U.S. FOOD & DRUG ADMINISTRATION

Welcome To Today's Event

Thanks for joining us!

Today's Topic:

Biocompatibility Town Hall #1: Risk Assessment Approaches for Addressing Biocompatibility Endpoints

September 9, 2026

U.S. FOOD & DRUG ADMINISTRATION

Biocompatibility Town Hall #1: Risk Assessment Approaches for Addressing Biocompatibility Endpoints

Misti Malone, PhD
Associate Director
Office of Product Evaluation and Quality
Immediate Office

Shuliang Li, PhD
Senior Standards Advisor
Office of Strategic Partnerships and Technology Innovation
Division of Standards and Conformity Assessment

Chandramallika (Molly) Ghosh, PhD, DABT
Biocompatibility Focal Point Co-Advisor
Office of Product Evaluation and Quality
Office of Health Technology 5

Simona Bancos, PhD
Biocompatibility Focal Point Co-Advisor
Office of Product Evaluation and Quality
Office of Health Technology 1

Center for Devices and Radiological Health
U.S. Food and Drug Administration

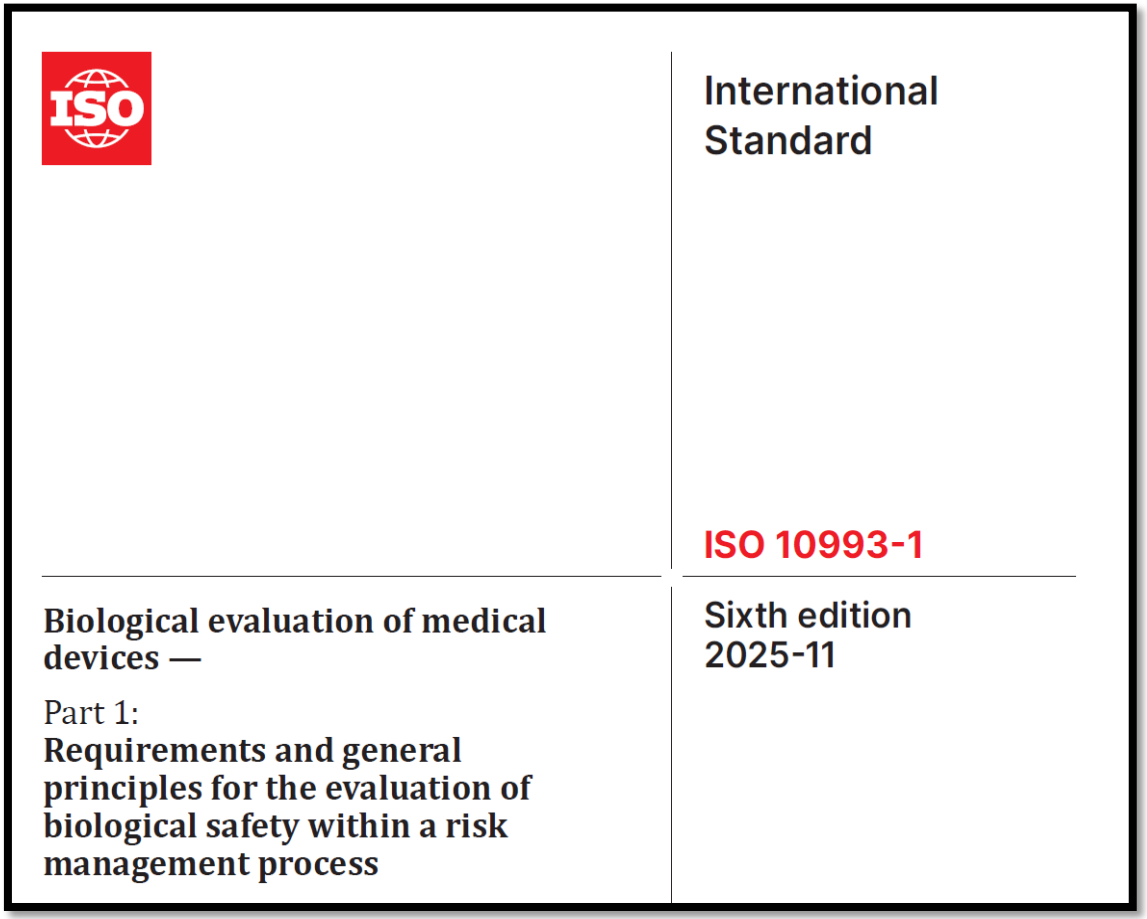
Introduction & Background

Shuliang Li, PhD
Senior Standards Advisor
Office of Strategic Partnerships and Technology Innovation
Division of Standards and Conformity Assessment

Learning Objectives

- Identify updates to ISO 10993-1:2025
- Describe risk assessment approaches for evaluating biocompatibility endpoints for medical devices
- Share considerations and examples for using risk assessment to address material-mediated pyrogenicity and the systemic endpoints

