GUIDE

BIOLOGICAL ASSESSMENT
OF MEDICAL DEVICES ACCORDING TO THE ISO 10993-1 STANDARD

OCTOBER 2021 EDITION

GMED property document - 720 RDM 0801-47a rev 1 of 11/10/2021 /
720 DM 0801-47a Rev 2 of 11/10/2021

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CONTENTS

A INTRODUCTION

This guidance document is applicable to all classes and types of medical devices.

In order to carry out a biological evaluation according to the current standard, some of the general principles are reminded below:

- The biological evaluation of any material or medical device intended for use in human shall be part of a structured biological evaluation plan within a risk management process;
- This risk management process involves the identification of biological hazards, the estimation of the associated biological risks, and the determination of their acceptability;
- This approach combines the review and evaluation of all existing data from all sources with, where necessary, the selection and application of additional tests;
- It enables a full evaluation to be made of the biological responses to each medical device, relevant to its safety in use;
- The biological evaluation shall be planned, carried out, and documented by knowledgeable and experienced professionals;
- The risk management plan shall identify aspects of the biological evaluation requiring specific technical competencies and shall identify the person(s) responsible for the biological safety evaluation;
- Information on material chemical constituents, and possible other substances that can be present in the medical devices or released from the medical device, and consideration of chemical characterization shall precede any biological testing;
- The biological evaluation is to be considered on the finished product, ready to be used;
- The biological safety of a medical device shall be evaluated over its whole life-cycle, taking into account the risks caused by potential modifications of the medical device over time, and if applicable, for the maximum number of processing cycles defined by the manufacturer.

→ The following recommendations also need to be considered:

Generally, biological responses that are regarded as adverse, caused by a material in one application, might not be regarded as such in a different situation (indication, condition of use, location in the human body) and vice versa.

Moreover, clinical investigations are not sufficiently sensitive to identify potential biocompatibility concerns. Indeed, clinical symptoms that result from the presence of a non-biocompatible material may not be identifiable, or not distinctive from those generated by another disease.

Each case is to be assessed individually. For example, if a metal stent has a polymer coating that may degrade over time, the results of the biocompatibility evaluation of the finished device may not be fully representative its long-term clinical performance, and the biocompatibility evaluation of the stent with and without the coating may be necessary.

Another example; for a system incorporating devices with different durations of contact, it is recommended to perform a biological hazards assessment individually for each device, and then to add those hazards to represent the ones for the entire system.

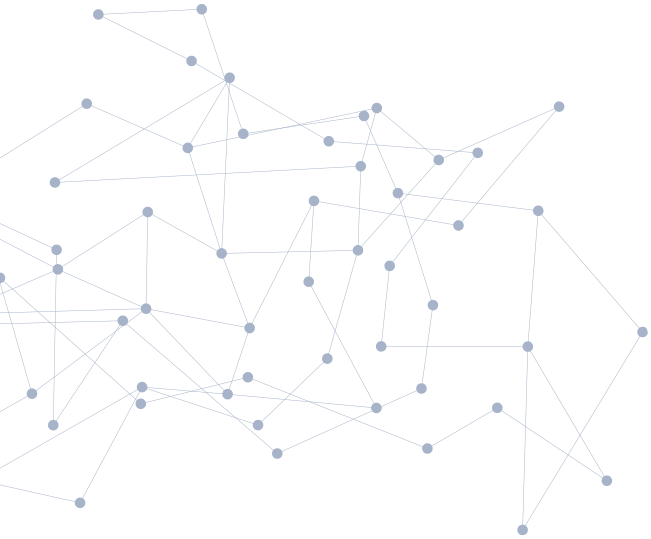
Note: The attention of the manufacturer is drawn to the fact that despite the realization of a biological evaluation compliant with the current applicable standard, that could include biological testing, this evaluation does not constitute any insurance against the emergence of adverse events.

B DÉFINITIONS

In order to harmonize the interpretation made under this guidance document, the following definitions are provided:

Degradation	Decomposition of a material or of the device over time.
Corrosion	Attack on metallic materials by chemical or electrochemical reactions.
Degradation product	Any particle or chemical compound that is derived from the chemical breakdown of the original material.
Leachable	Substance that is released from a medical device or material during its clinical use.
Extractable	Substance that is released from a medical device or material of construction when the medical device or material is extracted using laboratory extraction conditions and vehicles.

