GMED LNE GROUP Newsletter

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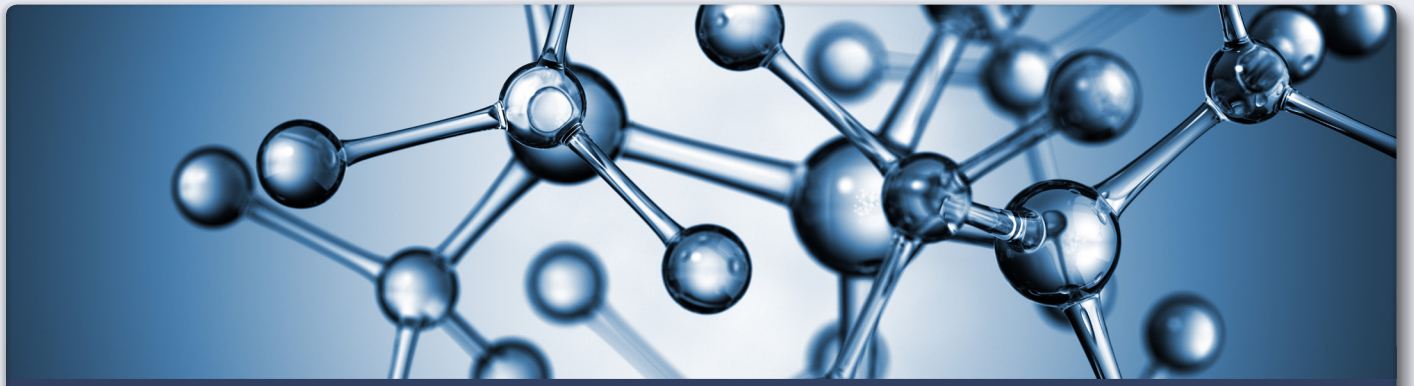
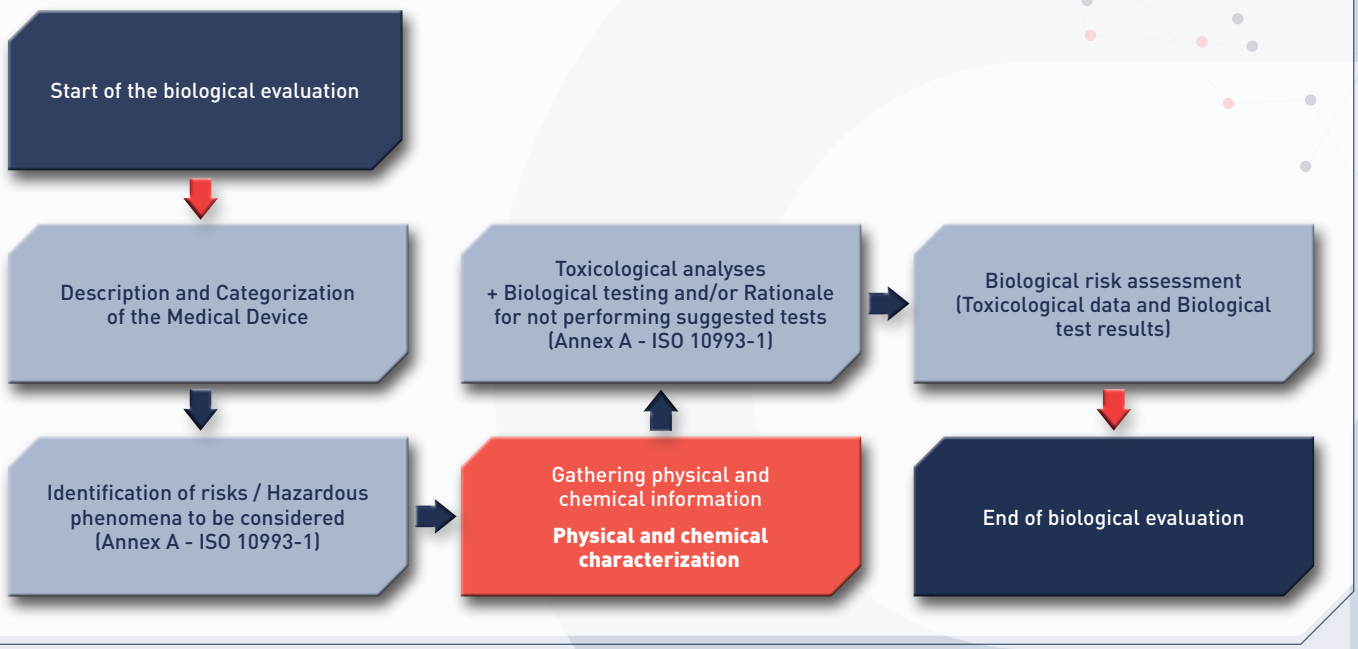
Version Française

