BIOLOGICAL EVALUATION OF MEDICAL DEVICES – ASSESSMENT OF BIOCOMPATIBILITY UNDER ISO 10993-1:2018

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With the introduction of the Regulation (EU) 2017/745 on medical devices, also known as Medical Device Regulation (MDR), manufacturers face enhanced requirements to obtain CE marking for their products within the European Union. In combination with the revision of the international standard ISO 10993-1, *Biological Evaluation of Medical Devices – Part 1: Evaluation and testing within a risk management process* in 2018, this applies to preclinical device testing as well. Consequently, the assessment of biological safety of medical devices increasingly gets into the focus of the notified bodies.

BIOLOGICAL SAFETY EVALUATION – WHAT AND WHY?

The importance of the biological safety evaluation is based on various risks impacting the biological response of the human body to a medical device: imagine implant rejection induced in response to an incompatible material or other undesired biological body reactions, like coagulation of blood. Also, potential degradation products or toxic leachables from materials, which are absorbed and physiologically distributed, are biological risks associated with the use of a medical device. Nevertheless, the absence of these unwanted reactions does not necessarily entail biocompatibility. In accordance with ISO 10993-1:2018, a medical device or material is biocompatible when it is able "to perform with an appropriate host response in a specific application." This definition implies that the intended purpose is essential to consider, leaving the question of to what extent a host response is appropriate during interaction with a medical device. Osborn and Newesely classified the compatibility of a biomaterial into three categories: biotolerant, bioinert and bioactive.[1,2] Biotolerant material is endured by the body for several months up to years, however not without tissue reactions, which are commonly controlled by medical treatment. Bioinert material does not initiate a response or interact with the biological tissue at all. Bioactive material is able to elicit specific cell or tissue responses with the aim of optimizing the function of the medical device. With this classification in mind, it becomes obvious that an appropriate host response is either intended or, if unwanted, capable of being controlled in order to enable the medical device to support the treatment in a safe way. In short, to demonstrate the biocompatibility of a medical device, the response of the hosting tissue to the introduced material within the intended purpose of the device needs to be considered.

THE ISO 10993-1:2018 AS A TOOL TO EVALUATE THE BIOLOGICAL SAFETY OF A MEDICAL DEVICE

In the MDR, the biological safety evaluation is part of the general safety and performance requirements addressed in Annex I, Chapter II regarding design and manufacture.[3] Specifically, article 10 deals with the chemical, physical and biological properties of medical devices. The most widely used standard to assess the potential biological risks of medical devices in accordance with the aforementioned requirements is the ISO 10993 series. This series consists of 20 standards developed by the ISO Technical Committee 194, *Biological and clinical evaluation of medical devices* (ISO/TC 194). ISO 10993-1:2018 is the fifth edition cancelling and replacing ISO 10993-1:2009 and incorporating the technical correction from 2010 (ISO 10993-1:2009/Cor.1:2010). It is generally accepted as state of the art although it is not harmonized. The main changes from the previous version involve the replaced Annex B with "Guidance on the conduct of biological

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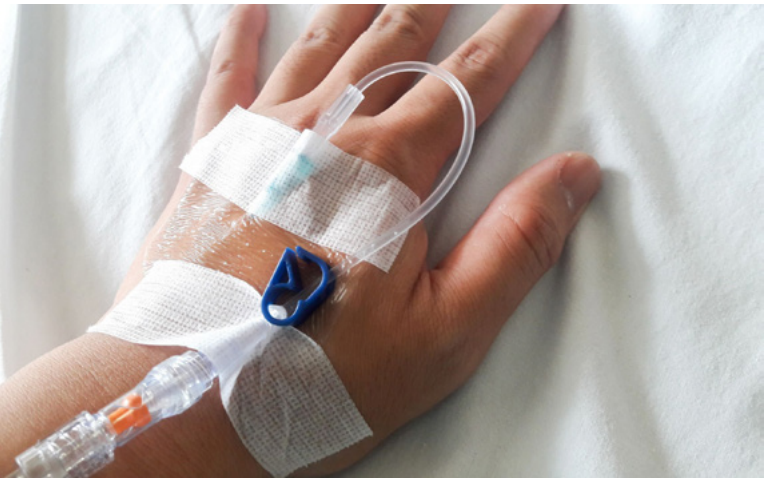

