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Biological evaluation of medical devices —

Part 9: Framework for identification and quantification of potential degradation products

Évaluation biologique des dispositifs médicaux —

Partie 9: Cadre pour l'identification et la quantification des produits potentiels de dégradation

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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).

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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 www.iso.org/iso/foreword.html.

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

This third edition cancels and replaces the second edition (ISO 10993-9:2009), which has been technically revised.

The main changes compared to the previous edition are as follows:

a) biodegradation changed to degradation;

b) information on test methods amended to consider nanomaterials and relevant material specific standards.

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.

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Introduction

This document is intended to present the general principles on which the specific material investigations to identify and quantify degradation products described in ISO 10993-13 (polymers), ISO 10993-14 (ceramics) and ISO 10993-15 (metals and alloys) are based.

Information obtained from these studies is intended to be used in the biological evaluations described in the remaining parts of ISO 10993.

The materials used to construct medical devices can form degradation products when exposed to the biological environment, and in the body these products might behave differently to the bulk material.

Mechanical wear, which is not in scope of this document, causes mostly particulate debris, whereas non-mechanical degradation can lead to the release of free ions or to different kinds of reaction products in the form of organic or inorganic compounds.

The degradation products can be either reactive or stable and without biochemical reaction with their environment. Accumulations of substantial quantities of stable degradation products can, however, have physical effects on the surrounding tissues. Degradation products might remain at the location of their generation or might be transported within the biological environment by various mechanisms.

The level of biological tolerability of degradation products depends on their nature and concentration, and should be primarily assessed through clinical experience and focused studies. For theoretically possible, new and/or unknown degradation products, relevant testing is necessary. For well-described and clinically accepted degradation products, further investigation might not be necessary.

Note that the safety and efficacy of a medical device can be compromised as a result of any unintended or premature degradation, which should be considered in the risk management of the device.

This document can be applied to the degradation of materials used in any kind of product that falls within the definition of “medical device” in ISO 10993-1, even if such products are subject to different regulations from those applying to medical devices, e.g. the scaffold in a tissue engineered medical product, or a carrier matrix to deliver drugs or biologics.

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Biological evaluation of medical devices —

Part 9:
Framework for identification and quantification of potential degradation products

1 Scope

This document provides general principles for the systematic evaluation of the potential and observed degradation of medical devices through the design and performance of *in vitro* degradation studies. Information obtained from these studies can be used in the biological evaluation described in the ISO 10993 series.

This document is applicable to both materials designed to degrade in the body as well as materials that are not intended to degrade.

This document is not applicable to:

a) the evaluation of degradation which occurs by purely mechanical processes; methodologies for the production of this type of degradation product are described in specific product standards, where available;

NOTE Purely mechanical degradation causes mostly particulate matter. Although this is excluded from the scope of this document, such degradation products can evoke a biological response and can undergo biological evaluation as described in other parts of ISO 10993.

b) leachable components which are not degradation products;

c) medical devices or components that do not contact the patient's body directly or indirectly.

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 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 10993-13, *Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices*

ISO 10993-14, *Biological evaluation of medical devices — Part 14: Identification and quantification of degradation products from ceramics*

ISO 10993-15, *Biological evaluation of medical devices — Part 15: Identification and quantification of degradation products from metals and alloys*

3 Terms and definitions

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

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

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

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

3.1
degradation
decomposition of a material

3.2
absorb
action of a non-endogenous (foreign) material or substance passing through or being assimilated by cells and/or tissue over time

3.3
leachable
substances that can be released from a medical device or material during clinical use

3.4
corrosion
attack on metallic materials by chemical or electrochemical reactions

Note 1 to entry: The term is sometimes used in a general sense for the deterioration of other materials but is in this document reserved for metallic materials.

3.5
substance
single chemical element or compound, or a complex structure of compounds

3.6
component
one of the different parts of which a device is composed

3.7
degradation product
particle or chemical compound that is derived from the chemical breakdown of the original material

3.8
service environment
anatomical location for the intended use of the device including surrounding fluids, tissues and biomolecules

4 Principles for design of degradation studies

4.1 General

The approach to the assessment of degradation varies with the nature of the material under investigation, the medical device and the anatomical location of the specific device. The *in vitro* degradation models chosen for evaluation shall be representative of these factors. The studies to be conducted do not require a biological environment, but one that simulates the conditions of the intended clinical use.

Experience has shown that some *in vitro* models do not reflect all aspects of the service environment (e.g. mechanical processes) that can influence the degradation process. All such factors should be taken into account when modelling the service environment *in vitro*.

Experience has also shown that material property changes during degradation can result in different biological responses. The user is urged to be aware of those property changes and apply the relevant materials-specific standards (e.g. crystallization of polymers).

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