BIOLOGICAL EVALUATION: CHEMICAL CHARACTERIZATION ACCORDING TO EN ISO 10993-18:2020



The purpose of the medical device is to provide a benefit to the patient, directly or indirectly, by allowing the diagnosis, prognosis, treatment or mitigation (etc.) of a disease. Nevertheless, because of its design, manufacture, or intended use, it can also pose safety problems, in particular biological risks in humans during use, if no evaluation is performed. Therefore, the biological evaluation of a medical device must be conducted as soon as there is direct or indirect contact with the human body (patient and/or user) in order to assess the biological safety of the medical device during its clinical use.
Among the various steps in this process, **physical and chemical characterization is the critical first step in the biological evaluation process.** It is to be carried out after the categorization of the medical device, i.e. after establishing the nature and duration of contact with the body.

CHARACTERIZATION IN THE BIOLOGICAL EVALUATION PROCESS



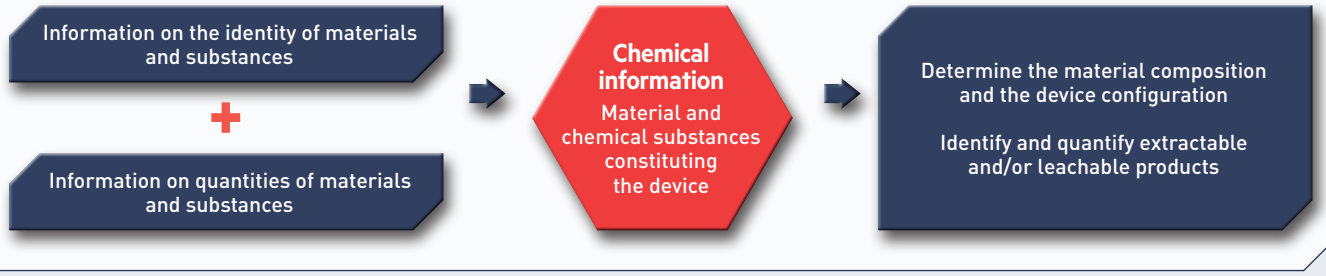
A WHAT IS PHYSICAL AND CHEMICAL CHARACTERIZATION?

The physical and chemical characterization step involves obtaining all of the information on the constituent materials of the device and on the related physical and chemical properties. It allows the level of biological risk associated with the medical device to be determined for the patient and/or the user. It can then be decided whether this biological risk is acceptable based on the clinical use of the device.

Chemical characterization is one of the 2 components of the characterization step, the other being physical characterization.

Process and requirements of chemical characterization are set out by EN ISO 10993-18. This standard outlines the recommendations for obtaining the chemical information relating to the constituent materials of the device, i.e. information on the identity of these materials and the quantity of the latter in contact with the body.

