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Biological evaluation of medical devices —

Part 18: Chemical characterization of medical device materials within a risk management process

Évaluation biologique des dispositifs médicaux —

Partie 18: Caractérisation chimique des matériaux des dispositifs médicaux au sein d'un processus de gestion du risque

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices.*

This second edition cancels and replaces the first edition (ISO 10993-18:2005), which has been technically revised. The main changes compared to the previous edition are as follows:

— greater integration and harmonization with ISO 10993-1, ISO 10993-12, and ISO 10993-17;

— a revised and expanded chemical characterization process flowchart;

— a strengthened explanation that analytical testing is not necessarily required;

— added a number of definitions (e.g. medical device configuration, materials of construction, and material composition);

— clarified testing approaches unique to chemical characterization (i.e. digestion and dissolution for hazard identification);

— added discussion of considerations related to analytical method qualification;

— added informative annexes on general principles, vehicle extraction considerations, and the analytical evaluation threshold (AET; concentration threshold below which extractables or leachables identification is unneeded).

A list of all parts in the ISO 10993 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

ISO 10993-1 serves as a framework in which to plan a biological evaluation which, as scientific knowledge advances our understanding of the basic mechanisms of tissue responses, minimizes the number and exposure of test animals. Preference is given to the assessment of chemical/physical properties and testing with *in vitro* models in situations within a risk assessment process. These methods are used when the results yield equally relevant information to that obtained from *in vivo* models.

The characterization procedure and its associated flowchart is based on the principles in ISO 10993-1; specifically, that the biological evaluation and risk assessment process is most efficient and effective if it is based on the minimum amount of acceptable and necessary chemical information that can establish that a medical device presents an acceptable health risk.

ISO 10993-1:2018, 4.2 states that in the selection of materials to be used in medical device manufacture, the first consideration shall be fitness for purpose with regard to characteristics and properties of the material, which can include chemical, toxicological, physical, electrical, morphological and mechanical properties. Furthermore, ISO 10993-1:2018, 6.1 states that gathering physical and chemical information on the medical device or component is a crucial first step in the biological evaluation process and its associated process of material characterization.

Lastly, ISO 10993-1:2018, and by reference ISO 14971, points out that a biological risk analysis depends on what is known about the material formulation, what nonclinical and clinical safety and toxicological data exist, and on the nature and duration of body contact with the medical device.

The requirements specified in this document are intended to yield the following information, which will be of value in assessing the biological response to the materials as represented in the final product.

— The identities and quantities, as appropriate, of the materials of construction of the medical device (device configuration).

— The identities and quantities, as appropriate, of the chemical constituents in each material of construction (material composition).

— The identities and quantities, as appropriate, of chemical substances used in the medical device's manufacturing process, including processing aids and residues.

— The potential of the medical device and/or its materials of construction to release chemical substances to which a potentially affected individual could be exposed to during clinical conditions of use.

The composition of the materials of construction is mainly established by the suppliers of these materials. The composition can change during manufacture of a medical device. Other medical device characteristics are chiefly established by component suppliers or device manufacturers to address the performance and quality requirements to be met by the finished medical device as well as the production, storage and distribution processes experienced by the medical device.

Biological evaluation of medical devices —

Part 18:
Chemical characterization of medical device materials within a risk management process

1 Scope

This document specifies a framework for the identification, and if necessary, quantification of constituents of a medical device, allowing the identification of biological hazards and the estimation and control of biological risks from material constituents, using a generally stepwise approach to the chemical characterization which can include one or more of the following:

— the identification of its materials of construction (medical device configuration);

— the characterization of the materials of construction via the identification and quantification of their chemical constituents (material composition);

— the characterization of the medical device for chemical substances that were introduced during manufacturing (e.g. mould release agents, process contaminants, sterilization residues);

— the estimation (using laboratory extraction conditions) of the potential of the medical device, or its materials of construction, to release chemical substances under clinical use conditions (extractables);

— the measurement of chemical substances released from a medical device under its clinical conditions of use (leachables).

