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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 during the entire lifetime of the device.

The General Safety and Performance Requirements (GSPR) of the Medical Device Regulation (MDR) specify requirements related to biological safety. The biological evaluation must take into account, among other things:

1. The choice of materials used, especially as regards their toxicity; the influence of surface properties and the impact of processes on material properties (MDR GSPR 10.1);
2. The compatibility between the materials used as well as biological tissues, cells and body fluids, taking into account the intended purpose of the device (MDR GSPR 10.1);
3. Minimisation of risks from contaminants and residues, with particular attention to be paid to the tissues exposed as well as the duration and frequency of exposure (MDR GSPR 10.2);
4. Minimisation of risks from substances and particles potentially released from the device, and the risk of wear potentially impacting the biological safety during clinical use, where appropriate (MDR GSPR 10.4);
5. Minimisation of risks from particles, with special attention to nanomaterials (MDR GSPR 10.6);
6. Minimisation of risks from aging of the materials when used in situations where the device cannot be maintained or calibrated (such as implants; MDR GSPR 14.2). From a toxicity point of view, this means that material changes shall be taken into account in the risk assessment.

The updated standard EN ISO 10993-1:2020, '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 medical device in order to establish fulfilment of relevant GSPR requirements.

As biological evaluation is part of the risk management process of a device, EN ISO 10993-1 shall 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, manufacturers should screen the candidate materials at an early stage to eliminate those that are toxic, and to select those for which sufficient data on biocompatibility and toxicity is available for the respective intended use. Consequently, a precise characterisation of a material is an essential first step. **The final evaluation, however, must be performed on the finished product under consideration of the processing and the conditions of use.**

Sets of data may be necessary for determining the potentially adverse or toxic effects of medical devices. The EN ISO 10993-1 evaluation 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 taken into account the specific use conditions as well as the material and historical (clinical and non-clinical) data already available. Table A.1 of the EN ISO 10993-1 emphasises that obtaining chemical and/or physical information is an important first step in the biological evaluation. The biological evaluation must take into account the endpoints cytotoxicity, sensitisation,

irritation or intracutaneous reactivity, acute systemic, subacute, subchronic and chronic toxicity, material-mediated pyrogenicity (as part of systemic toxicity), genotoxicity, hemocompatibility and implantation effects. Based on a risk assessment, further endpoints need to be considered, e.g. carcinogenicity, degradation, toxicokinetics, immunotoxicity, reproductive/developmental toxicity or other organ-specific toxicities. **The endpoint selection depends both on the material characteristics of the device and on the intended purpose (nature and duration of contact).**

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

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

Within the conformity assessment procedure the review of biological evaluations according to the requirements of the MDR, all existing data relevant for demonstration of biological safety (i.e. also clinical data with relevance to biological endpoints) shall be submitted by the applicant.

The following lists key aspects that need to be covered in the biological evaluation documentation in order to fulfil relevant GSPRs and EN ISO 10993-1 requirements:

1. Purpose/objective

- Indicate the purpose of the document.
- List relevant regulatory requirements and standards considered.

2. Device description

- Provide device description (MDR Annex II 1; description can be located in other documents of the TD and only referenced in biological evaluation documentation).
- Reference intended purpose/intended use of the medical device.
- Indicate categorisation according to EN ISO 10993-1 based on:
  - The nature of body contact (5.2[1]);
  - The total duration of contact considering potential multiple or repeated use (5.3[1]).

  Note: The category defines which biological effects need to be considered at minimum (table A.1 of EN ISO 10993-1).

3. Material characterisation

- Gather physical and chemical information on the medical device as it is the first step of each biological safety assessment. Material characterisation and chemical characterisation (if needed including extractables and leachables testing) shall precede any in-vivo testing (4.1 b, 4.3 h, 4.4, 6[1]).
- List all materials and substances 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 (4.1, 4.3 a–f, 6.1[1]).
- Consider the chemical, toxicological, physical, electrical, morphological, mechanical properties for the selection of the materials (4.2[1]).
- Review available toxicity and prior-use data for each chemical used in the material/process 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.) (4.1 d, 4.3 b, 6.1[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, 6.1[1]).
- Consider source (supplier) of materials and its impact on the biological safety (4.9[1]).
- Where appropriate, define total surface area contacting the body or body fluids (6.3.1 b[1]).
- Describe the manufacturing process or refer to the applicable section of the technical documentation (6.1).
- Based on the material and chemical data set, a toxicological risk assessment must be possible. If any gaps are identified, chemical analytical testing (EN ISO 10993-18:2020) shall be taken into account first (4.3, 6.1, 6.2[1]).
- Assessment regarding substances which are carcinogenic, mutagenic or toxic to reproduction (CMR 1A and 1B substances), and substances having endocrine-disrupting properties (ED substances) with regard to the 0.1% w/w threshold to clarify if specific labelling requirements must be met (GSPR 10.4).
- When qualitative analysis alone does not provide sufficient data for the toxicological risk assessment to be completed, quantitative chemical analysis should be performed and documented (EN ISO 10993-18:2020). Measurement of the level of a substance released from a medical device is important in order to allow the

[1] Clause of EN ISO 10993-1.

assessment of compliance with the allowable limit derived for that substance from health-based risk assessment (EN ISO 10993-17). Persons applying the EN ISO 10993-17 shall be toxicologists or equivalently qualified.