The attention of the manufacturer is drawn to the definitions provided in the dedicated sections in the applicable ISO 10993 series of standards, leading to additional meanings and clarifications to facilitate the understanding of the standards and their interpretation.



C SUGGESTED METHODOLOGY

For the purposes of assessment by GMED, the manufacturer shall document all the stages as mentioned below, knowing that all the supporting data used for the demonstration have to be provided, should the data be from the literature, from the experience or generated through testing, and whatever the testing type is (physical, chemical or biological).

Note that each step described below corresponds to each section of the GMED assessment report for biological evaluation.

1 → Stage 1 - Identification of the standards and references applied for the medical device related to biological evaluation

- Standards and references applied for the medical device subject to biological evaluation;
- When specific standards exist for the type of medical devices (example: ISO 7405 standard – Dentistry – Evaluation of biocompatibility of medical devices in dentistry), it is recommended to use the most specific standard, or the one with the highest level of requirement.

2 → Stage 2 - Formulation, description, manufacturing and use of the medical device

Formulation of the medical device:

- Identification of the construction materials of the medical device(all materials in direct and indirect contact with the human body);
- Information regarding the formulation of each component (qualitative and quantitative):
  - Chemical name, CAS number if relevant;
  - Proportion / amount / weight percent of each chemical component present in the medical device;
  - Function of each chemical component in the medical device.

Description of the medical device: The characteristics of the finished device have to be described, taking into account the physical effects when it impacts the biocompatibility (see ISO/TR 10993-19 standard for further information). Depending on the considered device and the demonstration to achieve, information on the following aspects shall be provided:

- **Porosity:**
  - Classical;
  - Connectivity;
  - Scaffolds.
- **Morphology:**
  - Crystalline;
  - Amorphous;
  - Multiple phases;
  - Hard/soft surfaces.
- **Surface energy/charge:**
  - Hydrophobic;
  - Hydrophilic;
  - Protein adsorption;
  - Protein repulsion.
- **Abrasion resistance:**
  - Stability of treated surface;
  - Surface friction.
- **Topography:**
  - Surface chemical mapping;
  - Roughness (smooth, pitted, grooved, irregular terrain, textured).
- **Particles:**
  - Size;
  - Size distribution;
  - 3D shape.
- **Shape and Form**
- **Swelling:**
  - Water absorption;
  - Solvent absorption;
  - Shape change;
  - Surface crazing;
  - Weight gain.

Where applicable, and in relation to the physical properties intrinsic to the medical device, the manufacturer has to define the expected and claimed biological effect, such as an expected tissue response or an expected response from an appropriate host in a specific application, i.e. cell attachment or cell repulsion or cell proliferation or bacterial and / or protein interaction, ...

For example, an orthopedic implant may promote tissue growth, or a heart implant may promote adhesion of certain bacteria or proteins.

Manufacturing of the medical device:

- List of the manufacturing steps of the medical device and location(s) of corresponding manufacturing;
- Processing adjuvants/additives used, expected process contaminants and residues;
- Packaging materials that directly or indirectly contact the medical device;
- Known or suspected impurities, if relevant;
- Sterilization method used, including the number of cycles claimed, if relevant.

Use:

- Intended use of the medical device, clinical performance claimed;
- Lifetime claimed;
- Shelf-life;
- Storage conditions.

3 → Stage 3 - Categorization of the medical device: nature and duration of contact

Nature of contact with the human body:

- **Non-contacting devices:** neither direct nor indirect contact with the body;
- **Surface-contacting devices:** skin/ mucosal membranes/ breached or compromised surfaces;
- **External communicating devices:** blood path, indirect/ tissue, bone, dentin/ circulating blood;
- **Implant devices:** tissue, bone/ blood.

Duration of contact with the human body:

- **Limited exposure (A):** devices whose cumulative sum of single, multiple or repeated durations of contact is up to 24 hours;
- **Limited exposure (A) with transitory-contact:** devices with very brief/transitory contact with the human body;
- **Prolonged exposure (B):** devices whose cumulative sum of single, multiple or repeated contact duration is likely to exceed 24 hours but doesnt exceed 30 days;
- **Permanent contact (C):** devices whose cumulative sum of single, multiple or repeated long-term contact duration exceeds 30 days.