This document can also be used for chemical characterization (e.g. the identification and/or quantification) of degradation products. Information on other aspects of degradation assessment are covered in ISO 10993-9, ISO 10993-13, ISO 10993-14 and ISO 10993-15.

The ISO 10993 series is applicable when the material or medical device has direct or indirect body contact (see ISO 10993-1 for categorization by nature of body contact).

This document is intended for suppliers of materials and manufacturers of medical devices, to support a biological evaluation.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

ISO 14971, *Medical devices — Application of risk management to medical devices*

3 Terms and definitions

For the purposes of this document, the definitions in ISO 10993-1 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available from https://www.iso.org/obp

— IEC Electropedia: available from http://www.electropedia.org/

3.1
accelerated extraction
extraction whose duration is shorter than the duration of clinical use but whose conditions do not result in a chemical change to the substances being extracted

Note 1 to entry: See also Annex D.

3.2
analytical evaluation threshold
AET
threshold below which the analyst need not identify or quantify leachables or extractables or report them for potential toxicological assessment

Note 1 to entry: See Annex E.

3.3
analytically expedient
situation where an extraction vehicle can be directly evaluated with generally available analytical methods with the sensitivity and selectivity necessary to achieve a designated reporting threshold such as the AET

3.4
analytical screening method
method whose purpose is to discover, identify and semi-quantitatively estimate the concentration of all relevant analytes in a test sample above an established reporting threshold (such as the AET)

3.5
analytical targeting method
method whose purpose is to quantify, with an appropriately high degree of accuracy and precision, specified analytes in a specified test sample over a specified concentration range

3.6
chemical characterization
process of obtaining chemical information, accomplished either by information gathering or by information generation, for example, by literature review or chemical testing

3.7
chemical information
qualitative and quantitative, if applicable, knowledge related to the configuration, composition and production of the medical device and/or its materials of construction, thereby establishing the identities and amounts of constituents present in the materials and device

Note 1 to entry: See also 5.2.1, 5.2.2, 5.2.3, and Annex B.

Note 2 to entry: Chemical information can be used to establish the hypothetical worst-case release of chemicals from a medical device, predicated on the circumstance that all chemicals present in the device are released from the device under its clinical conditions of use.

3.8
clinically established
medical device, component, or material of construction which has been used extensively for specified and established clinical uses for which biocompatibility has been established

3.9
component
item which forms one part of a medical device, but is not itself a medical device

3.10
constituent
chemical that is present in a finished medical device or its materials of construction

Note 1 to entry: Constituents may be intentionally present (e.g. an additive such as an antioxidant) or unintentionally present (e.g. an impurity or degradant).

3.11
convertor
person or company who converts or fabricates a basic raw material into a semi-finished product (e.g. a former of lengths of rod, tubing, or plastic components)

3.12
digestion
process of completely solubilizing a medical device, one or more of its components or one or more of its materials of construction by breaking it down into its fundamental structural units, including its elemental constituents or monomeric units

3.13
dissolution
process of completely solubilizing a medical device, one or more of its components or one or more of its materials of construction, generally preserving the molecular structures of its constituents

3.14
exaggerated extraction
extraction that is intended to result in a greater number or amount of chemical constituents being released as compared to the amount generated under the clinical conditions of use

Note 1 to entry: It is important to ensure that the exaggerated extraction does not result in a chemical change of the material or the substances being extracted.

3.15
exhaustive extraction
multi-step extraction conducted until the amount of material extracted in a subsequent extraction step is less than 10 % by gravimetric analysis (or achieved by other means) of that determined in the initial extraction step

3.16
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

3.17
extraction power
ability of an extraction vehicle to extract (or leach) substances from a medical device, component or material of construction

Note 1 to entry: The extraction power of an extraction vehicle is impacted by its physicochemical properties, including, but not limited to, its polarity, pH and dielectric constant.

3.18
extraction vehicle
medium (solution or solvent) which is used to extract (or leach) a test article for the purpose of establishing the test article's extractables or leachables profile

Note 1 to entry: It is preferred that extraction vehicles be analytically expedient.