4. Biological evaluation strategy

The evaluation of a medical device requires a structured programme of assessment (4.1, see also flowchart figure 1, Annex B[1]).

Based on the material characterisation, biological and toxicological hazards can be identified. Gathering physical and chemical information is crucial for hazard identification and risk analysis (EN ISO 14971).

- List all known possible biological hazards (4.5[1]). Determine the relevant applicable endpoints which must be considered (Annex A). Endpoints that need to be considered are not only dependent on the intended use and the device category but also on the materials used (e.g. potential genotoxic hazards, see footnote d of table A.1[1]).
- A thorough evaluation of any existing non-clinical and clinical data or human exposure data specifically relevant for certain endpoints as well as any experience specifically relevant for certain endpoints shall be analysed before any further testing is considered (4.1, 4.10, 6.2[1]).
- Specify data gap and identify options to fill the gap. Testing shall be considered and carried out where necessary to complete the data set (4.6, 4.11, 6.2, 6.3[1]).
- Consider that chemical characterisation with an appropriate toxicological threshold (4.3[1]) (chemical and toxicological data sets according to EN ISO 10993-18 and EN ISO 10993-17) is supportive for the biological evaluation of endpoints such as systemic toxicity.
- Assign appropriate extractables and leachables testing and biological in-vitro and in-vivo testing to all identified potential biological effects.
- Select representative test samples for biological and chemical testing. The test item shall be the sterile final product or representative samples taken from the final product, or materials processed in the same way as the final product (including packaging and sterilisation; 6.3.1 a[1]).

Note 1: 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 why and how risk assessments are a part of the material characterisation and biological evaluation.

Note 2: EN ISO 10993-1 mentions several times that the 'history of safe (clinical) use' shall be considered in the biological evaluation and that this information can be used to cover biological endpoints. However, the term 'history of safe (clinical) use' is relatively vague and, except for one example in section B.3.1.4[1], it is not further explained. What is actually meant here? Just claiming that the device under evaluation or a comparable reference or predecessor product is marketed, would not be considered sufficient. The manufacturer should analyse the clinical experience data with focus on biocompatibility and look for observations related to the specific endpoints that are intended to be covered. The data analysed should not only include complaint data but also other available information (e.g. clinical or PMCF studies, literature or registry data). Potential genotoxic and carcinogenic hazards, however, cannot be covered with almost absolute certainty by clinical data; for each applicable endpoint (including genotoxic and carcinogenic endpoints) an evidence-based evaluation shall be provided.

5. biological safety evaluation over the whole lifecycle

The biological safety of a medical device shall be evaluated by the manufacturer not only initially (after manufacturing, packaging and sterilisation) but over the whole lifecycle of a medical device. Potential changes of chemical or physical properties of the medical device may take place and possibly affect the biological safety over lifetime (4.7[1]).

Depending on the intended use of the medical device, several additional timepoints could be relevant for the biocompatibility evaluation such as after shelf life/prior to intended use or at the end of intended use.

Sources for changes of chemical properties could be:

- Chemical migration of substances from the primary packaging system to the medical device (e.g. for liquids);
- Chemical migration of substances from parts of the medical device with no contact to patient to other parts of the medical device with direct/indirect contact to patient;

[1] Clause of EN ISO 10993-1.

- Residues of cleaning/disinfection agents or influences from sterilisation derived from processing;
- Interaction/chemical reaction of substances or degradation/corrosion of substances over time.

Sources for changes of physical properties could be:

- Change of surface characteristics of medical device, e.g. by degradation and corrosion.

If testing is deemed necessary for demonstration of biological safety at the end of shelf life, representative (e.g. aged) test samples shall be selected.

