ISO 10993-1 and Biocompatibility Requirements for Medical Devices

Empowering Trust®

Executive Summary

The U.S. Food and Drug Administration (FDA) requires device manufacturers seeking pre-market approval under its 510(k) program to submit testing data verifying the biocompatibility of any device or material that comes in direct or indirect contact with a patient. Yet, according to the FDA, as many as one-third of 510(k) submissions provide inadequate information regarding device biocompatibility, or failed to provide any biocompatibility data at all.[1] For device manufacturers, these shortcomings often result in the rejection of a 510(k) submission or best case, an extended delay in its review by the FDA.

ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process, provides detailed guidance on the assessment of potential biological hazards associated with all types of medical devices, including active, nonactive, implantable and non-implantable. Most recently updated in 2018, the current version of the standard also places a greater emphasis on the use of chemical characterization and in vitro modeling in situations where these methods provide information as valid or as relevant as that generated by in vivo testing.

In this white paper by UL, we'll provide an overview of the structure and requirements presented in the latest version of ISO 10993-1 and provide details on the biological safety evaluation process set forth in Annex B of the standard.

What is biocompatibility?

Modern medical devices are comprised of a diverse range of materials and components, each with their own unique physical and chemical characteristics. Although many of these materials present a minimal risk when incorporated into products intended for general use, their inclusion in medical devices significantly expands the scope of potential safety considerations. These can include the leaching of device materials due to heat or wear during normal operation or the migration of chemicals from the device.

Additional material risks associated with medical devices can also be introduced through manufacturing and post-production processes and usage that adversely affect components and materials. For example, contact with lubricants or other chemical substances during production or maintenance can compromise the chemical integrity of the device. Similarly, extended use can degrade some components, while sterilization and disinfection techniques may increase potentially harmful chemical emissions.

In patients, adverse biological reactions to implantable medical devices can range from irritation, pain or discomfort to developmental or reproductive effects to the outright rejection of the device itself. Even in cases in which devices have limited, short-term contact with patients, such as contact with skin or with internal organs and tissues during a surgical procedure, biological reactions can produce allergic reactions that can compromise patient health.

In the context of medical devices, biocompatibility is defined as "the ability of a medical device or material to perform with an appropriate host response in a specific application."[2] More specifically, biocompatibility testing is intended to provide assurances that the benefits associated with the use of a specific medical device are not impacted by unintended adverse biological effects attributable to the device or its materials.

About ISO 10993-1:2018 and the risk management process

The ISO 10993 series of standards currently consists of more than 20 individual standards that address various aspects of biocompatibility in medical devices. The standard ISO 10993-1:2018, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management system is intended to address the framework of the evaluation and testing process used to assess medical device biocompatibility.

Published in October 2018, the Fifth Edition of ISO 10993-1 represents a significant shift from the approach taken in earlier editions of the standard. ISO 10993-1:2018 no longer prescribes a list of specific biocompatibility tests applicable to all types of medical devices. Instead, the standard now focuses on the biological evaluation of a medical device or medical device material within the framework of a risk management process.

A guidance issued by the U.S. FDA provides a useful explanation of the biocompatibility risk management process as prescribed in ISO 10993-1:

"Such a process should generally begin with assessment of the device, including the material components, the manufacturing processes, the clinical use of the device including the intended anatomical location, and the frequency and duration of exposure. Considering this information, the potential risks from a biocompatibility perspective should be identified…Once the risks have been identified, the sponsor/expert should assess what information is already available regarding those risks and identify the knowledge gaps that remain. Considering the potential biological impact, a plan should be developed to address the knowledge gaps either by biocompatibility testing or other evaluations that appropriately address the risks. The interpretation of the overall biocompatibility evaluation should be considered in the appropriate benefit-risk context."[3]

The risk management process presented in the current edition of ISO 10993-1 recognizes the inherent complexity in the design, development and manufacture of medical devices, and the range of factors that can impact biological compatibility. These factors include device geometry and design, the chemical and physical properties of raw and finished materials, the manufacturing process, intended clinical applications and uses, and host response.

