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Biological evaluation

The purpose of a biological evaluation of a medical device is to ensure – from a biological and toxicological perspective – that the device is safe for both the patient and the user.

The Essential Requirements of the Medical Devices Directive (MDD) and the General Safety and Performance Requirements of the Medical Device Regulation (MDR) provide some details as to what aspects of biological safety of the device should be considered, namely

1. the choice of materials used as regards toxicity (MDD 7.1/MDR 10.1);
2. the compatibility between the materials used and biological tissues, cells and body fluids, taking account of the intended purpose of the device (MDD 7.1/MDR 10.1);
3. minimisation of risks from contaminants and residues, with particular attention to be paid to the tissues exposed and the duration and frequency of exposure (MDD 7.2/MDR 10.2); the concept minimisation rather than acceptable risk is used here as residues, and contaminants are expected to add risks without any further benefit;
4. safe use of the device with the substances they will enter into contact with during their normal use (MDD 7.3/MDR 10.3);
5. minimisation of risks from substances leaking from the device (MDD 7.5/MDR 10.4);
6. minimisation of risks from unintentional ingress from substances into the device (MDD 7.6/MDR 10.5);
7. minimisation of risks from particles, with special attention to nanomaterials (MDR 10.6);
8. minimisation of risks from aging of the materials when used in situations where the device cannot be maintained or calibrated (such as implants; MDD 9.2/MDR 14.2). From a toxicity point of view, this means that breakdown products of the materials used should be taken into account in the risk assessment of long-term devices.

EN ISO 10993-1, 'Biological evaluation of medical devices – part 1: Evaluation and testing within a risk management process', provides guidance on how to perform a biological evaluation of a device.

However, as biological evaluation is part of the risk management process of a device, EN ISO 10993-1 should be used in connection with EN ISO 14971, 'Medical devices – application of risk management to medical devices'.

A material for a medical device may appear suitable on the basis of its physical properties, cost and availability, but might contain toxic chemical components. Therefore, strategic thinking manufacturers screen the candidate materials at an early stage to eliminate those that are toxic, and to select those that are sufficiently biocompatible and nontoxic for their intended use. Consequently, a precise characterisation of a material is an essential step. The final assessment, however, must be performed on the finished product under actual conditions of use.

Sets of tests may be necessary for determining the potentially adverse or toxic effects of medical devices. The EN ISO 10993-1 test matrix (table A.1) should not be considered as a checklist for the different tests that have to be performed, but rather as a guide for qualified toxicologists who also take into consideration material information and historical data from similar devices. Table A.1 of the EN ISO 10993-1:2018 emphasises that obtaining chemical and/or physical information is an important first step in the biological evaluation. Toxicological endpoints are cytotoxicity, sensitisation, irritation or intracutaneous reactivity, systemic toxicity (acute), subchronic toxicity, pyrogenicity (as part of systemic toxicity), genotoxicity, implantation and hemocompatibility. Based on a risk assessment, further tests need to be considered, e.g. tests for chronic toxicity, carcinogenicity, biodegradation, toxicokinetics, immunotoxicity, reproductive/developmental toxicity or other organ-specific toxicities.

The manufacturer of a medical device is responsible for assuring its biological safety and for documenting the assessment of toxicological risks.

Accepting a certain level of toxicity using a medical device implies some level of risk for patients. Therefore, the manufacturer has to assess this risk level, and determine whether or not the benefits of the device outweigh it.

Guidance for preparation of documentation of biological evaluation according to EN ISO 10993-1:2018

1. Purpose/objective

- Purpose of the document
  - Mention all relevant standards here.