CHEMICAL CHARACTERIZATION (EN ISO 10993-18)



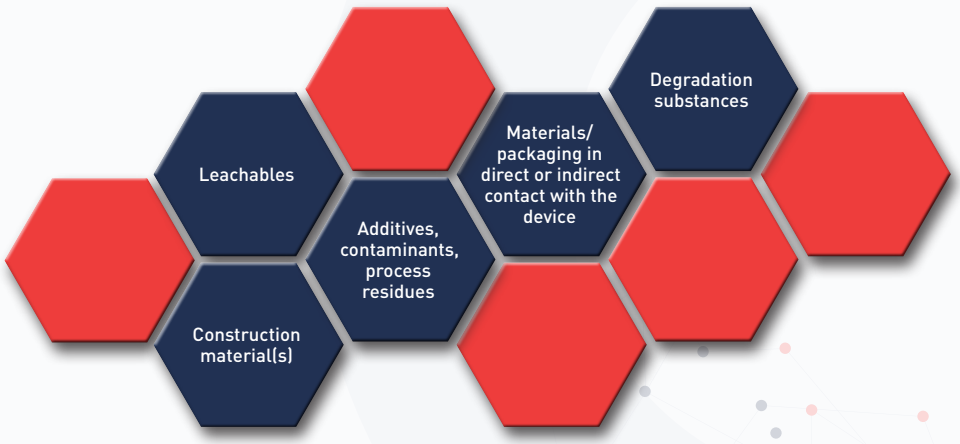
The chemical characterization of a medical device provides the necessary inputs for the biological evaluation and the toxicological risk assessment relating to the device (see ISO 10993-1 and ISO 10993-17).

Chemical characterization alone may not be sufficient to establish the biocompatibility of materials and medical devices. It cannot be a unilateral substitute for biological testing. However, chemical characterization combined with risk assessment may be sufficient to conclude whether the medical device is biologically safe.

B WHAT SHOULD BE CONSIDERED AS PART OF CHEMICAL CHARACTERIZATION?

All materials present in the device or on the device, and coming into contact with the body, should be considered.
This is obviously the constituent material per se and also any chemical substance or material that has come into contact with the device material and which may still be present on or in the material: manufacturing additives, residual processing/cleaning aids (manufacturing oil, cleaning product, etc.), but also degradation products, packaging in contact with the device and the potential leachables from such packaging, etc.

MATERIALS AND CHEMICALS FOR CONSIDERATION AS PART OF CHEMICAL CHARACTERIZATION



This implies that the medical device is characterized in its final state, as it will be used by the patient. Accordingly, characterization is to be performed on the device after it has undergone all of the stages in the manufacturing process and, if applicable, in its packaging (in contact with the device).
In addition, if the medical device changes over time during its clinical life-cycle, **all the states of the device must undergo biological evaluation.**

For example:
- A metal stent has a polymer coating that may separate over time: the biological evaluation must then be conducted on the stent with and without coating.
- For an *in-situ* polymerizing and absorbable sealant: Separate characterization and consequently separate biological evaluation of the pre-polymerized, polymerized and degrading sealing shall be conducted.
- Conversely, for a cement which is prepared from 2 compounds prior to implantation by the surgeon, chemical characterization must be conducted on the prepared cement as it is used, and not to the 2 substances taken individually which do not represent the cement in the use for which it is intended.

C HOW TO OBTAIN CHEMICAL INFORMATION ON THE DEVICE?

This information can be obtained in 2 ways:
- **by collecting information: established** quantity and identity of materials and chemicals;
- **by generating information: measured** quantity and identity of materials and chemicals.