Given the dynamic combination of factors with an infinite number of variables, prescribing specific tests is neither practical nor likely to provide conclusive results. It can also lead to unnecessary testing that is costly and time-consuming, thereby contributing to potential delays in the introduction of innovative medical devices to the market.

Instead, the risk management process in ISO 10993-1 places on medical device manufacturers the full responsibility to:

1. Thoroughly and carefully identify all of the potential biological risk factors unique to their device
2. Evaluate the extent of the potential risk attributable to those factors
3. Determine the steps necessary to mitigate those risks that are inconsistent with patient health and well-being

At the same time, the current edition of ISO 10993-1 recognizes that advances in scientific research often outpace the science behind current standards. This is especially the case with physicochemical characterization testing, which has increasingly demonstrated its ability to reliably predict chemical interactions. Hence, as part of the risk assessment process, the standard now encourages the use of chemical testing and other predictive in silico models and in vitro methods when such techniques have been demonstrated to provide relevant test results that are comparable to those obtained through *in vivo* testing.

Other key changes in ISO 10993-1:2018

In addition to the emphasis on a risk management process, ISO 10993-1:2018 also incorporates the following changes from the prior edition (ISO 10993-1:2009):

Terms and definitions: A total of 21 new terms and definitions have been added to Clause 3 – terms and definitions. The terms and definitions added to the standard include geometry device configuration, nanomaterial, physical information, chemical information, no contact and transitory contact.

Contact issues: Clause 5 of ISO 10993-1:2018 adds two additional categories of medical devices. Non-contacting devices include those medical devices (or components) that have neither direct nor indirect contact with the body, and where biocompatibility information would not be necessary. Transitory-contacting medical devices are those with limited exposure to the body such as lancets, hypodermic needles and capillary tubes that are used for less than one minute (and) ... generally would not require testing to address biocompatibility.

Nanomaterials: The current edition of the standard also includes additional information on the evaluation of nanomaterials and absorbable materials.

Biocompatibility of gas pathways: References to the ISO 18562 series of standards, Biocompatibility evaluation of breathing gas pathways in healthcare applications, are now incorporated throughout the standard.

Annex A: Annex A, "Endpoints to be addressed in a biological risk assessment", provides a more detailed framework for the development of a biocompatibility evaluation plan for medical devices, based on the category of device and the nature of contact the device has with the body. Table A.1 in the Annex now includes endpoints for six additional characteristics, including:

1. physical and/or chemical information;
2. material mediated pyrogenicity;
3. chronic toxicity;
4. carcinogenicity;
5. reproductive/development toxicity; and
6. degradation.

These additions bring the total number of endpoints to be addressed to 15.

Annex B: Formerly titled "Guidance on the risk management process", Annex B is now titled "Guidance on the conduct of biological evaluation within a risk management process". The revised Annex B now incorporates content from its predicate standard ISO TR 15499-2016, which bears the same title as the now revised Annex B.

Editing: Finally, ISO 10993-1:2018 reflects significant editing changes throughout the document from the prior version to improve readability and comprehension.

The biological safety evaluation process

As previously noted, ISO 10993-1:2018 provides a framework for the biological evaluation of medical devices based on a risk management process. Appropriately, the standard references ISO 14971, Medical devices – Application of risk management to medical devices, for many of the specific requirements applicable to the biological evaluation of medical devices.

Importantly, both standards specify that biological evaluation activities "shall be planned, carried out, and documented by knowledgeable and experienced professionals." In many cases (especially for smaller companies or start-ups without the requisite expertise), compliance with this requirement means that device manufacturers will need to work with an independent consultant or third party testing organization to develop and execute the critical aspects of a biological evaluation of their devices.

Annex B of ISO 10993-1 provides detailed guidance on conducting a biological evaluation of a medical device within a risk management context consistent with the requirements of the standard. In summary, the process described in Annex B involves three distinct aspects, as follows: 1) the biological evaluation plan (BEP); 2) risk assessment and testing; and 3) the biological evaluation report (BER).