FDA Partial Recognition of ISO 10993-1: 2025



Overview of ISO 10993-1: 2025

- Realignment with the risk management framework described in ISO 14971:2019, including:

  Risk analysis, risk estimation, risk evaluation, risk control, residual risk, risk management

- Added new terminology/concepts:

  Intermittent contact, bioaccumulation, reasonably foreseeable misuse, application biological evaluation process over device life cycle

Select Updates to ISO 10993-1

	2018 Version	2025 Version
Terms	“endpoints”	“biological effects”
Device Categorization	3 categories (surface, externally communicating, implant) Subcategorized by tissue type (intact skin, intact mucosal, tissue, blood)	Added consideration to determine exposure duration based on daily, intermittent, bioaccumulation. Externally communicating device category is removed. Categorized by tissue type (intact skin, intact mucosal, breached or compromised surfaces and internal tissues other than blood, circulating blood)
General	Biological evaluation can include both a review of relevant existing nonclinical and clinical data and actual testing.	Greater emphasis on using existing data and chemical information before conducting biological testing. Emphasize conducting biological evaluation with the risk management framework per ISO 14971.

Select Updates to ISO 10993-1

	2018 Version	2025 Version
Material-mediated pyrogenicity	Marked as an endpoint to be addressed in the main table for all devices except for intact skin and mucosal membrane contact.	Removed from main table and addressed under “other biological effects”*
Genotoxicity	Genotoxicity assessment is NOT required* for prolonged mucosal membrane, breached or compromised surface or prolonged indirect blood path contacting devices.	Requirement* for genotoxicity assessment for all medical devices with prolonged contact, except for medical devices with only intact skin contact
Carcino-genicity	Carcinogenicity assessment is NOT required* for long-term intact mucosal membrane contacting devices.	Requirement* for carcinogenicity assessment for long-term intact mucosal membrane contacting devices.

**While manufacturers are encouraged to use FDA-recognized consensus standards in their premarket submissions, conformance is voluntary, unless a standard is 'incorporated by reference' into regulation.*

ISO 10993-1:2025 SIS Excerpts

Extent of Recognition

Partial recognition. The following part(s) of the standard is (are) not recognized:

Phrase "consumer products or" in clause 6.5.11.3
Clause 6.9 Biological risk estimation

Rationale for Recognition

This standard is relevant to medical devices and is recognized on its scientific and technical merit and/or because it supports existing regulatory policies.

NOTE 1: ISO TC194 WG1 experts are developing technical reports on the application of ISO 10993-1:2025, covering topics such as intermittent contact, bioaccumulation, reasonably foreseeable misuse, and application throughout the medical device life cycle. We encourage you to contact the review offices about implementing related clauses before you begin biological evaluation of your medical devices.

NOTE 2: The additional genotoxicity evaluation requirements specified in Tables 2, 3, and 4, and Clause 6.5.7 of ISO 10993-1:2025 may not align with Table A.1 in Attachment A of the guidance listed below (reference 1) for all prolonged contact devices. We encourage you to contact the review offices to discuss implementation of these requirements before you begin biological evaluation of your medical devices.

This standard is recognized in part because:
Phrase "consumer products" in clause 6.5.11.3 is in conflict with an existing published final guidance, see Attachment G of the guidance listed below (reference 1). Not all materials in consumer products are included in Attachment G of the guidance listed below.
Clause 6.9 Biological risk estimation is in conflict with another FDA-recognized standard, see clauses 5.5, 6, and 7 of ISO 14971:2019 listed below (reference 2).

Transition Period through July 1, 2029

Technical Contacts

- Shuliang Li, PhD Shuliang.Li@fda.hhs.gov
- Molly Ghosh, PhD, DABT Molly.Ghosh@fda.hhs.gov

Recognized Consensus Standards: Medical Devices

Summary

- Transition period: 3 years. Manufacturers can continue to follow ISO 10993-1:2018 version until July 1, 2029.
- FDA may update the Standard Identification Sheet (SIS) when new technical specifications or reports for ISO 10993-1:2025 are published.
- No changes to FDA's Biocompatibility Guidance related to ISO 10993-1:2025 at this time as risk management and flexible approaches are supported, as appropriate.

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

Biological Risk & Risk Assessment

Misti Malone, PhD
Associate Director
Office of Product Evaluation and Quality
Immediate Office

What is meant by risk?