evaluation within a risk management process," which was formerly known as ISO/TR 15499. Furthermore, additional information on the evaluation of non-contacting and transitory-contacting medical devices as well as nanomaterials and absorbable materials was introduced. Also, gaps in the former standard have been filled with reference to the device-specific standard series ISO 18562, *Biocompatibility evaluation of breathing gas pathways in healthcare applications.* The first part of the series, ISO 18562-1:2017, covers general principles regarding biocompatibility assessment of medical device materials, which make up the gas pathway as a risk-based approach.

The main discussed change in ISO 10993-1:2018 is, however, the revised Annex A, *Endpoints to be addressed in a biological risk assessment*, which includes Table A.1 for categorization of the medical device and device-specific endpoint evaluation. Additional columns were introduced to this table, which comprise the following endpoints: material mediated pyrogenicity, chronic toxicity, carcinogenicity, reproductive/developmental toxicity and degradation. All endpoints to be considered are now indicated with E instead of an X, like it was before. The intention behind this modification is to detach from testing following a checkmark approach and perform an endpoint evaluation to determine if additional data sets are needed before testing is conducted. This aims to exploit available published and unpublished information as much as possible to save time and resources as well as to reduce redundant testing and unnecessary use of animals. The latter is especially important in line with the Directive 2010/63/EU on the protection of animals used for scientific purposes[4] and ISO 10993-2[5] which specifies animal welfare requirements in regulatory testing for biological safety. Adopting the 3R-principle of Russell and Burch[6], the main aims are to reduce tests that involve animals and reduce animals within tests. In relation, information concerning a specific endpoint should be acquired by validated *in vitro* rather than *in vivo* tests, if it is not available from other sources. Currently, manufacturers still perform testing according to the checkmark approach and submit the test reports without illustrating the coherence between the individual results, which commonly leads to deviations raised by the notified bodies.

CATEGORIZATION OF THE MEDICAL DEVICE AND CHARACTERIZATION OF ITS MATERIALS

The main question remains: How is the evaluation within a risk management process achieved and how does it help to save time, resources and redundant testing? It all starts with the categorization of the medical device which depends on the nature and duration of body contact. In general, biocompatibility of all materials that come into direct or indirect contact with a patient's body during intended purpose, or a user's body if the device is intended for protection, needs to be demonstrated. Accordingly, a biological safety evaluation is not applicable for non-contacting devices, like software applications or blood-collection tubes. The same applies to medical devices that have only transitory contact with the body (< 1 minute) such as lancets or hypodermic needles. An exception is the use of materials such as coatings or lubricants, which may remain in contact with body tissues after removal of the transitory contacting medical device. For these materials, a thorough biological safety assessment is necessary. When defining contact duration, special consideration should be given to cumulative duration by repeat use. A famous example is the use of a device for hemodialysis. A single treatment lasts a couple of hours but is needed three to four times a week for the rest of the patient's life. This expands the contact duration from limited to long-term exposure for which chronic toxicities need to be evaluated. This example clearly demonstrates how the categorization of a device facilitates appropriate tests selected in accordance with

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Table A.1 of ISO 10993-1:2018. Beyond the endpoints indicated within the row assigned to the respective categorization, device-specific evaluation of additional endpoints should be considered. Medicated nail polish, for example, may be categorized as a surface medical device on intact skin. As such, cytotoxicity, sensitization and irritation/intracutaneous reactivity should be evaluated in accordance with Table A.1. However, since the polish might be absorbed by the skin, evaluation of systemic toxicity contributes to biological safety as well.

