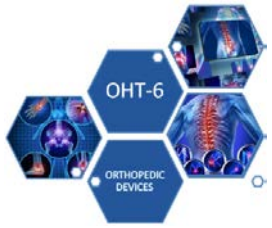
- If biocompatibility testing is needed as part of risk mitigation, Appendix C, Table 2, of the special 510(k) guidance provides summary information that could be included for this type of design control activity.

Device Change	Risks	Verification/Validation Method(s)		Acceptance Criteria	Summary of Results
Material change to polyethylene	Adverse tissue reaction from material change	Biocompatibility evaluation in agreement with recommendations in CDRH's Biocompatibility Guidance.[76] Based on our risk management procedures, biocompatibility testing was repeated for some endpoints.	Cytotoxicity (ISO 10993-5)[77] using the ISO minimum essential medium (MEM) Elution method. The protocol used the same test article preparation and extraction conditions as the predicate (MEM with 10% serum, 37 °C, 24 hours, at a surface area/volume ratio of 6 cm^2/ml), appropriate controls, extracts were not stored for more than 24 hours, and were not altered (e.g., filtered or pH adjusted). These testing conditions are the same as the predicate device, the extracts did not change color, appear turbid or have particulates, and there were no deviations/amendments from the protocol.	Reactivity grade shall be 0, which is the same as for the predicate device.	There was no evidence of the test extract causing cell lysis or toxicity (Grade = 0) for three replicates at 48 hours. Latex Positive Control = Grade 3 High Density Polyethylene Negative Control = Grade 0 The test article is non-cytotoxic.

Use of analytical chemistry testing using International Organization for Standardization (ISO) 10993-1820 and/or toxicological risk assessment using ISO 10993-1721 to address biocompatibility are not appropriate in a special 510(k).
https://www.fda.gov/media/116418/download



Complex Devices: Additional Considerations



Complex Devices: Additional Considerations*

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

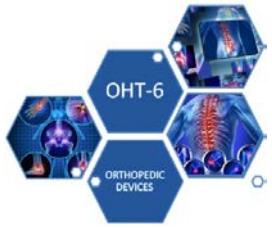
- Device degradation studies
- Additional implantation endpoints
- Biological evaluation over time: some combination of biological testing, analytical chemistry, theoretical discussion may depend on type of material and indication
- Biocompatibility testing: justification for sample preparation/non-standard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

Devices with wear particle generation concerns (type/volume)

- Biological response resulting from wear particles (implantation study)

➢ A Q-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 Q-submission is recommended to discuss biocompatibility assessment approach

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

Thank You!

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