Biological risk defined as:

- ISO 10993-1:2025 - combination of the probability of occurrence of biological harm and the severity of that biological harm
- ISO 10993-1:2018 - combination of the probability of harm to health occurring as a result of adverse reactions associated with medical device or material interactions, and the severity of that harm

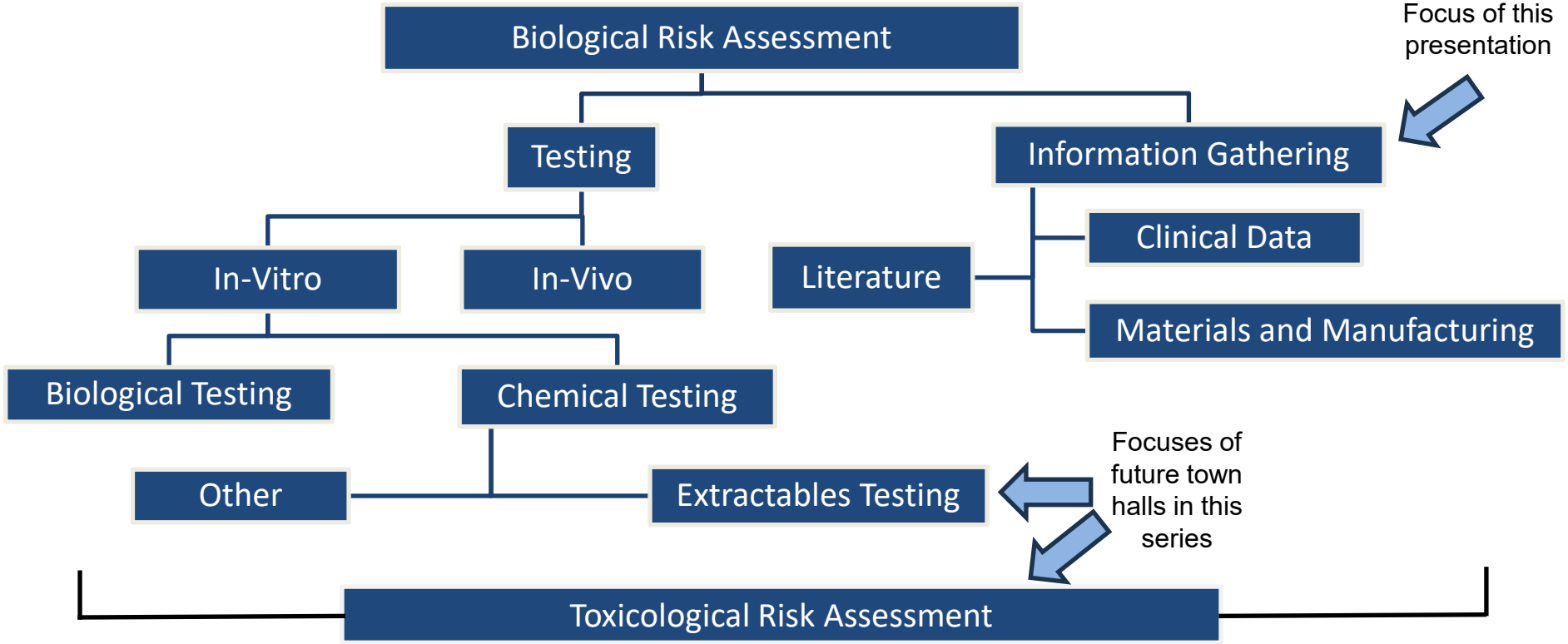
Potential biocompatibility risks include:

- Material or chemical toxicity
- Unacceptable biological response to physical characteristics of the device
- Aspects of manufacturing and processing that could alter the physicochemical characteristics of the device, resulting in an unacceptable risk

Risk Management Process

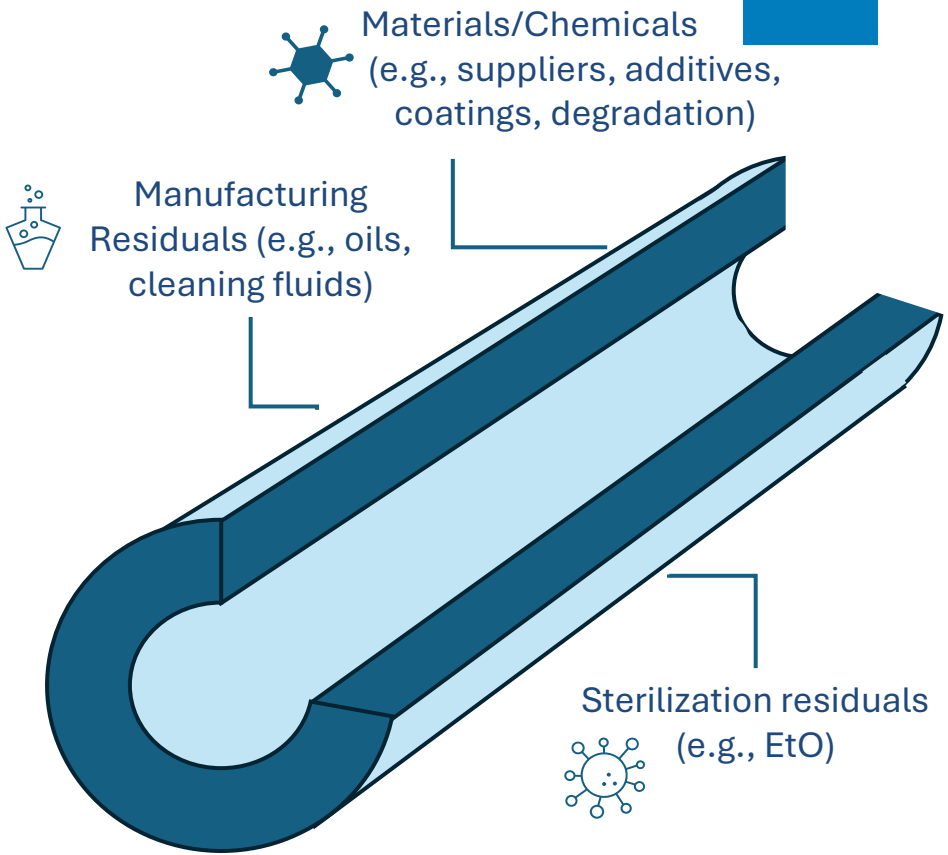
- Assessment of the device:
  - material components
  - manufacturing processes
  - clinical use of the device including the
    - intended anatomical location,
    - patient population, and
    - the frequency and duration of exposure
- Risk assessment: Conducted in accordance with ISO 10993-1, ISO 14971, and FDA's Biocompatibility Guidance