After device categorization, material characterization is conducted which is considered "prerequisite information needed for risk assessment".[7] The actual conduction of this step is ensured by a newly introduced column in Table A.1, "physical and/or chemical information," which implies quantitative as well as qualitative characterization of all used materials that potentially come into direct or indirect contact with the human body. This column is the only one marked with an "X", however this does not necessarily imply that testing needs to be performed, but that information has to be acquired. The relevant information may be gathered from material safety data sheets, certificates, clinical data, previous testing as well as a literature research. Consideration should be given not only to the medical device itself but also to processing aids like intended additives, colorants, process residues or contaminants, etc. Also, the impact of packaging, sterilization, storage and transport on biocompatibility should be taken into account. Regarding sterilization, special attention was given to ethylene oxide residuals, for which the evaluation is covered by its own standard, ISO 10993-7. Actual testing is usually required to evaluate the interactions between materials or specific impact of sterilization or packaging on biocompatibility.

The device's physico-chemical, morphological and topographical characteristics – including porosity, shape, surface morphology and particle size – need to be examined in accordance with ISO/TR 10993-19:2006. In addition, the chemical characterization provides information about the specific substances in the device, including which of them are released during the intended application. It is performed in accordance with ISO 10993-18 on chemical characterization of materials or, if nanomaterials are included, with ISO/TR 10993-22. Recently, the revised ISO 10993-18:2020 was published which cancels and replaces the first edition ISO 10993-18:2005. The main changes include:

- A greater integration and harmonization with other standards of the series
- A revised and expanded chemical characterization process flowchart
- A strengthened explanation that analytical testing is not necessarily required
- Clarified testing approaches unique to chemical characterization

In addition, definitions were added as well as informative annexes on general principles, vehicle extraction and the analytical evaluation threshold. Furthermore, considerations related to analytical method qualification are discussed.

As mentioned earlier, one intention of the revised ISO 10993-1:2018 is to reduce redundant testing and unnecessary use of animals. The chemical characterization is a crucial step to achieve this aim, especially in products where the release of substances from the materials, known as extractables and leachables, has been excluded. If patients are not exposed to substances that may be introduced to the systemic circulation, waiving certain tests for toxicokinetics or systemic toxicity is justified. Nevertheless, consideration should be given to potential release of unintended degradation products, which are covered by no less than four standards in the ISO 10993 series, indicating its importance. ISO 10993-9 describes general principles and 10993-13, 10993-14 and 10993-15 specify the evaluation for degradation products from polymers, ceramics and metals, respectively. Where the release of extractables and/or leachables has not been excluded, the allowable limits for release of these

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substances under worst case conditions need to be established in accordance with ISO 10993-17:2002, a standard currently approved for revision (ISO/AWI 10993-17). Where the bioavailability of leachable components is below an acceptable toxicological threshold, a waiver for toxicokinetics or systemic toxicity testing may be justified. The omission of tests is further justified if the material characterization reveals an equivalency to an already-marketed device. In this case, a history of safe clinical use of the combination of all materials, chemicals and processes in the intended application without changes to the physical properties needs to be demonstrated in accordance with Annex C of ISO 10993-18:2020. After conducting the material characterization, the composition and properties of the medical device and its materials should be sufficiently known in order to evaluate the endpoints related to the respective device in its category. Like for material characterization, information of specific toxicities may be acquired from various sources in addition to an objective literature search in accordance with Annex C of ISO 10993-1:2018.

BIOLOGICAL EVALUATION WITHIN A RISK MANAGEMENT PROCESS

Biological safety is defined as "freedom from unacceptable biological risk in the context of the intended use".[7] Therefore, it seems obvious that the biological safety evaluation is part of a risk management process conducted according to the requirements of ISO 14971. As such, the acquired information related to the biological safety of the medical device is subject to biological risk assessment. Material characterization is essential for the identification of toxicological hazards, including additives, processing aids, substances released during product use or others that potentially cause an adverse biological reaction. The evaluation of predefined biological endpoints in line with Table A.1 aids in the identification of specific toxicological hazards dependent on the medical device category.