The biological evaluation plan (BEP)

ISO 10993-1 requires that device manufacturers (or their designated contract professional) develop a formal, written biological evaluation plan (BEP) to meet the requirements of the standard. Annex B makes clear that "simply planning to conduct testing against all of the aspects of biocompatibility" does not meet the threshold established in the standard.

According to Clause B.2.2 of the Annex, the biological evaluation plan (BEP) should, at a minimum, include specific information in each of the following areas:

- Arrangements for gathering of applicable information from published literature, in-house and supplier data, and other sources as required to conduct a thorough risk analysis;
- Arrangements for conducting the biocompatibility evaluation, including any specific technical competencies requirements relevant to the medical device;
- Arrangements for the review and approval of the BEP as part of the overall design control process;
- Arrangements for the review of the evaluation's conclusions and the approval of any additional testing that may be required; and
- Arrangements for the final review and approval of the outcomes of the biological risk assessment, including any applied risk control measures, and the documentation and disclosure of any residual risk.

Risk assessment and testing

Annex B defines risk assessment as "the combination of the processes of risk analysis in which risks are identified and estimated and risk evaluation in which risks are evaluated to identify those which require mitigation (risk control)."

Risk analysis

According to Annex B, risk analysis is "the process of identifying the specific hazards and assessing their significance," and includes the "identification and characterization of the indirect and direct tissue-contacting materials and components of the medical device ... on the final form of the medical device in its manufactured state."

An essential part of the risk analysis is the characterization of the physical and chemical material properties of the device, its components, and its materials that are relevant to the biological safety of the device. Some of the factors that fall under the scope of such a characterization include:

- Wear, load and fatigue, especially in load-bearing medical devices;
- Friction and the potential for associated irritation;
- Chemical interactions in material combinations in the device;
- Thermal degradation;
- Manufacturing processes that can result in environmental stress cracking, morphological changes or degradation;
- Interactions with the anticipated use environment, such as bodily fluids and acids, and decontamination processes; and
- Transportation and aging

This section of Annex B notes that materials information may be obtained through a review of literature, vendor or in-house data, or through a comparison with existing products that utilize the same materials and manufacturing process as the medical device being evaluated.

The chemical characterization of the device typically involves a further assessment of the toxicological risks of the device's materials, and includes an analysis of the nature of the toxic effects and the dose response relationship regarding those effects. Specific toxicity endpoints to be considered as part of the chemical characterization should include:

- Systemic toxicity
- Subacute toxicity
- Genotoxicity
- Chronic toxicity
- Carcinogenicity

Annex A of ISO 10993-1 provides additional details on the relevant toxicity endpoints that should be considered as part of the chemical characterization process.

Depending on the device category, additional testing in the following areas may also be required:

- Cytotoxicity
- Sensitization
- Irritation or intracutaneous reactivity
- Implantation effects
- Hemocompatibility
- Pyrogenicity

Risk estimation

Risk estimation is the process of "assigning values to the probability of occurrence of harm and the severity of that harm." Estimating the probability of occurrence from chemical toxicity is based in large part on the previous assessment of the chemical characterization of the medical device and the nature and dose response relationship of any toxic effects, while estimating the severity of harm depends on the nature of the response to those effects.

A complete and thorough review of all available information, including published literature, results of previous in-vivo testing, in-house data and any documented clinical history of the device and its component materials, may provide sufficient information to reasonably estimate the effects from both the physical and chemical characteristics of the device, as well as the severity of harm that may be attributable to those characteristics. This section of Annex B stresses the importance of such a review to identify those specific areas where currently available information is sufficient to assess the probability and severity of harm. This approach is intended to limit the scope of any further testing to those specific characteristics for which available knowledge and information is insufficient to estimate risk.