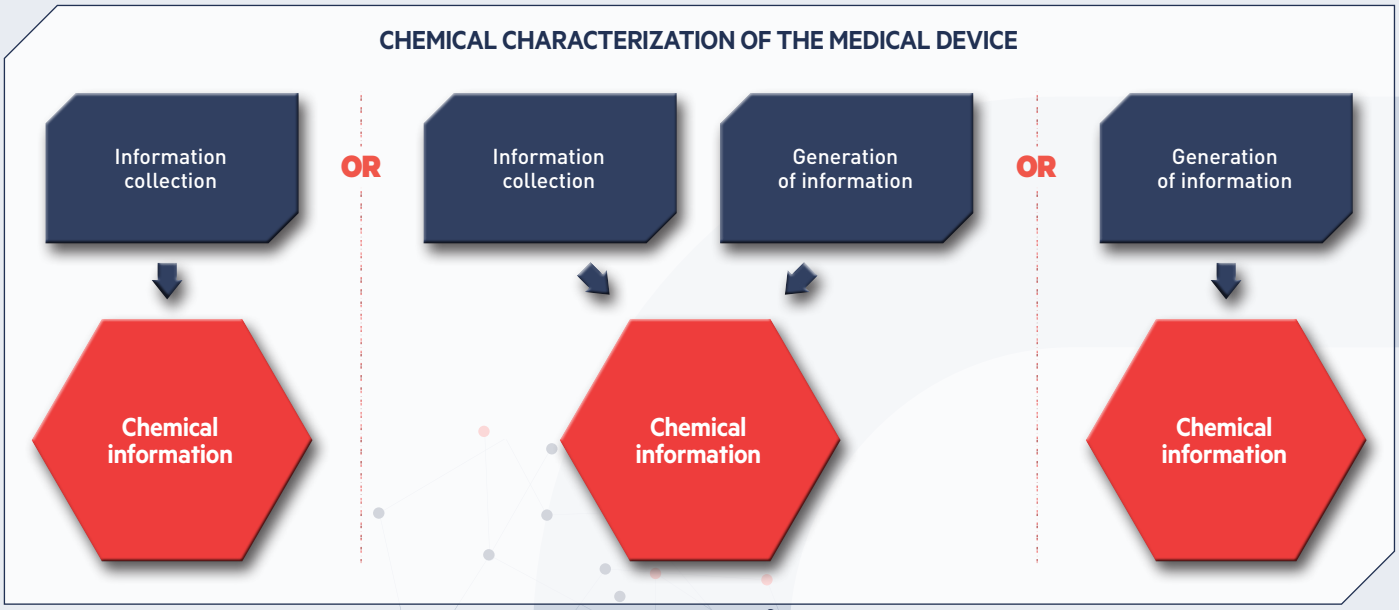
1 - Collecting information

Qualitative and quantitative information should be collected through relevant documentary sources and from the appropriate stakeholders in the production chain (e.g.: subcontractors, material distributors, distributors of processing aids).

Information can also be collected from another medical device whose biological equivalence with the device under evaluation has been established.

2 - Generating information

Information will be generated through chemical analyses (e.g.: using chemical analyses to establish the composition of the material or using chemical analyses to establish the identity and quantity of extractables as part of an extraction study).
Information does not need to be generated if the collection has provided all of the necessary chemical information on the medical device, including substance residues related to the manufacturing process.



The extraction study is generally the most common approach or, at least, the one mostly used to gain knowledge of extractables and/or leachables.
Medical device manufacturers often know the identity and quantity of the constituent raw materials in their medical device. What is perhaps less well known or less easy to obtain by collecting information are the substances resulting from the manufacturing processes and possibly leached by the medical device or the compounds possibly leached from the constituent material of the medical device.

The extraction can be simulated, exaggerated or exhaustive. The last method is mostly applied. Obviously this does not mean that it is suitable or possible for all types of medical devices in their clinical use nor that it is required for the chemical characterization of the device according to its clinical use.