Biological Risk Assessment



Risk Assessment

- Define contact category, tissue type, duration (limited, prolonged, long-term), and frequency
- Collect qualitative and quantitative information
  - Materials/Chemicals
  - Manufacturing aids
  - Manufacturing processes (e.g., passivation, cleaning, sterilization)
- Leverage existing devices and experience (e.g., similar devices, MAF, standards)



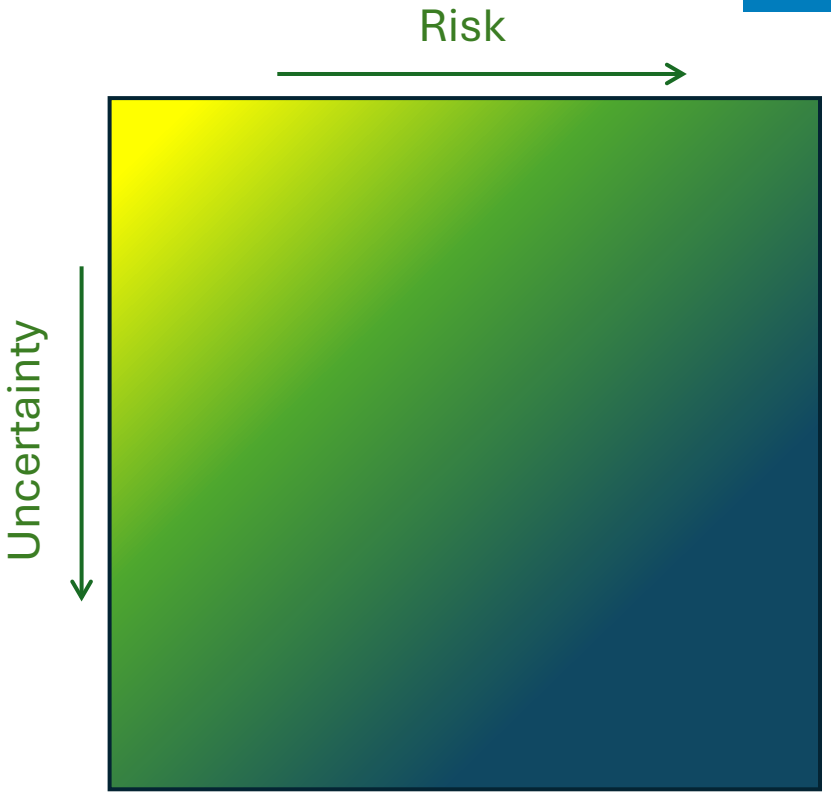
Biocompatibility Risk-based Evaluation

A risk assessment may be sufficient with lower risk and more knowns:

- Well-known or standardized materials and processes
- Unlikely to contain chemicals with known risk
- Similarity to marketed device

Biological/Chemical testing more likely with higher risk or higher uncertainty:

- Novel materials
- Chemicals with new or increased risks
- Novel or unknown processes



Considerations for Material Mediated Pyrogenicity (MMP) Assessment

Chandramallika (Molly) Ghosh, PhD, DABT
Biocompatibility Focal Point Co-Advisor
Office of Product Evaluation and Quality
Office of Health Technology 5

Background

A pyrogen is any substance that induces fever.

- Bacterial Endotoxins - evaluated as part of the sterility assessment
- Material-mediated pyrogenicity (MMP) - chemicals, including manufacturing residuals, that may leach from devices during clinical use

Pyrogenicity assessment is critical for patient safety:

- Implantable devices
- Devices with direct or indirect contact with cardiovascular system, lymphatic system, or cerebrospinal fluid regardless of duration of contact
- Devices labeled as “non-pyrogenic”

Current Considerations

Limitations of Rabbit Pyrogen Test (RPT) per USP <151>:

- Often uses high number of devices; e.g., 105 glaucoma devices for a single study.
- Failures are rare according to current research[1].

