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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

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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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Materials-specific or product-specific degradation standards that address identification and quantification of degradation products should be considered in the design of degradation studies. ISO 10993-13 (for polymers), ISO 10993-14 (for ceramics) or ISO 10993-15 (for metals and alloys) shall apply if no suitable material-specific standard exists. Devices composed of two or more material types should consider all relevant degradation standards.

ISO 10993-13, ISO 10993-14 and ISO 10993-15 consider only those degradation products generated by a chemical alteration of the finished device. They are not applicable to degradation of the device induced during its intended use by mechanical stress, wear or electromagnetic radiation. For such degradation other methods should be considered.

4.2 Preliminary considerations

Careful consideration of the potential for intended or unintended degradation of a material is essential to the evaluation of the biological safety of a device. Part of this consideration is an assessment of the chemical characteristics and known degradation mechanisms, followed by an assessment of the need for, and design of, experimental degradation studies.

It is neither necessary nor practical to conduct degradation studies for all medical devices. Refer to Annex A to determine when degradation studies should be considered. The assessment of the need for experimental degradation studies shall include a review of the literature and/or documented clinical experience. Guidance on proper reviewing of the literature can be found in ISO 10993-1. Such an assessment can potentially result in the conclusion that no further testing is needed.

Guidance on the biological evaluation of leachables including degradation products is given in ISO 10993-1, ISO 10993-16 and ISO 10993-17. See ISO 10993-18 for guidance on the chemical characterization of materials and their leachables used in medical devices. See ISO/TS 10993-19 for guidance on the physico-chemical, morphological and topographical characterization of materials. Consideration of these standards prior to conducting degradation studies can prove helpful in distinguishing degradation products from other leachables.

NOTE Despite the difference between degradation products and other leachables, it can be possible to combine a study on degradation products with a study on other leachable components. Distinguishing between degradation products and other types of leachables might not be necessary for further biological evaluation studies. However, when a reduction of the level of leachable components is deemed necessary as a risk control measure, this information is important. Additionally, some degradation products cannot leach from the device but can still impact the properties of the device.

4.3 Study design

A degradation study plan complete with the purpose of the study shall be designed and documented to address the issues identified in 4.1. The approved study plan shall define the analytical methods by which the following characteristics of degradation products are to be investigated:

a) chemical properties;

b) physicochemical properties;

c) physical morphology (as applicable).

The approved study plan shall also describe the methods used to generate degradation products. The methods for generating degradation products should be optimized and scientifically justified. The degradation products should be identified and quantified using methods described in ISO 10993-18.

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The approved study plan for multi-component devices shall take into account each individual component/material and shall consider synergistic effects on the degradation of the different components as well as the possibility of secondary reactions between/among the degradation products.

NOTE Degradation can in most cases be modelled by *in vitro* tests. During degradation pH needs to be controlled to a clinically relevant range, especially if pH can affect degradation product composition. The user needs to be aware that both the degradation rate and amount of generated by-products can be affected if pH is different from that expected for the service environment.

4.4 Characterization of degradation products from medical devices

The degradation products produced in the study can be particulate or soluble compounds or ions. Appropriate analytical methods to characterize these products shall be used and reported in the study report. These methods shall be adequately qualified for their intended purpose. If particles are generated, they shall be characterized with regard to size, shape, surface area and other relevant characteristics.

Because the physical and chemical properties of particulate materials can change at the nanoscale (approximately 1 nm to 100 nm), this can affect their toxicological properties. For those medical devices composed of or containing nanoscale materials, the user is referred to ISO/TR 10993-22 for a thorough consideration of the impact on the risk assessment of nanoscale products.

If biological evaluation of the degradation products is required, then care shall be taken in the design of the degradation study in order to ensure that it does not interfere with the biological assay.

Considerations for the degradation study are provided in Annex B. The protocol shall include

a) identification and characterization of device and/or material and intended use,

b) identification and characterization of possible mechanism of degradation,

c) identification and characterization of known, probable and potential degradation products, and

d) test methodologies.

The extent and rate of release of degradation products depends on variables such as manufacturing processes that alter surface composition and structures; migration to the surface from within the material; solubility in, and chemical composition of, the physiological milieu; etc.

5 Study report

The study report shall include the following information, where relevant:

a) description of material(s) or device (see B.2), including intended use and nature of body contact;

b) description of proposed degradation mechanism(s) (e.g., hydrolytic, enzymatic, oxidative, etc.), and how the degradation study is appropriately designed to assess the proposed mechanism(s);

c) description of the degradation study procedures (e.g. test article, sample size, degradation media, ratio of test article vs. degradation media, study conditions, experimental steps and parameters, sampling strategy, monitoring and observation, etc.);

d) description of analytical methods, including quantification limits and controls;

e) statement of compliance to appropriate good laboratory practices and/or to quality management systems for test laboratories (e.g. ISO/IEC 17025);

f) identification and quantification of degradation products (e.g. form and condition of degradation products, their stability and controls used);

g) summary of results;

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h) interpretation and discussion of results.

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Annex A
(normative)

Consideration of the need for degradation studies

Degradation studies shall be considered if:

a) the device is designed to be absorbed by the body or

b) the device is intended to be implanted for longer than thirty days or

c) an informed consideration of the material(s) system indicates that toxic degradation products could be released during body contact.