Note: Chemical characterization ≠ exhaustive extraction study

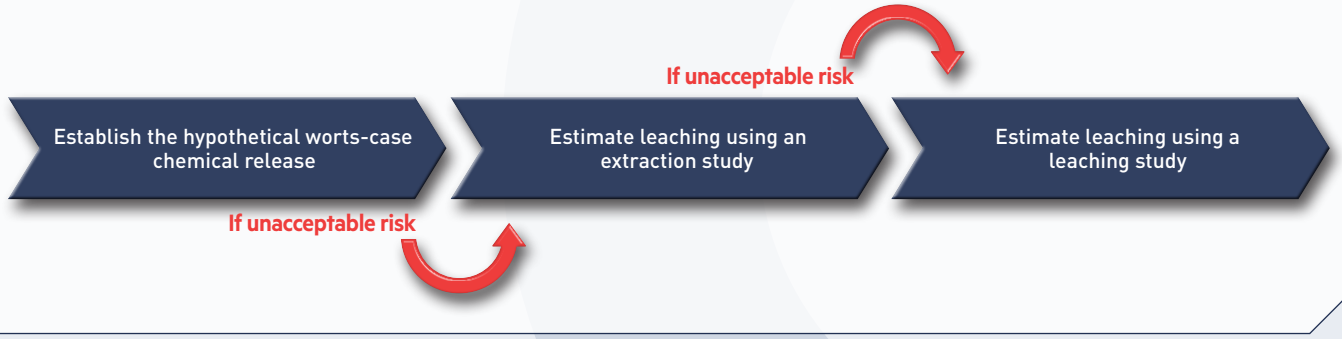
In the collective unconscious, chemical characterization is often synonymous with exhaustive extraction study. This is not correct.
Chemical characterization can be obtained by collecting information. This also applies to processing aids. Moreover, depending on the device and its clinical use, information can be generated by studies of extractables under exaggerated or simulated conditions or by studies of leachables or other chemical analyses.
When chemically characterizing the medical device, it is important to remember to specify the approach used, i.e. collection and/or generation of information. If the generation of information is selected, it is important to specify by which analysis, or which successive analyses, this is achieved (and the related methods/conditions).

D WHAT IS THE HYPOTHETICAL WORST-CASE CHEMICAL RELEASE IN THE CHEMICAL CHARACTERIZATION PROCESS?

The greatest potential impact of a medical device is to be considered in the chemical characterization process. It is achieved if the device entire composition is transferred in its entirety to the potentially affected individual during clinical use. For example, if a device completely dissolves during clinical use.
This is the starting point for any manufacturer.

- Based on this assumption, if exposure to the composition of an entire medical device is deemed acceptable, then the chemical characterization process should be considered complete. Such a hypothesis is a worst-case scenario and is less refined because it exceeds the conditions of clinical use. But it can quickly demonstrate the safety of the medical device within the worst-case scenario.
- However, if exposure to the composition of an entire medical device is deemed unacceptable, then additional data should be collected or generated. The manufacturer then embarks on a gradual process that reflects as closely as possible the clinical conditions under which the medical device is actually used. The manufacturer will seek to establish leaching that best reflects reality. This can be achieved by characterizing extractables following exhaustive, exaggerated or simulated extraction or by characterizing leachables following leachables study.
In addition, the extraction conditions must be designed to provide a reasonable overestimation of the risk compared to the conditions of clinical use, without creating risks that would not exist under normal conditions of use.
For example: the use of a solvent or a temperature that would cause the device to deteriorate whereas this would not occur in real conditions.

STEPWISE APPROACH TO THE CHEMICAL CHARACTERIZATION PROCESS



Note: Exhaustive extraction

When characterizing extractables following extraction under exhaustive conditions, the manufacturer assumes the most unfavorable leaching compared to characterization following exaggerated or simulated extraction. This suggests that all of the chemical substances extracted in worst-case scenarios would be released/leached in their entirety during the clinical use of the medical device.
If based on the characterization of extractables and their toxicological data, the risk is not acceptable; this risk cannot ultimately be classified as acceptable, only based on declaration that the conditions considered reflect the worst-case scenario. Additional data must be collected/generated at this point.

E WHAT ARE TTC AND AET AND WHAT ARE THEY USED FOR?