([1] Table 5 in L.K. Borton and K.P. Coleman [2025];
Note: The citation of this table is not to be interpreted as CDRH agreement of the MMP approach proposed in this paper.)

ISO 10993-1 (2025), Clause 6.5.10.5

Medical devices containing constituents that have previously elicited a pyrogenic response or chemical entities where the pyrogenic potential is unknown (e.g., use of a novel material) should be evaluated for material-mediated pyrogenicity.

In many cases, it can be sufficient to present a rationale that;

- *The composition of the finished medical device (including processing aids and manufacturing contaminants) does not present a significant biological risk of material-mediated pyrogenicity, and*
- *There are adequate controls to prevent pyrogenic contamination during manufacturing.*

Further information on material-mediated pyrogenicity is provided ISO 10993-11:2017, Annex G.

NOTE The evaluation for the presence of bacterial endotoxins and other microbial pyrogens is outside of the scope of this document and is addressed by ISO 11737-3.

Objectives

- Clarify expectations for **MMP evaluation for medical devices.**
- Identify device categories where risk assessment may be appropriate in **lieu of nonclinical testing.**
- Support FDA's mission to reduce animal testing.

MMP Risk-Based Considerations

MMP testing (i.e., RPT) typically recommended for the following:

1. Devices with *absorbable/degradable materials* with no prior history of safe use in medical devices with similar or worst-case tissue contact or not well characterized;
2. Devices with *biologically derived materials* with no prior history of safe use in medical devices with similar or worst-case tissue contact, or not well characterized;
3. Devices with any material with no history of safe use in medical devices with similar or worst-case tissue contact;
4. Devices labeled non-pyrogenic.

For all other devices, material and manufacturing-based justifications may be acceptable.

Important Considerations

- *History of Safe Use*: Device materials and materials used in formulation and processing with no history of failed MMP testing.
- *Similar Tissue Contact*: Clause 6.7, ISO 10993-1: 2025, "Sufficient similarity is where any differences do not result in any new or increased biological risks."
- *Worst-case Tissue Contact*
  - Nature of body contact (e.g., implant vs. surface contacting device; direct vs. indirect tissue contact);
  - Duration of tissue contact (e.g., long-term vs. limited);
  - Tissue contacting surface area of the device/material.

Example of Device and Manufacturing Material Information*

- Chemical name and trade name
- Chemical Abstract Services Registry Number (CAS #)
- Material supplier
- Certificate of analysis (CoA), Safety Data Sheet (SDS)
- Master file (MAF) number
- Material standard (e.g., American Society for Testing and Materials [ASTM])
- Summary of biocompatibility tests performed by the material supplier
- Material properties
- Manufacturing information (see slide 27)

** Not a comprehensive list*

Example of Material Information*

Polymers	Metals / Metal Alloys	Ceramics
• Stereoisomeric composition	• Appearance (e.g., powder)	• Primary oxide/compound content
• Chemical composition	• Density	• Aids/stabilizers
• Copolymer ratio	• Purity	• Trace/impurity elements
• Molar mass, MW distribution	• Elemental impurity composition	• Appearance
• Viscosity	• Residual/trace element content	• Particle size distribution
• Residual solvents/catalyst	• Wt. % of each alloying element	• Density
• Elemental impurities	• Grade and standard of conformance	• Porosity
• Crystallinity	• Surface treatment (e.g., passivation)	
• Thermal properties (e.g., Tg)		

** Not a comprehensive list. Not all information may be needed for MMP assessment.*

Example of Material Information (cont.)*

Absorbable / Degradable
• Stereoisomeric composition
• Chemical composition
• Molecular structure / Crystallinity
• Molar mass, MW distribution
• Viscosity
• Degradation Products
• Purity/trace elements
• Thermal properties (e.g., Tg)
• Processing (e.g., extrusion)

Biological-derived Materials
• Species/strain; type/grade; description of organ/tissue
• Description of the production processes; viral inactivation
• Potential for cross-contamination
• Physico-chemical characteristics
• Chemical composition and presence of impurities
• Statement that the animal derived material/ processing complies with applicable recognized clauses of ISO 22442 standard series (e.g., source, traceability, collection)
• For animal derived material, statement that the sponsor follows the FDA guidance: "Medical Devices Containing Materials Derived from Animal Sources"

** Not a comprehensive list. Not all information may be needed for MMP assessment.*

Additional Information*

Manufacturing Information

- Detailed description of the manufacturing processes,
- Manufacturing equipment in contact with the device material/components,
- Manufacturing conditions,
- Identification of manufacturing materials known to cause MMP,
- Description of the relevant quality controls.

Supplementary Information

- MMP assessment or RPT on prior device version(s).
- Marketing experience with the device material(s).