2. Device description

- Classification according to MDD/AIMDD/MDR
  - Mention the intended use of the medical device.
- Categorisation according to EN ISO 10993-1 based on the:
  - nature of body contact (Section 5.2 of ISO 10993-1:2018. In the following, only standard sections are mentioned in brackets.),
  - duration of contact/period of time (5.3).
  (The category defines which effects need to be considered at least [table A.1].)
- List all materials used in the manufacture having direct or indirect body contact, including auxiliary materials, additives, process contaminants and residues, leachables, degradation products, other components that interact with the final product, etc., or refer to the applicable section of the Technical Documentation (4.3 a-f).
  - Where appropriate, mention suppliers.
  (Note: Reevaluation is necessary if source or specification of the materials used change [4.9a].)
  - Where appropriate, define total surface area contacting the body or body fluids.
  - Characterise chemical, toxicological, physical, electrical, morphological, mechanical properties for the materials used (4.2).
- Describe the manufacturing process or refer to the applicable section of the Technical Documentation (6.1).
- If relevant for the biological evaluation, describe the performance and characteristics of the final product as well as physical characteristics (4.3 g, h).
- List all known possible biological hazards (4.5).

3. Strategy of the biological evaluation programme

The selection and evaluation of any material or device intended for use in humans require a structured programme of assessment (4.1), see: EN ISO 10993-1:2018, flowchart (fig. 1).

Biological safety cannot be demonstrated adequately using a 'checklist' approach!

Toxicological hazard is a property of the chemical constituents of the materials from which a medical device is made, and should be considered in relation to the hazard identification. Under the risk management framework (EN ISO 14971), physical and chemical material characterisation is crucial for hazard identification and risk analysis.

The biological evaluation programme shall address the interaction of:

- the risk management approach with chemical characterisation (EN ISO 10993-18),
- the toxicological hazard identification and risk analysis,
- the determination of allowable limits of leachables (EN ISO 10993-17) and the overall biological safety evaluation.

Furthermore, a thorough evaluation of any existing nonclinical and clinical data or human exposure data, as well as any experience relevant to the medical device shall be made by expert assessors before any further testing is considered.

4. Overview of tests performed in biological evaluation

- Assign appropriate tests to the biological effects. (Only tests leading to evident results shall be performed.)
- Chemical analysis for the evaluation of extractables if appropriate. (When qualitative analysis alone does not provide sufficient data for a toxicological risk analysis to be completed, quantitative chemical analysis is to be performed and documented [EN ISO 10993-18]. Measurement of the level of a leachable substance in a medical device is important in order to allow the assessment of compliance with the allowable limit derived for that substance from health-based risk assessment [EN ISO 10993-17].)
- *In vitro* and *in vivo* test methods (If the level of a toxic substance is too high, i.e. above the allowable limit, then the device should be evaluated by *in vitro* and/or *in vivo* methods.)
- Testing shall be performed on the sterile final product or representative samples taken from the final product, or from materials processed in the same manner as the final product (including sterilisation; 6.3.1 a).
- Description of the test samples used (if known, give LOT/Ref. No., etc.)
- Statement on the sterile state of the test sample (If the test sample has not been sterilised, a rationale shall be given that sterilisation has no influence on the biocompatibility of the final device.)
- Give a rationale for the selection of the sample tested.
  - Worst-case scenario?
  - Sample size necessary to meet minimum surface area requirements specified in each test
- Assure that no residues coming out of the packaging may negatively influence the product performance and safety.

5. Test results

- Copies of test reports need to be submitted.
- Evidence for test laboratory qualification must be provided (e.g. ISO/IEC 17025, accreditation certificate for the respective method at the time of testing), and methods must be appropriately validated (4.6, 6.3.2).
- For qualitative results, interpretation and data acceptance criteria shall be given.
- Positive results – what to do?
  - Verification of results
  - Chemical characterisation of leachables
  - Overall interpretation of the biological evaluation of the device
  - Relevance of clinical use

6. Justification for tests not performed

- The quality and the extent of documentation as well as the assessment with regard to the intended use determine whether or not biological tests shall be performed with the final product, and to which extent.
- If the material has a documented safe history of use in a specified role that is equivalent to that of the device under design, testing might not be needed. Relevant preclinical studies and clinical experience as well as actual testing shall be the basis of such a decision (4.1).
- Each device should be examined on its own features. Data may be available from suppliers or in literature. In this case, full transferability has to be demonstrated. Test systems, test sensitivity and concentrations used should be taken into consideration.
- Waiving of tests shall be recorded (7d).