Annex B also reiterates that the amount of data required for risk estimation varies depending on the intended use of the medical device being evaluated. For example, data requirements and the depth of analysis may be less stringent for devices that have limited contact with patient skin or tissue, compared with devices whose intended use requires prolonged patient contact.

Risk evaluation

As the term implies, risk evaluation marks the point in the biological evaluation process where the information compiled in the risk analysis and risk estimation phases is evaluated for its significance in terms of risk and for determining the steps to take to control that risk.

This section of Annex B emphasizes that a final outcome of a risk determination regarding the biocompatibility of a medical device must consider the whole medical device and all of its components, and that the determination is limited "for a particular material in relation to a defined set of circumstances, which include the purpose for which it is used and the tissues with which it comes in contact."

Further, the risk evaluation "should be conducted by assessors with the necessary knowledge and expertise to determine the appropriate strategy for the evaluation and ability to make a rigorous assessment of the available data and to make sound judgments on the requirements for any additional testing.

Risk control

Risk control, the final phase of the risk assessment process, involves identifying and implementing measures to reduce the identified risks. Most frequently, changes in the design of the medical device can help to mitigate or eliminate the risks that have been identified. Some possible design change strategies include:

- Changes that avoid more hazardous exposure routes, or that reduce patient exposure time;
- Changes that optimize the shape and surface properties of the device to decrease the likelihood of reduced blood flow;
- Changes that help to prevent device failures, such as particulation or coating; delamination, that could produce adverse biological responses;
- Changes to device materials that could reduce the risk of toxicity; and
- Changes to the production process to reduce or eliminate process additives or hazardous residues.

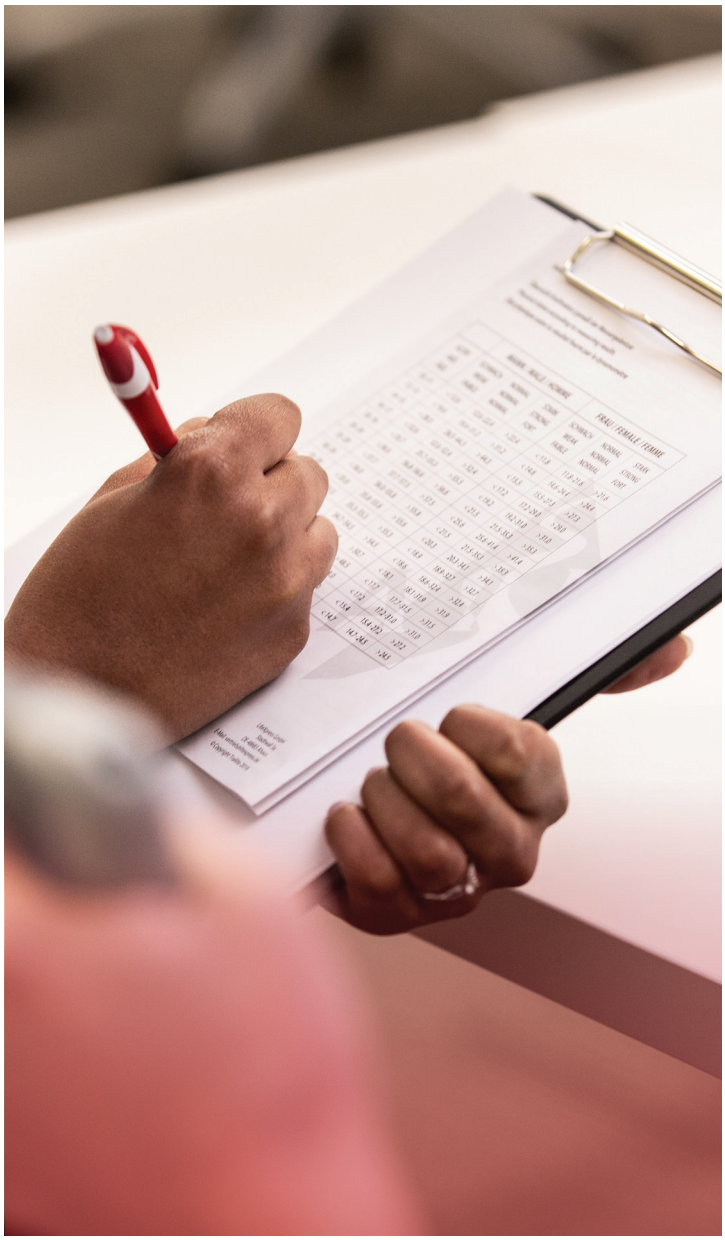
This section of Annex B also encourages manufacturers to explore alternatives to additional testing whenever possible to mitigate risk. Some possible alternatives include using available testing data to develop more accurate risk estimates than those based on worst case assumptions, or providing users with clear warnings or counterindications regarding the device's use.

