Insight Brief

Biocompatibility: Trends and Best Practices for ISO 10993-1 Compliance

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Biocompatibility and compliance in medical devices

Medical devices that either directly or indirectly contact the human body require rigorous biocompatibility testing compared to devices with little to no biological contact.

ISO 10993-1:2018 *Biological evaluation of medical devices – Part 1:* Evaluation and testing within a risk management process is the cornerstone standard for medical device biocompatibility.[1]Compliance protects patients from adverse effects caused by device materials, chemicals, surface topography, and geometry.

To comply with ISO 10993-1, manufacturers must understand and follow the standard's testing and risk assessment requirements as well as related regulatory guidelines. Manufacturers must also integrate biocompatibility assessments into a broader risk management framework as outlined in *ISO 14971: 2019 Medical devices – application of risk management to medical devices.*[2]

Navigating biocompatibility and risk management requirements is a daunting task for many medical device manufacturers. But with the right approach, it's possible to streamline compliance efforts, reduce time-to-market, and ensure the highest standards of patient safety.

Meeting diverse regulatory requirements

Regulatory bodies often have specific interpretations and expectations around ISO 10993-1. For example, the FDA emphasizes biological testing unless detailed justifications are provided to address all relevant biocompatibility endpoints.[3] The EU's Medical Device Regulation (MDR) emphasizes physio-chemical characterizations.[4]

To ensure the biocompatibility approach complies with global regulatory expectations, manufacturers must adapt their compliance strategies to regional nuances. Collaborative efforts with regulatory consultants and early engagement with authorities can streamline this process.

Material characterization and testing

Material and chemical characterization, outlined in ISO 10993-18, is one of the first steps in evaluating medical device biocompatibility. First, scientists evaluate available information to determine if the device requires analytical testing. If so, they engage in material characterization and testing. That involves first identifying materials in the device, then evaluating their potential biological risks, and assessing the physiochemical impact of downstream processes such as manufacturing, packaging, and sterilization.[5]

Material characterization relies on diverse data sources that vary in complexity based on the device's risk profile. Sources typically include technical datasheets, safety datasheets, and certificates of analysis, as well as direct chemical analyses like extractables and leachables (E&L) testing.

To maintain quality through the entire device lifecycle, manufacturers must implement strict qualification and change notification procedures for materials vendors and suppliers. Doing so also helps mitigate supply disruptions.

Integration with risk management

Many manufacturers struggle to align biological evaluations with comprehensive risk assessments as outlined in ISO 10993-1.[1] Lack of integration may create gaps in documentation or unanticipated regulatory pushbacks.

To lower the risk of these scenarios, we recommend manufacturers develop a biological evaluation plan (BEP) as part of the risk management process. The plan helps ensure testing aligns with identified risks, minimizes the risk of regulatory deficiencies, and reduces the odds of unnecessary biocompatibility testing.

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Data reporting and interpretation

Interpreting and reporting biocompatibility data in a biological evaluation report (BER) is a critical yet complex task. Documentation errors or insufficient justifications for test omissions can lead to delays or rejections during regulatory submission reviews. Best practices include employing cross-functional teams to review test data and leveraging checklists to verify compliance with reporting standards, among others.

Case study: How a new testing approach helped a device company resolve FDA deficiencies

CHALLENGE:
A company with an implantable neurological device received FDA deficiencies due to equivocal results in their exhaustive extraction testing and toxicological risk assessment. The FDA's interpretation of ISO 10993-18 sets rigorous standards for exhaustive extraction which were challenging for the device materials to meet.

SOLUTION:
To avoid unproductive follow-on testing, IQVIA MedTech identified an alternative pathway to address the systemic biological endpoints. IQVIA MedTech advised the company to conduct in vivo systemic toxicity studies, in vitro genotoxicity testing, and a rationale based on the device's materials and manufacturing methods.

SUCCESS:
The alternative approach successfully addressed systemic toxicity and carcinogenicity endpoints without further chemical characterization testing. It also fully resolved the FDA deficiencies on exhaustive extraction and toxicological risk assessment.

Case study: Expanding a manufacturing rationale to meet Notified Body expectations

CHALLENGE:
An orthopedic device company with a metallic implant obtained 510(k) clearance from the FDA using a brief paper-based biocompatibility rationale based on raw materials and manufacturing processes. When submitting documentation for CE Marking, the company received nonconformities from the European Notified Body BSI, which requested full evidence of evaluations or justification for each biological endpoint per ISO 10993-1.

SOLUTION:
To meet BSI's expectations, IQVIA MedTech expanded the paper-based rationale into an ISO 10993-1-compliant biological risk assessment. The risk assessment evaluated the raw materials of the device, the manufacturing processes, and the effectiveness of surface-finishing steps and downstream cleaning in removing manufacturing residues. The risk assessment also incorporated real-world clinical experience with the device (i.e., post-market surveillance data).

SUCCESS:
IQVIA MedTech's risk assessment resolved the biocompatibility nonconformities without the need for additional testing.