** Not a comprehensive list. Not all information may be needed for MMP assessment.*

Hypothetical Examples

Scenario 1	**Neurological Device** Polymer component for implant
Scenario 2	**Orthopedic Device** Metal alloy implant
Scenario 3	**Ophthalmic Device** Bacterial derived sodium hyaluronate (NaHy) for an implant
Scenario 4	**Gas Pathway Device** Polymeric & metallic components

Scenario #1

- Device component: Subcutaneous neurological device
- Component categorization: implant, long-term contact (>30 days), tissue/bone
- Manufacturing change: change in polymer (e.g., PEEK) material

Considerations for MMP Assessment (not limited to):	
Materials	Common material for long-term implant. FDA database review can confirm cleared/approved devices with identical PEEK formulation and acceptable MMP testing results, including for long-term implants.
Manufacturing	Safety Data Sheets for related manufacturing agents. Detailed manufacturing information and standard processes/cleaning for this material type.

Scenario #2

- Device: Orthopedic implant
- Device categorization: implant, long-term contact (>30 days) tissue/bone
- Device material: Stainless steel (SS), titanium (Ti) alloy

Considerations for MMP Assessment (not limited to):	
Materials	Device materials conform to an FDA-recognized consensus standard with documented history of safe use in orthopedic devices.
Manufacturing	The device undergoes surface treatment (e.g., passivation, electropolishing, anodization) per an FDA-recognized consensus standard, where applicable, and has a validated final cleaning process.

Scenario #3

- Device: Ophthalmic implant
- Contact: Implant, prolonged (>24 hr to >30 days), tissue/bone
- Device materials: Bacterial-derived NaHy, USP-grade NaCl, phosphates

Considerations for MMP Assessment (not limited to):	
Issues with RPT	For intravenous administration, 100x dilutions required due to high MW & viscosity. Particulates present regardless of high-fold dilutions.
Materials	CoA and detailed material characterization (e.g., nucleic acid, proteins, elemental impurities).
Manufacturing	Detailed manufacturing information (e.g., processes, equipment).
Add'l Considerations	At the completion of surgery, a very small residual amount remains inside the eye. No direct contact with circulating blood.

Scenario #4

- Device: Gas pathway
- Device categorization: external communicating, indirect, long-term (>30d)
- Device materials: polymers (PP, PC, ABS, PE), metals (Al, steel)

Considerations for MMP Assessment (not limited to):	
Materials & Manufacturing	Simple, well-characterized polymers with known processes and processing aids.
Intended Use	Condensate unlikely to reach systemic circulation.
Special Controls	ISO 18562-4: 2024, Clause 5.3.1(c) Note 6: "Concerns regarding material-mediated pyrogenicity can be addressed by using well-known materials for which a pyrogenic effect is not expected."

Biological Risk Assessment for Systemic Endpoints

Simona Bancos, PhD
Biocompatibility Focal Point Co-Advisor
Office of Product Evaluation and Quality
Office of Health Technology 1

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 – long term (> 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	X	O	X		X					
		C	X	X	X	X	O	X	X	X		X			
	Breached or compromised surface	A	X	X	X	X	X								
		B	X	X	X	X	X	X		X					
		C	X	X	X	X	X	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X	X				X				
		B	X	X	X	X	X	X			X				
		C	X	X	X	X	X	X	X	X	X	X	X		
	Tissue+/bone/ dentin	A	X	X	X	X	X								
		B	X	X	X	X	X	X	X	X					
		C	X	X	X	X	X	X	X	X		X	X		
	Circulating blood	A	X	X	X	X	X		X*		X				
		B	X	X	X	X	X	X	X	X	X				
		C	X	X	X	X	X	X	X	X	X	X	X		
Implant device	Tissue+/bone	A	X	X	X	X	X								
		B	X	X	X	X	X	X	X	X					
		C	X	X	X	X	X	X	X	X		X	X		
	Blood	A	X	X	X	X	X		X	X	X				
		B	X	X	X	X	X	X	X	X	X				
		C	X	X	X	X	X	X	X	X	X	X	X		

Purpose: Evaluate systemic toxicity, genotoxicity, carcinogenicity, and reproductive/developmental toxicity through risk assessment, biological testing, and/or chemical testing.

Risk assessment based on materials, chemicals, processing, etc.

Biological testing (e.g., animal study, cell assay)

Chemical Testing (e.g., per ISO 10993-18)