6. Characterisation of sample(s) tested

- Describe test samples used (traceable identifiers such as model name and/or model no., LOT/ref. no., etc.). If the test sample has been modified or 'pre-conditioned' (e.g. washed, cut, etc.), this shall be described and evaluated with regard to any impairment of representativeness for the final device as used in patient/routine.
- Provide a statement on the sterile state of the test sample and the sterilisation method applied (if applicable).
- If the test sample has been sterilised for a device which is, however, not applied sterile, a rationale shall be given why sterilisation has no influence on the biocompatibility of the final device and therefore on the representativeness of the test results obtained. Analogously, if sterile filtration of an extract is performed, a rationale for representativeness of the test results shall be provided.
- Provide a rationale for the selection of the sample tested.
- If a test sample is taken from a product family, it shall be demonstrated that the selected test sample can be considered as representative or worst case for all other product variants.
- If the test sample has not been packaged in routine packaging configuration, a rationale shall be given why packaging has no influence on the biocompatibility of the final device and therefore on the representativeness of the test results obtained with test samples not packaged in routine packaging configuration.
- If the test sample has not been manufactured according to the specifications in routine production a rationale shall be given why manufacturing processes have no influence on the biocompatibility of the final device and therefore on the representativeness of the test results obtained with test samples not manufactured according to the specifications in routine production.
- Define sample size necessary to meet minimum surface area requirements specified in each test.

[1] Clause of EN ISO 10993-1.

Note 1: Why the finished device should be tested: EN ISO 10993-1, EN ISO 10993-12 and EN ISO 10993-18 specify testing of finished devices. This is important to cover all potential chemical/physical influences from manufacturing and subsequent processes.

Note 2: Performing chemical characterisation and biological testing of materials only is not sufficient.

7. Test results

- For your submission, please compile all tests performed, e.g. as shown in **Client Checklist Biocompatibility** (formerly known as 'Checklist for the Assessment of Biocompatibility').
  Note: The **Client Checklist Biocompatibility** has been created to facilitate compiling of submission data and to harmonise the documentation as well as the review process within TÜV SÜD. Please address any questions regarding the new checklist to biocompatibility@tuvsud.com.
- Copies of laboratory test protocols and reports to be submitted for the biocompatibility review of the TÜV SÜD assessor (MDR Annex II 6.1 b).
- Evidence for test laboratory qualification must be provided (e.g. ISO/IEC 17025 accreditation certificate, including scope showing accreditation for the applied chemical analytical test methods and biological test methods at the time of testing) (6.3.1[1]).
- Analytical methods must be appropriately qualified (EN ISO 10993-18:2020 section 6.5).
- For all obtained results, interpretation and data acceptance criteria shall be given (7e–f[1]).

Note 1: The validity of tests performed according to standards which have meanwhile been superseded shall be verified by a gap analysis to show that the product is still in compliance with the valid (revised/new) standards.

Note 2: If several changes to the product and manufacturing have been made over the years, validity of representativeness of historical test data must be justified and/or additional data may be necessary.

Note 3: What to do in case of positive/out-of-specification results? The manufacturer should consider verifying these results: chemical characterisation of leachables and extractables can support in analysing and identifying the cause for these positive/out-of-specification results. Any data obtained should be assessed according to their relevance for the intended clinical use and the risks included. Risk mitigation strategies are required according to the principles given in EN ISO 14971.

8. Justification for tests not performed

The quality and the extent of material characterisation data and other available 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[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 justified (7 d[1]). However, the applicable endpoint shall be assessed.

9. Summary/overall biological safety evaluation

Based on the interpretation of all the data collected and generated, the manufacturer shall finally come to the conclusion that the overall biological safety is given. The overall biological safety conclusion has to be documented for the entire device system.

The biological evaluation report shall contain all the aspects addressed above in section 1 to 8 including

- The assessment strategy, the acceptance criteria applied, the material characterisation and the rationale for selection or waiving of tests (7 a-c[1]);
- The interpretation of results, confirmation that risk analysis and risk control have been completed (7 e-f[1]);
- The final assessment of the data reviewed and a biological safety conclusion (7 g[1]).

The documentation should include an appraisal of the biological and 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 biological and toxicological risks are not higher than those currently deemed acceptable for existing devices.

10. Re-evaluation of the biological safety

In accordance with the requirement of EN ISO 10993-1, clause 4.7, to evaluate the biocompatibility over the whole lifecycle, the manufacturer also has to monitor and evaluate the biological safety of their certified devices until the last one is finally disposed, i.e. from first to last produced lot (see definition of 'lifecycle' in EN ISO 14971:2019, clause 3.8). The biological evaluation documentation is therefore expected to be a documentation on an on-going biological evaluation process but not a one-time composition only for certification.

Consequently, a re-evaluation of the biological safety and an update of the biological evaluation report are always necessary in case of product and process changes which may have an impact on the biological risk assessment, or if there is any evidence of potential adverse biological effects (4.9[1]).

Please adress any questions regarding biocompatibility for MDR certifications assessments to
biocompatibility@tuvsud.com.

[1] Clause of EN ISO 10993-1.

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