What's next for biocompatibility evaluation?

Medical device manufacturers must navigate a complex maze of requirements to prove a device is biologically safe. As understanding of biocompatibility evolves, ISO 10993-1 will become even more challenging to follow.

For example, calls for alternatives to ethylene oxide (EtO) sterilization are gaining momentum for some devices.[6] Changing the medical device sterilization method may impact its biocompatibility. Therefore, these changes will trigger a wave of new biological evaluations.

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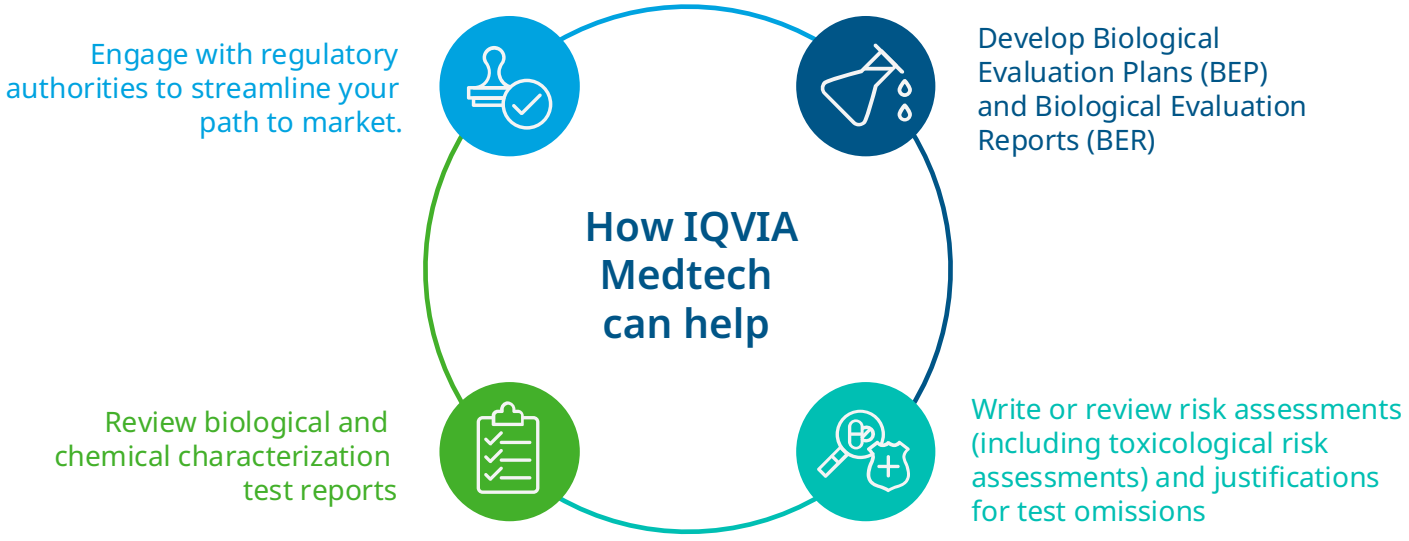
Regulatory bodies are also responding to reports of health concerns related to per- and polyfluoroalkyl substances (PFAS), which are used in a wide array of medical devices.[7] PFAS material alternatives must be identified and then supported by biological evaluation activities, including chemical characterization, risk assessments, and/or biocompatibility testing. To ensure the new materials do not adversely impact biological safety.

The FDA's draft guidance formalizes the agency's recommendations for chemical characterization.[8] However, the draft guidance may prompt testing laboratories and medical device companies to adjust their chemical characterization practices, increasing development time and agency interaction. An experienced consultant can work with all parties to help streamline the path to both compliance and submission.



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About the authors

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Dr. Allen is a biocompatibility expert and former FDA medical device reviewer with 9 years of experience in the medical device industry. Dr. Allen has extensive experience in biological evaluation including biological risk assessment, biological testing, hemocompatibility evaluation, and rationales based on materials and manufacturing processes. As a biocompatibility consultant, Dr. Allen helps clients to develop and execute efficient biocompatibility evaluation strategies that avoid unnecessary testing. Dr. Allen is also active in the international biocompatibility community, providing biocompatibility regulatory recommendations to a global audience.

Prior to MCRA, Dr. Allen spent 3 years at FDA in the Center for Devices and Radiological Health (CDRH). Dr. Allen's work at CDRH included lead review and biocompatibility review in the Division of Cardiovascular Devices (now known as OHT2), where he reviewed vascular and endovascular devices. Dr. Allen also represented the FDA's view on biocompatibility evaluation at cardiovascular device conferences. Prior to serving as a lead reviewer, Dr. Allen served as an AIMBE Scholar at FDA, focusing on strategic projects for the Office of Device Evaluation (now known as OPEQ), including device reclassifications from class III to class II. Dr. Allen received his B.S. and Ph.D. from the University of Pittsburgh in bioengineering, where he researched the application of absorbable polymers in synthetic vascular graft designs.

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