After hazard identification, risks are estimated through the combination of the probability of occurrence of harms and the severity of these harms. Finally, these risks are evaluated, and risk control measures are implemented and verified. The outcome of the biological risk assessment determines whether additional testing is required. In general, testing should only be performed if the existing data, including data related to material characterization, is insufficient to conduct a risk assessment. If existing data leads to the conclusion that risks are acceptable, further support of biological safety is not necessary. In addition, if risks are not acceptable, further testing should not be conducted. This risk-based approach comes with further advantages besides the reduction of biological safety testing. For example, if a specific endpoint was evaluated to be relevant for a medical device, the risk management process enables its consideration within risk control with the aim of decreasing the probability of this harm to reoccur. As a result, the residual risk might be acceptable without extensive reevaluation or even retesting.

BIOLOGICAL EVALUATION AS A THREE-TIERED APPROACH

In accordance with ISO 10993-1:2018, the biological evaluation should be structured as a three-tiered approach. First, as a requirement of the risk management process in accordance with both ISO 10993-1 and ISO 14971, a biological evaluation plan (BEP) should be established by an expert assessor possessing the necessary knowledge and experience. This can also be a group of assessors comprised of specific experts for research and development, medical experts or quality and risk management, among others. The BEP provides a detailed description of the medical device including all relevant information about processing, packaging, transportation and storage. Additionally, the plan outlines all available information leading to the identification and characterization of hazards and exposures including the methods for the generation of this knowledge. Based on this information, the biological risk assessment is conducted, which is essential to determine a risk-based testing plan. Aside from documentation of the tests to be performed, a justification for omission of further testing is important, as this demonstrates compliance to ISO 10993-1:2018. Two common deviations are related to the BEP: not having a BEP at all and lack of training or experience in the curricula vitae of the authors or reviewers. It should be clearly demonstrated that the evaluators are able to "interpret its [ISO

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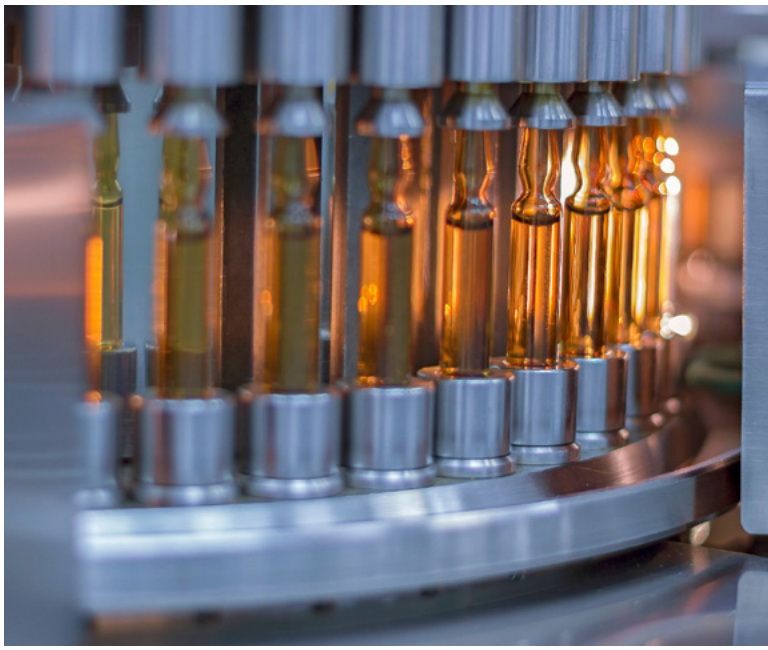
10993 series] requirements and judge the outcome of the evaluation for each medical device, taking into consideration all the factors relevant to the medical device, its intended use and the current knowledge of the medical device provided by review of the scientific literature and previous clinical experience".[7]