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

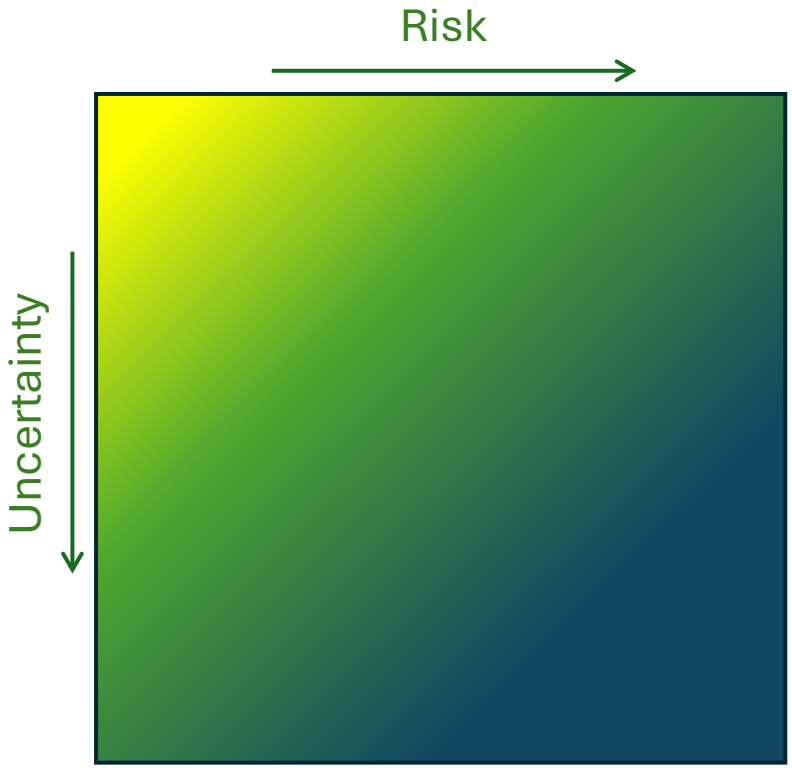
Biocompatibility Risk-based Evaluation

A risk-based assessment may be sufficient with lower risk and more knowns:

- Well-known or standardized materials and processes
- Unlikely to contain chemicals with known risk(s)
- Similarity to marketed device

Biological/Chemical testing more likely with higher risk or higher uncertainty:

- Novel materials
- Chemicals with new or increased risks
- Novel or unknown processes



Biocompatibility Risk-based Evaluation*

A risk-based assessment may be sufficient with lower risk and more knowns:

- Well-known or standardized materials and processes
- Unlikely to contain chemicals with known risk(s)
- Similarity to marketed device

→

- Metals and polymers conforming to an applicable standard or MAF.
- Similarity to previous versions or other marketed devices.
- Well-known suppliers and processes.
- Processing aid/chemical with SDS.

Biological/Chemical testing more likely with higher risk or higher uncertainty:

- Novel materials
- Chemicals with new or increased risks
- Novel or unknown processes

→

- Concerning or unknown chemicals (e.g., additives, extractables).
- Complex or novel polymers (e.g., absorbable, in situ polymerizing).
- Complex or unknown processes (e.g., electrospinning).

**Note: these are general examples; additional specific considerations may apply to the device under review*

Hypothetical Examples

Scenario 1	**Cardiovascular Device** Metal alloy implant
Scenario 2	**Orthopedic Device** Polymer implant
Scenario 3	**Ophthalmic Device** Alternate processing aid
Scenario 4	**Cardiovascular device** New injection molding machine for a polymer component

Scenario #1

- Device: Bare metal vascular stent
- Device categorization: implant, long-term, contact with circulating blood
- Device materials: metallic (stainless steel, cobalt chrome, nitinol, platinum)

Considerations for Risk Assessment (not limited to):	
Materials	Well-characterized metals, often conforming to standards.
Manufacturing	Surface treatment (e.g., passivation, electropolishing) per FDA-recognized standard, where applicable, & has validated final cleaning process.
Supplemental Info	Engineering testing (e.g., corrosion, nickel elution/leaching) and animal studies.
Conclusion	No expected toxicity, genotoxins, or carcinogens based on the materials or manufacturing. Risk assessment acceptable in lieu of biological or chem-ical testing to address systemic toxicity, genotoxicity, and carcinogenicity.

Scenario #2

- Device: Orthopedic polymer implant
- Device categorization: implant, long-term, tissue/bone
- Device material: common polymer (e.g., PEEK)

Considerations for Risk Assessment (not limited to):	
Materials	Well-characterized material, conforming to an applicable Master File with raw material biocompatibility and manufacturing.
Manufacturing	Process description to confirm no manufacturing chemicals used during manufacture (e.g., all machining done without the use of cutting fluids/lubricants/cleansers other than water).
Conclusion	Biocompatibility risk from manufacturing process can be mitigated. No additional testing.

Scenario #3

- Device: Intraocular lens, acrylic
- Device categorization: implant, long-term, tissue/bone
- Manufacturing Change: Change to surfactant and related process

Considerations for Risk Assessment (not limited to):	
Materials	Safety Data Sheet for new surfactant provided.
Manufacturing	Detailed description of related processes, e.g., extent of contact with the device, amount used, contact temperature, contact duration. Process includes downstream cleaning validation.
Conclusion	The new surfactant and process conditions are unlikely to impact biocompatibility profile. No new testing.

Scenario #4

- Device: Circulatory support system, polymeric component
- Device categorization: External communicating, prolonged, circulating blood contact
- Manufacturing Change: New polymer injection molding machine

Considerations for Risk Assessment (not limited to):	
Materials	No changes to materials, and polymer does not include additives.
Manufacturing	Detailed comparison of molding parameters (e.g., temperature range, shear history experienced by the polymer during injection molding, cooling conditions). Additional performance testing.
Conclusion	Minor differences in the molding parameters are unlikely to impact biocompatibility risk. No new testing.