Single contact: *one device used alone or several of this device used during a unique contact duration and uninterrupted.*
Multiple contacts: *one device which needs to be changed repeatedly at the end of its lifetime, which contact durations of its use are added.*
Repeated contact: *a device with uninterrupted use and during different contact durations, which are added.*

4 → Stage 4 - Identification of potential biological risks of the medical device / biological hazards

Based on the composition of the medical device, its use and its categorization, the manufacturer is invited to define the parameters to be evaluated when assessing the biological risk (see informative Annex A of ISO 10993-1 standard or other risks specific to certain types of medical devices, such as degradation potential or toxicokinetics for example).

5 → Stage 5 - Physical and chemical information for biological risk analysis / medical device characterization

Gathering physical and chemical information on the medical device or component is a crucial first step in the biological evaluation process. Sufficient qualitative and quantitative toxicological data should be available to assess the biological risk.

Consideration of the chemical characterization process shall precede any biological testing.

The chemical characterization process must be carried out according to ISO 10993-18 standard, version in force, on the basis of data from several sources (literature, supplier documentation, chemical databases...) whether or not supplemented by tests on the composition of the medical device or its constituent materials.

This aims to conduct the toxicological risk assessment using appropriate toxicological thresholds and thus determine whether or not it is necessary to conduct additional biological tests (see Annex B of ISO 10993-1 standard, ISO 10993 -17 and ISO 10993-18 standards).

Gathering and generating of information on material characterization shall address as a minimum:

- The chemical constituents of the medical device and possible residual processing additive and processing aids used in its manufacture in relation with the data described in Stage 2;
- The presence and the nature of leachable substances of the medical device during clinical conditions of use;
- The estimation of the potential of the medical device or its materials of construction to release chemical substances during clinical conditions of use (extractables);
- The possible combinations/interactions between the chemical constituents;
- The measurement/ proportion/ amount/ weight percent of each chemical component identified;
- Sufficient chemical data (quantitative and qualitative) to serve as the basis for a toxicological risk assessment (see questions raised in Figure 1 of ISO 10993-1 standard).

The characterization shall identify the potential presence and the nature of degradation products. The characterization is performed according to ISO 10993-9 standard, and then 10993-13, 10993-14 and 10993-15 standards, current versions. If relevant, this characterization is applied at different stages of the device lifetime.

For the devices undergoing a change (e.g. polymerization) and/or degraded in situ, the tested product has to be representative of the device in its final version. Moreover, it is also recommended to evaluate the biocompatibility at different states of the modification and/or degradation, to ensure that the initial products, intermediate products and products of final degradation have been assessed.

It should be noted that chemical characterization is usually insufficient to identify all the risks of the device in its final form, because it does not take into account the properties of the final medical device, especially the surface ones.

Chemical characterization process and data collection:

It is recommended to establish a chemical characterization protocol giving rise to a protocol for identifying, selecting, collecting and reviewing all the existing data/studies used to thoroughly characterize the medical device, and if necessary, for carrying out chemical characterization tests according to ISO 10993-18 standard.

- Literature search to perform according to the results obtained at the previous stage, taking into account the categorization of the medical device (nature and duration of the contact);
- Use of historical data held by the manufacturer, if relevant;
- For leachables which have known toxicological data, verification of the adequate safety margin;
- If several leachables, potential synergy to evaluate;
- Assessment of the time of release/quantity of leachable;
- If relevant, use of the ISO 10993-17 standard for the assessment of toxicological risks in relation to toxicological thresholds and the calculation of acceptable safety margins;
- Same considerations for the degradation products: existing toxicological data, time of degradation, etc.
- Where applicable, the implementation of chemical characterization tests according to ISO 10993-18 standard must be the subject of a protocol describing the methodology of appropriate tests leading to the associated tests report;
- The competence of the test laboratory, the justification of the selection of the test articles, the tests conditions, the analytical evaluation thresholds are to be documented in addition to the results obtained;
- Justified conclusion, based on the state of art and the analyzed data;
- Dated and signed report by the competent assessors, along with the articles used.

Recommendations for literature research:

- It is recommended to establish a protocol for the identification, selection, collection and review of all available existing studies/data;
- The objectives of the literature review have to be clearly defined;
- The criteria for including or excluding data have to be defined with an appropriate rationale;
- The literature review shall clearly assess the quality of the documents and the extent to which the literature relates to the specific characteristics and features of the material or device under consideration, taking into account the intended use of the device, especially:
  - Relevance of the experimental animals used in the selected studies for the biological evaluation of the device considered;
  - Conditions of use of the material or device in the selected documents and the intended use of the device considered.
- Justified conclusion, based on the state of art and the analyzed data;
- Dated and signed report by the competent assessors, along with the articles used.