It is both essential and difficult to document detailed information from different sources and to determine how this information is evaluated in a risk-based approach leading to a conclusion about biological safety. As part of the technical documentation, the related requirements are addressed in Annex II of the MDR (Article 6.1.b). Accordingly, the documentation needs to "be presented in a clear, organized, readily searchable and unambiguous manner." Where testing was conducted, "detailed information regarding test design, complete test or study protocols, methods of data analysis, in addition to data summaries and test conclusions" needs to be included. A description of the test sample is essential and must pertain to the final medical device or representative samples from the final device or material processed in the same manner as the final medical device (including sterilization, packaging, etc.). Furthermore, the application of standardized and/or validated test methods in accordance with common laboratory quality practice (e.g. GLP, ISO/IEC 17025) should be demonstrated. Where testing was not conducted, "the documentation shall incorporate a rationale for that decision".[3] Actually, the way the biological evaluation is documented can result in one of the most common deficiencies when submitted to notified bodies. When the results are presented without assessment of coherencies or a clear final conclusion, it is difficult for the reviewer to judge which residual toxicological risks exist and whether the device is actually biologically safe in its intended application. It may be advantageous to retrieve feedback for the BEP from the notified bodies before initiation of any testing. Within the scope of a change review, the manufacturer may be able to ensure the validity of test procedures (or the justifications for omitting testing), and of the scientific rationales used for risk mitigation. Furthermore, the feedback may be valuable if proposing non-standardized methods for sample preparation or testing. In the light of the upcoming MDR, however, a change review may be time intensive.

The second step in the three-tiered approach is the actual testing in accordance to the BEP. Finally, all relevant evidence derived from the first two steps are consolidated in a biological evaluation report (BER), where a final conclusion and a statement on biocompatibility and safety is provided for the use of the device within its intended purpose in the intended patient population.



BIOLOGICAL EVALUATION AS A DESIGN VERIFICATION PROCESS

As part of the risk management process, evaluation of biological safety should be fully integrated into the quality management system (QMS) of the manufacturer, but risk management is not the only required QMS element. Document control, design and development, and complaint handling are also essential processes. According to ISO 13485:2016, a regular review of design and development changes is required throughout the life cycle of the medical device. Consequently, reevaluation has to be performed if there are any changes in patient contact material that might affect biological safety. This includes design changes as well as changes in material or material source, manufacturing processes or storage conditions as well as a change in the intended purpose of the device, the intended target population or the biological environment in which the device is intended to be used. Since the extent of reevaluation depends on the extent of the actual change, conducting a comprehensive biological safety evaluation is generally not necessary.

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SUMMARY AND CONCLUSION

Evaluation of the biological safety of medical devices is more and more a focus of notified bodies. The introduction of the MDR in combination with the 2018 modification of ISO 10993-1 requires a definite rethinking in assessing the biological safety of medical devices. Manufacturers need to move from conducting tests by check marking in accordance with the device category and adopt a risk-based approach to determine a testing strategy. This requires fundamental knowledge about the materials used, their source and their interactions, as well as processing steps (including sterilization, packaging, transport and storage) and the device's intended purpose. Furthermore, a BEP needs to be implemented in which the available information related to biocompatibility of the device is compiled, analyzed and subjected to biological risk assessment. The outcome builds the basis for the testing strategy which represents the second step of a three-tiered approach in conducting the evaluation. The third step is compiling the results from evaluation and testing within a BER leading to a final conclusion about biological safety and compatibility. This approach often results in recruiting an entire team to conduct the biological safety evaluation within a risk management process. The advantages are a reduction in redundant testing and unnecessary animal use in addition to savings in time and resources. Another major advantage is that comprehensive evaluation and testing is not needed for follow-up devices as only changes need to be reevaluated. At best, the history of safe clinical use restricts further evaluation, or the biological risk assessment excludes detailed evaluation and testing based on the acceptability of a specific risk.

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For more information, contact **info-medicaldevices@nsf.org** or visit **www.nsf-prosystem.com**

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