7. Summary/overall evaluation

- Review of available toxicity and prior-use data for each material/chemical with body contact (where appropriate, include data on residual contaminants (e.g. cleaning aids), additives, catalysts, solvents used in synthesis, sterilisation agents and other processing chemicals, mold release agents, residual monomers, degradation products, experience from clinical use, etc.)
- Toxicological risk assessment of leachables (establishment of allowable limits for leachable substances [EN ISO 10993-17])
- Critical evaluation of the literature review (Annex C)
- Compilation of tests performed according to table A.1 – example:

Test	Protocol No./Project No. Laboratory No./Report date	Result conclusion
Cytotoxicity MTT	XY/yyyy-mm-dd	In this study, under the given conditions, no substances with significant cytotoxicity (leading to a cell growth inhibition of more than 30 %) were released from the test item.

- Further relevant information that can be mentioned in the table:
  - Test sample (part tested), e.g. catheter shaft, balloon material, whole device
  - Specification (polymer type, supplier, trade name, additives), e.g. PUR, Pellethane® 2363-90A
  - Status of test material (final product, sterile)
  - Type of body contact, e.g. circulating blood
  - Contact duration, e.g. limited contact duration (≤ 24 h)
  - Standard/norm, e.g. EN ISO 10993-5:2009
  - Extract preparation (medium, surface/mass-to-volume ratio, temperature, time)
  - Compilation of tests performed in addition
- The validity of tests performed according to standards which have meanwhile been superseded shall be verified by a gap analysis to show whether the product is still in compliance with the valid (revised/new) standards.
- Overall residual risk-benefit evaluation (Annex B.3.3)
- Post-production information (Annex B.3.4)
- Biological evaluation report according to Annex B.4.5.3:
  - Summary of the results of the overall evaluation
  - Confirmation that risk analysis and risk control have been completed
- Final assessment of the data reviewed
  (The documentation should include an appraisal of the toxicological significance of the data. This shall be done by a person experienced in the assessment of the biological safety of medical devices. Suitability of the materials for the intended use should be judged on the basis that there is sufficient information to provide a realistic level of assurance that the risk-benefit ratio is acceptable or that toxicological risks are not higher than those currently deemed acceptable for existing devices.)

8. Conclusion

- A final statement of the manufacturer is necessary.
  (The manufacturer might conclude that in their opinion, based on the submitted documentation, the product safety is ensured for its intended use.)

Some notes for better understanding

Why is a material characterisation important?

- Part of the assessment of the overall biological safety of a medical device (EN ISO 10993-1, ISO 14971)
- First step in the biological evaluation process
- Novel or unknown material
- Equivalence to known material
- Identification of adverse effects
- Performance over lifetime (dynamic on-going process)
- Casual problem-solving
- Dentification of toxicological hazards
- MDR: addressing Requirement 10.4 for CMR and endocrine-disrupting substances
- Early stage identification of irregularities

Only performing chemical characterisation of materials is not sufficient

With similar processes, historical performance data of the device can provide a certain level of assurance. However, with new products and new processes, there is the need for a better understanding not only of the identity of the residue, but of the significance of the residue.

One of the greatest challenges in chemical characterisation is performing adequate assessment of biological or toxicological risks from extractables or chemical residues that can compromise patient safety. EN ISO 10993-17 clearly states to the medical device community why and how risk assessments are a part of material biocompatibility.

Why the finished device should be tested

EN ISO 10993-1 specifies testing of finished devices. This is important to cover all potential chemical/physical influences from manufacturing and subsequent processes. However, it can be helpful to also collect some data on the biocompatibility of the device components.

Manufacturer's experienced the following best practise:

1. to assemble vendor data on candidate materials,
2. to conduct screening of materials,
3. to conduct confirmatory testing on a composite sample from the finished device.

But there is a risk in testing only a composite sample of the finished device. If an adverse result occurs, it can be difficult to track down the component causing the problem, and it may end up by repeating testing on individual components. Screening device materials minimises this risk. Inexpensive nonanimal studies such as cytotoxicity and hemocompatibility tests can be used to screen device materials.

Your contact partner at TÜV SÜD Product Service can provide further information.

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