The TTC *"Threshold of Toxicological Concern"* is the threshold of toxicological concern for a chemical. This is the level of exposure below which there would be no appreciable risk to human health.
The TTC approach consists of defining a toxicological threshold applicable to a given medical device or to a set of substances, depending of clinical exposure and using a worst-case hypothesis, thus establishing an amount of leachable products below which the quantity present is deemed insufficient to induce toxicity, regardless of the identity of the substance.

The whole context of the TTC approach is defined in ISO/TS 21726.

The AET *"Analytical Evaluation Threshold"* is the analytical evaluation threshold below which the analyst need not identify or quantify leachables or extractable or report them for potential toxicological assessment.
This threshold concept is introduced in the 2020 version of EN ISO 10993-18.

Note: AET is not applicable to all substances!

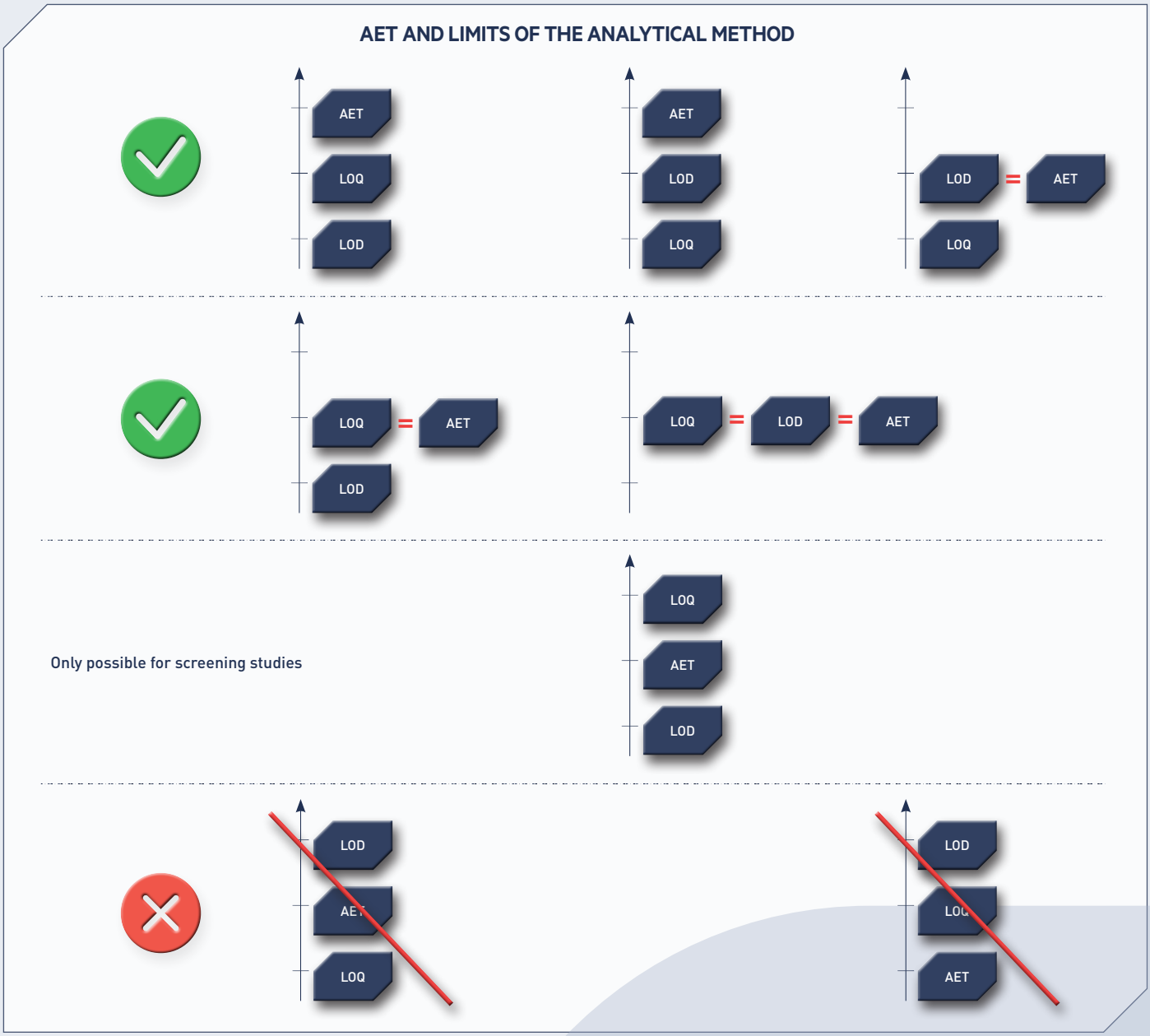
- **Applicable** only to organic leachables and extractables
- **Not applicable** to highly toxic substances = cohorts of concern (these cohorts are excluded from the TTC approach, because their mere presence is considered to pose a risk for the patient). A non-exhaustive list of cohorts of concern is given in ISO/TS 21726.

