Directives 90/385/EEC and 93/42/EEC

MEDICAL DEVICES

Guidance document for the presentation of biological evaluation

According to ISO 10993-1 standard (current version)

This guidance document is applicable to all classes of medical devices.
A - Introduction

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

- The biological evaluation of any material or medical device intended for use in human shall form part of a structured biological evaluation program within a risk management process.
- 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.
- Identification of material chemical constituents 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.

Moreover, the following recommendations have also to be considered:

Generally, clinical investigations are not sufficiently sensitive to identify biocompatibility concerns. Clinical symptoms that result from the presence of a non-biocompatible material may not be identifiable, or indistinguishable from another disease.

Each case is to be assessed individually. For example, if a metal stent has a polymer coating that may separate over time, then the results of a final device biocompatibility assessment may not fully reflect the longer-term clinical performance of the device, and biocompatibility evaluation of the stent with and without the coating may be needed.

Other example, for systems that include devices with different lengths of contact, it is recommended to perform a biological hazards assessment individually for each device, and then to add those hazards to get the ones of the entire system.

*For the purposes of assessment by LNE/G-MED, the manufacturer shall document all the stages mentioned below, knowing that all the 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). The identification of the potential hazards (see stage 3) is also to be provided.*

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

In order to harmonize the interpretation made in this guidance document, the following definitions are expressed below:

**Degradation:** Decomposition of the device, leading to a loss of mechanical and/or physical properties of the device over time

**Extractible:** Compounds released from the device due to constraints applied during its use (example: corrosion products)

**Leachable:** Release from the device of adjuvant gained during its manufacturing and sterilization (example: ethylene oxide residues)

C – Suggested methodology

**Stage 1 – Identification of the standards and documents applied for the medical device related to biocompatibility**

- Standards and documents applied for the medical device (if a non-harmonized document is claimed, the justification of the equivalence to the harmonized standard is to be provided).
- In the case specific standards exist for some medical devices (example: ISO 7405 – Dentistry – Evaluation of biocompatibility of medical devices in dentistry), it is recommended to use the more specific standard, or the one which is the most demanding.

**Stage 2 – Formulation, description, manufacturing and use of the medical device**

**Formulation of the medical device:**

- Identification of the components in the medical device:
  - Chemical name, CAS number if relevant
  - Weight percent of each chemical component present in the medical device
  - Function of each chemical component in the medical device

**Description of the device:** The characteristics of the finished device have to be described according to the ISO 10993-19, current version. Depending on the considered device and the demonstration to achieve, some information on the following aspects have to be provided:

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

On the basis of the intrinsic physical properties of the medical device, the manufacturer is invited to define the expected cell behavior. Example: cell attachment (human general, human blood cells, human specific cells, bacteria general, bacteria specific class), cell repulsion (human general, human blood cells, human specific cells, bacteria general, bacteria specific class), cell proliferation.

Manufacturing of the medical device:

• List of the manufacturing steps of the medical device and place(s) of corresponding manufacturing (in line with the information provided at the section "Manufacturing" of the main report)
• Processing additives used
• Known of 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
• Expire date
• Storage conditions
Stage 3 – Categorization of the medical device: nature and duration of contact

Nature of contact with the human 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 single, multiple or repeated use or contact is up to 24 hours
- **Prolonged exposure (B)**: devices whose cumulative single, multiple or repeated long-term use of contact is likely to exceed 24 hours but not 30 days
- **Permanent contact (C)**: devices whose cumulative single, multiple or repeated long-term use or contact exceeds 30 days

Cumulative single contact: one device used alone or several of this device during a unique contact duration and uninterrupted

Multiple contact: one device which needs to be change repeatedly at the end of its lifetime, which contact time of its use are added

Repeated contact: a device with uninterrupted use and during different contact times, which are added

Stage 4 – Material characterization

- **Crucial first step in the biological evaluation process**
- **Material characterization is performed according to ISO 10993-18, current version**
- **As a minimum, the characterization shall address the chemical constituents of the medical device and possible residual processing additives used in its manufacture: Identification of the presence and the nature of leachable substances**
- **The characterization shall identify, if potential of degradation, the presence and the nature of degradation products, which characterization is performed according to ISO 10993-9, and then 10993-13, 10993-14 and 10993-15, current versions, at different stages of the lifecycle of the device if relevant**
- **Biological hazards identified by the manufacturer and to be provided**

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

**Stage 5 – Analysis of the results and literature research method**

**Analysis of the results:**

- Literature research 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 leachable which have known toxicological data, verification of the adequate safety margin
- If several leachable, potential synergy to evaluate
- Assessment of the time of release / quantity of leachable
- If relevant, use of the ISO 10993-17
- Same considerations for the degradation products: existing toxicological data, time of degradation, etc...

**Realization of the literature research:**

- It is recommended to establish a protocol for the identification, selection, collation and review of all available studies/data
- The objectives of the literature review have to be clearly defined
- The criteria for selecting or excluding data have to be defined with an appropriate rationale
- The literature review has 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 particular 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.

**Conclusion of the analysis of the results:**

- Are the data issued from the literature review, if relevant the historical data held by the manufacturer, sufficient to address all the potential hazards identified at the stage 4?
  - Yes : proceed to stage 7
  - No : proceed to stage 6

It is reminded that the impact of the surface properties can only be assessed by placing the device in contact with the cells / tissues.
To conclude that no additional biocompatibility testing is needed, the manufacturer has to justify for each material, type and duration of contact with the tissue considered, physical form, formulation, manufacturing, component interactions, lifetime claimed, expire date and storage condition are identical to the data issued in the literature, and from his historical, if relevant. In cases where there are differences, it would be necessary to analyze and justify them.

Stage 6 – Biological testing program

- Determination of an additional biological testing program to be performed, in order to address the potential risks, that cannot be controlled by the bibliographical data

For the in vivo testing of medical devices made in situ (e.g. polymerization) or absorbable materials, the times when the evaluation is performed depends on the kinetics of polymerization and of degradation. It is recommended that assessments are targeted to demonstrate how the device materials degrade over time and continue until the absorbable material and/or its degradation products are no longer present in the tissue, if possible. Alternatively, it may be acceptable to provide a rational for ending the study earlier, if the rational includes an estimate of the percentage of absorbable material remaining in the tissue, and confirmation that a steady state biological tissue response is achieved.

Stage 7 – Global analysis of the results

It involves the following data:

- Historical data held by the manufacturer, if relevant
- Literature data
- Results of biological testing

Stage 8 – Risk management

Finalization of the risk management file:

- Does the global evaluation allow to demonstrate the control of all the potential risks at an acceptable level and to obtain a probable benefice for the health with regards to probable risks of injury, illness issued of the use of the device according to the intended use of the manufacturer?
- It is expected from the manufacturer a reference to the risk management, allowing the tracking of the analysis of biological hazards.
Stage 9 – Post market data

It is reminded to the manufacturer that despite the implementation of a biological evaluation compliant to the harmonized standard, which can include the realization of biological testing, this evaluation is not an assurance against the emergence of adverse events. As such, the follow up of negative reactions or events for humans is necessary in order to:

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

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

D – Re-evaluation of the biocompatibility file

The biocompatibility file 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
- 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 transport
- 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