6 → Stage 6 - Gap analysis and selection of biological endpoints for evaluation

- In connection with stages 4 and 5, assessment of the information available and comparison with the data necessary for the biological safety assessment of the medical device (see Clause 4, informative Annexes A and C of ISO 10993-1 standard) in order to identify options that can fill the gaps.

It is reminded that the impact of the surface properties can only be assessed by placing the device in contact with the cells/tissues.

Justification on the need to carry out additional tests or not:

- Are the data issued from the previous stages, and if relevant the historical data held by the manufacturer, sufficient to address all the potential hazards identified in stage 4?

  - **Yes:** proceed to **Stage 7**;

  - **No:** continue with the **Biological testing program.**

- To conclude that no additional biological testing is necessary, the manufacturer has to justify that, for each material: the type and duration of contact with the tissue considered, the physical form, the formulation, the manufacturing, the components interactions, the lifetime claimed, the shelf-life and storage conditions are identical to the data issued from the literature and from the manufacturer's historical data, if relevant, and that all biological hazards are addressed and the risks are considered acceptable. If there are differences or remaining gaps, it would be necessary to analyze each of them and justify them.

Biological testing program

- Definition of an additional biological testing program to be performed, in order to address the potential risks, that cannot be controlled by the literature data or by the physical, chemical, and toxicological information obtained;
- For each test selected in the testing program, the following information has to be documented in a report: the test methodology description, the claimed standard, the competence of the test laboratory, the justification of the selection of the test article (as being representative of the device), the operating conditions, the results obtained. The relevance of the tests has to be demonstrated.

For the in vivo testing of medical devices made in situ (e.g. polymerization) or of absorbable materials, the evaluation and/or the tests performed must take into account the kinetics of polymerization and of degradation during the lifetime of the device. It is expected to demonstrate how the device materials degrade over time and to analyze the biological risk and continue until the absorbable materials and/or its degradation products are no longer present in human body (e.g. a bio-resorbable bone substitute) or if necessary removed from the human body (e.g. an ophthalmic gel injected into the ocular cavity and then removed after surgery). Alternatively, it may be acceptable to provide a rationale for ending the study earlier, if the rationale includes an estimate of the percentage of absorbable material remaining in the tissue, and confirmation that a steady state biological tissue response is achieved.

7 → Stage 7 - Overall analysis of the results

Summary and analysis of all the data described and/ or results obtained in the previous stages

- A conclusion on the acceptability of each identified biological risk in order to confirm the biological safety of the medical device is expected;
- The conclusion can involve the following data:
  - Historical data held by the manufacturer, if relevant;
  - Literature data;
  - Results of the biological testing.

Risk management

- Finalization of the risk management file:
  Overall evaluation allowing to demonstrate the control of all potential risks at an acceptable level and the benefit to health from the use of the device as intended by the manufacturer, against probable risks of injury or illness from such use;
- It is expected from the manufacturer a reference to the risk management file, allowing the tracking of the analysis and the control of the biological hazards.

Post market data

It is reminded to the manufacturer that despite carrying the biological evaluation in accordance with the applicable standard, which may include carrying out biological testing, this evaluation is not an assurance against the emergence of adverse events. As such, the monitoring of adverse reactions or events in humans is necessary in order to:

- Verify the control of the actions;
- Identify new risks, if any;
- Update the scientific surveillance related to the toxicity and biological risks associated to the medical device.

In relation with the risk management file, the provisions in place for the collection, analysis and evaluation of production and post production information, specific to the biological evaluation will be verified.

D RE-EVALUATION OF THE BIOLOGICAL EVALUATION FILE

The biological evaluation has to be re-evaluated in case of following modification:

- Any change in the source or in the specification of the materials used (components and/or additives) in the manufacturing of the product (source or specification);
- Any change in the physical configuration of the final medical device (for example size, geometry, surface properties);
- Any change in the formulation, processing, primary packaging or sterilization of the product;
- Any change in the manufacturer's instructions or expectations concerning storage, e.g. changes in shelf life and/or transportation;
- Any change in the intended use of the product;
- Any evidence that the product may produce adverse effects when used in humans: Post market surveillance data.

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