TTC is a toxicity threshold based on the daily amount of a substance; AET, on the other hand, is a concentration-based threshold.
After an appropriate conversion of the toxicity threshold of the most toxic substances and after taking into account any uncertainty factors introduced by the analytical measuring devices, the amount becomes a concentration.

The AET must be defined and justified before starting the analytical studies planned for the identification and quantification of leachables or extractables, in order to ensure that the extraction conditions and the analytical methods used will generate limits of detection and quantification compatible with AET. Indeed, this makes sense, but it is essential to bear in mind that the expected precision of the analytical method is to be defined according to the AET, otherwise the extractable or leachable will not be identified or qualified correctly. This must be taken into account in the biological risk assessment.

In practice, the anticipated AET and limits of the analytical method are as follows:
- The LOD (Limit of Detection) of the analytical method must be less than or equal to the AET;
- The LOQ (Limit of Quantification) of the analytical method must be less than or equal to the AET.

The AET should be derived from a safety-based threshold (such as the TTC, or TCL *"Tolerable Contact Level"*) based on the identity of the materials or substances likely to be present in the extract should be known as much as possible in order to set the AET as accurately as possible and not to rule out the toxicological analysis of substances to be evaluated. However, if this is not feasible in practice, an analytical threshold, such as the limit of quantification (LOQ), can be used as a defined threshold with rationale.



Note: TTC concept (ISO/TS 21726)

The TTC threshold of toxicological concern was originally developed for materials in contact with food and to assess the risks of impurities present at very low levels for which no data were available. It was subsequently adapted to the impurities present in pharmaceutical products. This concept is now to be used for the biological evaluation of medical devices.

The TTC values in ISO/TS 21276 are taken from the ICH M7 guide. The thresholds are expressed in µg/day. Four different thresholds exist depending on the duration of contact. The longer the contact time, the lower the threshold.
These values are given for impurities with mutagenic potential. They are therefore considered to be conservative and can thus be applied to impurities with a carcinogenic and non-carcinogenic effect.

The TTC values listed in the ICH guide are more conservative than the thresholds defined in the Cramer classification which applies to impurities with non-carcinogenic potential.

F HOW TO ESTABLISH BIOLOGICAL EQUIVALENCE AND WHAT IT IS USED FOR?

As mentioned earlier, chemical characterization can be established on the basis of information collected. And this can be done by collecting chemical information on another device or on an earlier version of the device, the clinical use of which has been established. Conversely, this method will be appropriate if and only if **biological equivalence** exists between the two devices. **Apart from stating that information relating to an equivalent device can be used, this is the first source of collected information being described as to be considered in the flowchart of standard EN ISO 10993-18:2020.**

At this point, equivalence must be demonstrated according to the principles of assessing equivalence defined in EN ISO 10993-18:2020, the provisions and requirements of which are defined in chapter 5.3 and Annex C.
This is the only way in which a manufacturer can use this chemical information and apply it to the device under evaluation.