However, degradation studies might not be needed if sufficient material formulation, and manufacturing process information are available and degradation data relevant to degradation products in the intended use already exist.

NOTE Relevant degradation data can include information on degradation mechanism, degradation rate, identification and quantity of degradation products, and particle shape/size and distribution.

The need for *in vivo* studies shall be considered in light of results from *in vitro* studies.

Where appropriate, *in vitro* experiments shall be considered for investigating theoretically possible degradation processes. *In vivo* studies shall take into consideration ISO 10993-2. *In vivo* and *in vitro* studies shall also be considered for determining the probability of occurrence of degradation and the identification of probable degradation products and the degradation rate.

The flowchart in Figure A.1 illustrates the logic applicable to these considerations. For polymers that are intended to hydrolytically degrade, e.g. polylactide, the user is referred to ISO 13781.

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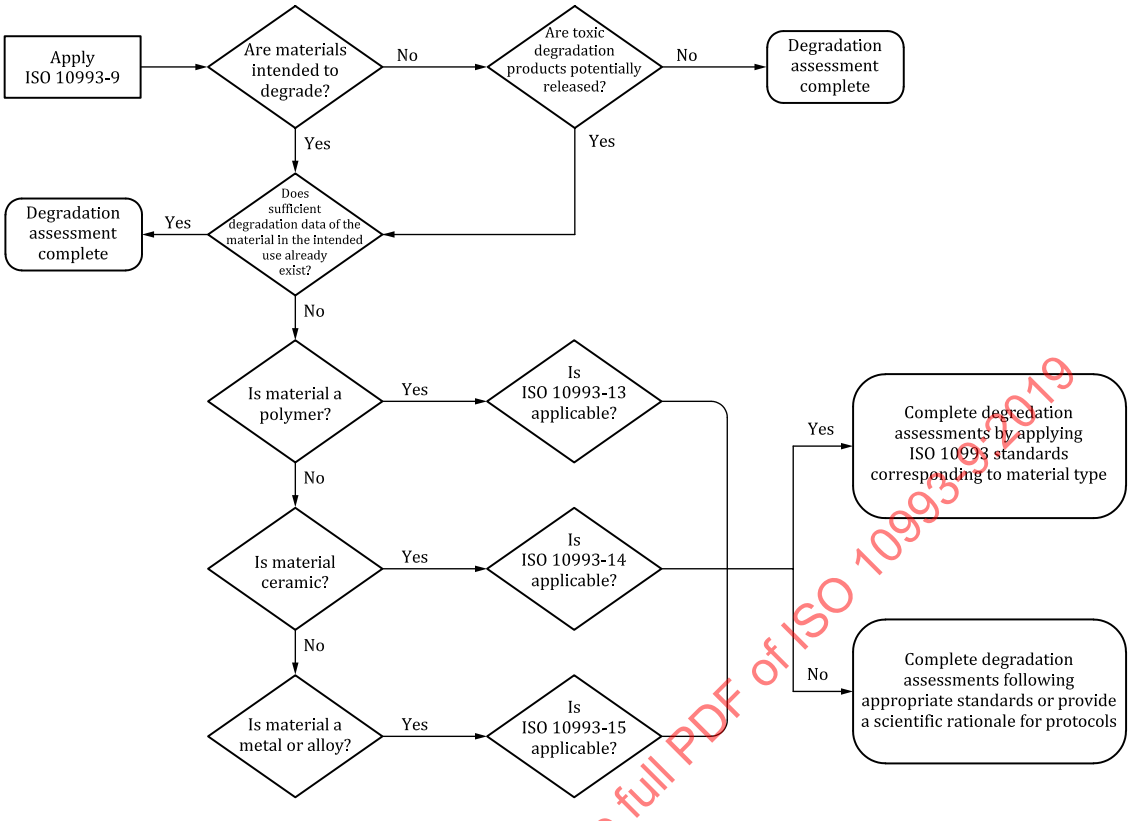

Figure A.1 — Flowchart illustrating consideration of the need for degradation studies

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Annex B
(informative)

Degradation study considerations

B.1 General

This annex contains aspects that need to be considered in the evaluation of possible degradation.

Appropriate practical studies should be considered in the case where essential information is missing on the degradation of devices or materials and the biological effects of potential degradation products.

B.2 Description of medical device and/or material

The following should be considered when describing the device or material under study:

a) name of medical device and/or material;

b) function of medical device;

c) intended use;

d) intended biological environment;

e) composition of the material;

f) conditioning of the material (e.g. processing, sterilization);

g) surface condition;

h) dimensions;

i) construction of device or material under study (e.g. single component, single component to be used with others and the nature of their interaction, or multicomponent device — assessment carried out for each component material);

j) contact duration;

k) shelf life;

NOTE For some products storage can impact degradation, and therefore degradation studies to support labelled shelf life can be important.

l) other relevant characterizations.

B.3 Assessment of potential and known degradation products

B.3.1 General

Degradation of material can occur within the bulk, or majority, of the material. Degradation can also occur at the surface of the material. Both bulk and surface degradation can occur at the same time and can influence one another.

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