Biological Risk Assessment – Conclusions

Conclusions & Additional Information

- Biological risk assessment using material and manufacturing information may be used for addressing MMP and systemic endpoints.
- CDRH continues to engage on consensus standards, working groups, and with stakeholders on risk-based approaches to support biocompatibility evaluation of medical devices.
- Focal Point Program includes representatives from each Office and is dedicated to supporting review consistency.
- For device-specific recommendations refer to the applicable device-specific consensus standard or guidance document.
- For specific proposed approaches consider using the Q-Submission program.

Biocompatibility Town Hall Series

Sept 9

Biocompatibility Risk Assessment

- Update on ISO 10993-1: 2025
- Risk Assessments, with examples from:
  - Material Mediate-Pyrogenicity
  - Systemic Toxicity, Genotoxicity, and Carcinogenicity

Sept 23

Chemical Characterization - Extractions

- Test article selection
- Solvent Selection
- Time & Temp
- Volume & Vessel
- NVR
- Particulates
- Replicates
- Examples

Oct 7

Toxicological Risk Assessment

- Overview of ISO 10993-17:2023 and ISO TS 21726:2019
- Key considerations for developing thresholds and screening
- Common deviations

Resources

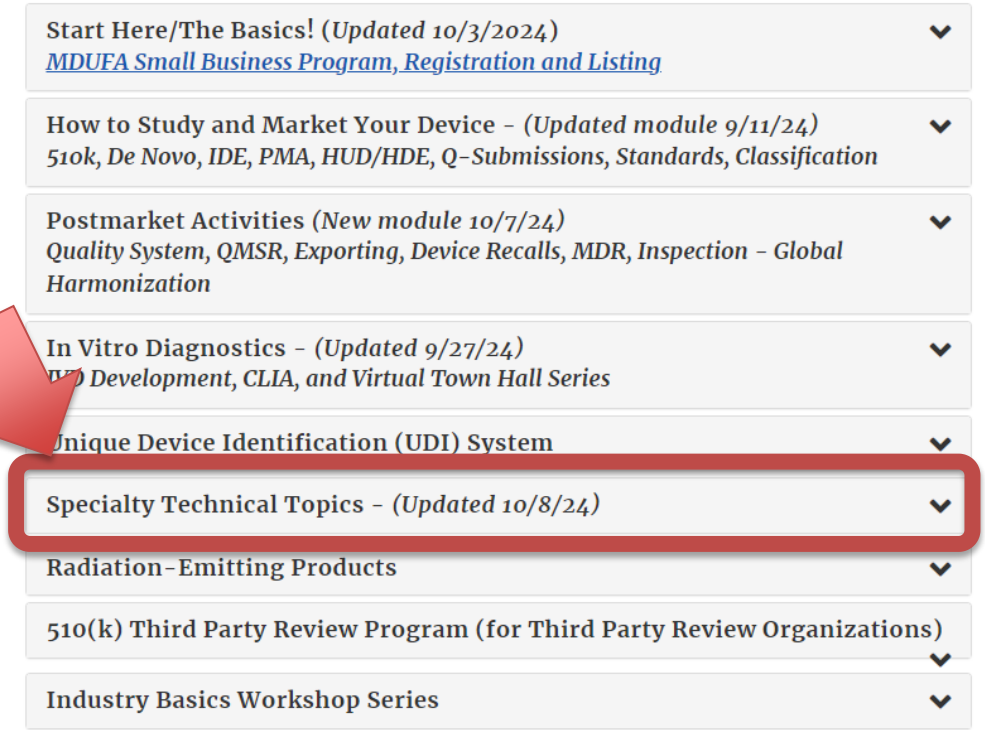
Slide Number	Cited Resource	URL
10	ISO 10993-1:2025 Supplementary Information Sheet (SIS)	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard__identification_no=47116
11, 35	Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" - Guidance for Industry and FDA Staff	www.fda.gov/media/142959/download
20	Borton and Coleman. “Material-mediated pyrogens in medical devices: Myth or reality?” *Altex*. Vol 43(1), 2025, p78-97	www.altex.org/index.php/altex/article/view/2977
27	Medical Devices Containing Materials Derived from Animal Sources – Guidance for Industry and FDA Staff	www.fda.gov/media/87251/download


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Previously Submitted Questions

Thanks for Joining Today!

- **Presentation, Slides and Transcript will be available at CDRH Learn**
  - www.fda.gov/Training/CDRHLearn
- **Additional questions about today's topic**
  - Email: CDRH.Biocomp@fda.hhs.gov
- **Additional questions about today's event**
  - Email: DICE@fda.hhs.gov
- **Upcoming CDRH Events**
  - www.fda.gov/CDRHEvents




FDA
U.S. FOOD & DRUG
ADMINISTRATION