Equivalence relates to the following:
- configuration;
- composition;
- production;
- processing;
- intended use.

Equivalence must be demonstrated and justified in relation to the following 5 aspects:
- chemical equivalence;
- physical equivalence;
- materials equivalence;
- contact equivalence;
- biological equivalence.

N.B.: the physical, morphological and topographical characteristics (see ISO/TR 10993-19 and ISO/TR 10993-22 as appropriate) should also be considered appropriate for determining the equivalence of the material; the chemical aspect alone is not sufficient.

Differences may exist between the comparator device and the device under evaluation. These will not prevent the claim of biological equivalence, provided that it is demonstrated and justified in a relevant way that they do not impact equivalence. For example: device data available for more invasive exposure compared to that under evaluation and for comparable application can be used and the equivalence confirmed. Or a device the manufacture of which has been modified, and this modification consists of a change in the processing aid. If the modified processing aid whose residues are present on the final device whose toxicological profile (quantity/quality) is not more unfavorable than that of the residue which it replaces, equivalence may be confirmed. In this case, the equivalence will be based on the collection or generation of information by analysis on the modified manufacturing aid and its comparison with the aid it is replacing. Likewise, precise information on the toxicological profile of the novel aid should be provided and compared to the toxicological profile of the aid being replaced.

Conclusion

Chemical characterization is one of the critical steps in the biological evaluation of the device. A thorough understanding of this characterization process and the methodology used will condition the chemical information and therefore the correct assessment of biological risks associated with the device under evaluation.
For instance, an error in the definition of AET, an inadequate definition of the extraction conditions or an overly high analytical threshold may jeopardize the evaluation of biological data and preclude assessment of real biological risks.
Furthermore, relevant characterization of the medical device is essential in order to establish its biological safety. However, it will also offer a means of establishing the biological evaluation of future generations of the medical device rapidly, efficiently and at lower cost.

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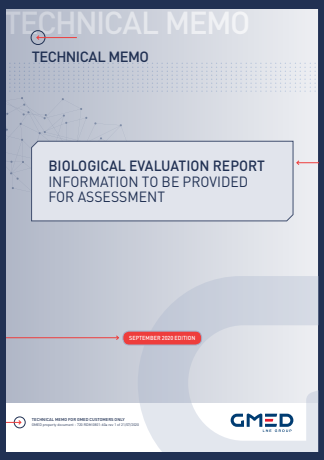
To go further

TECHNICAL MEMO

[ONLY FOR GMED CUSTOMERS]



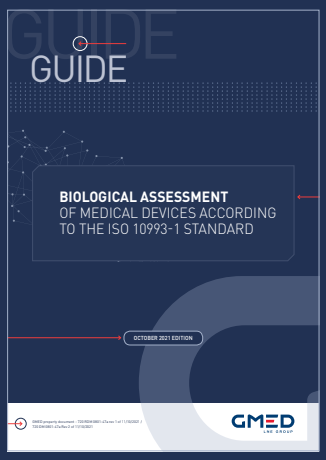
Biological evaluation report - Information to be provided for assessment

GMED has prepared this Technical memo to enable manufacturers to carry out the biological assessment of their medical devices according to ISO 10993-1, and to guide manufacturers in demonstrating their approach and assessment's results in this context.

→ **REQUEST THE TECHNICAL MEMO FROM YOUR CERTIFICATION PROJECT MANAGER**

GUIDE

Biological assessment of medical devices according to the ISO 10993-1 standard



The GMED teams have prepared this document in an aim to guide the medical device manufacturers in the presentation and demonstration of their biological assessment according to the ISO 10993-1 standard.
This guide, applicable to all medical devices (whatever their class and type), reviews the general principles, proposes a 7-step methodology corresponding to each section of GMED's biological evaluation report. The guide also sets out the conditions for a biological evaluation file re-assessment.

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