The biological evaluation report (BER)

The final aspect of the biological safety evaluation process for a medical device is the preparation of the biological evaluation report (BER). The BER is an essential document in submissions for device approval or certification by the relevant regulatory authority, as it helps support a manufacturer's claim of compliance with the risk management requirements of both ISO 10993-1 and ISO 14971.

At a minimum, the BER should include:

- Detailed information on the physical and chemical characteristics of the device and its materials that come in direct or indirect contact with patients;
- Information on the processing and manufacturing process that could potentially introduce contaminants;
- A review of available toxicity and prior use data relevant to the medical device and its components;
- Reports of all biological safety testing conducted as part of the risk assessment of the device; and
- An assessment of the risk assessment results.



Post-production considerations and other issues

Annex B of ISO 10993-1 acknowledges that "the processes of risk assessment are based on human judgment using the available information, supplemented by biological testing where required." As such, it stresses the importance of reviewing and updating the biological safety evaluation of medical devices placed on the market to reflect new information that may become available, such as from subsequent biocompatibility safety literature or research or from reports regarding the safety or performance of the device in actual clinical use.

UL's approach to biocompatibility testing of medical devices

UL offers medical device manufacturers and health sciences companies testing and evaluation services that address the requirements of the ISO 10993 series of biocompatibility standards, as well as testing to the material characterization requirements of ISO 10993-18. UL's team of qualified, experienced chemists, biologists and toxicologists evaluate the safety of medical device in a systematic approach. And our organizations medical device biocompatibility testing capabilities combined with our subcontractor network allow manufacturers to work with a single testing laboratory to meet the regulatory requirements for most of the world's medical device regulators.

Summary and Conclusion

Ultimately, few medical procedures are completely risk-free. When it comes to the development of medical devices, the risks associated with their use must be balanced against the potential health benefits that their use might provide to a patient. Therefore, it is important to remember that the interpretation of the results of a biological safety evaluation must be considered within the appropriate benefit-risk context.

Based on established and widely accepted risk management practices, ISO 10993-1 provides a logical and resilient framework within which to assess the biological safety of a medical device and to minimize the potential risk to patients. At the same time, the task of assessing biological safety and bringing safe and effective medical devices to market is not the job of one person. To be effective, it must instead be a collaborative effort between device manufacturer developers, testing laboratories, toxicologists, biologists and chemists.

At a time when healthcare systems around the world are straining to protect people from the effects of the COVID-19 pandemic, collaboration and cooperation are essential in supporting efforts to bring advanced devices and therapies to market.

For more information on ISO 10993-1 and how UL's biocompatibility testing services can support your company's efforts to develop safe and innovative medical devices., email medical.inquiry@ul.com or visit UL.com/healthcare.

End Notes

1. "Analysis of Pre-Market Review Times Under the 510(k) Program," U.S. Food and Drug Administration, Center for Devices and Radiological Health, November 9, 2011. Web. 1 February 2020. https://www.fda.gov/media/92002/download.

2. "ISO 10993-1:2018, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process." International Organization for Standardization (ISO). Web. 1 February 2020. https://www.iso.org/standard/68936.html (abstract).

3. " 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" June 16, 2016. Web. 1 February 2020. https://www.fda.gov/media/85865/download.