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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 10993-9 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This second edition cancels and replaces the first edition (ISO 10993-9:1999), which has been technically revised.

ISO 10993 consists of the following parts, under the general title *Biological evaluation of medical devices*:

— *Part 1: Evaluation and testing within a risk management process*

— *Part 2: Animal welfare requirements*

— *Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

— *Part 4: Selection of tests for interactions with blood*

— *Part 5: Tests for* in vitro *cytotoxicity*

— *Part 6: Tests for local effects after implantation*

— *Part 7: Ethylene oxide sterilization residuals*

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

— *Part 10: Tests for irritation and skin sensitization*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymeric medical devices*

— *Part 14: Identification and quantification of degradation products from ceramics*

— *Part 15: Identification and quantification of degradation products from metals and alloys*

— *Part 16: Toxicokinetic study design for degradation products and leachables*

— *Part 17: Establishment of allowable limits for leachable substances*

— *Part 18: Chemical characterization of materials*

— *Part 19: Physico-chemical, morphological and topographical characterization of materials* [Technical Specification]

— *Part 20: Principles and methods for immunotoxicology testing of medical devices* [Technical Specification]

Future parts will deal with other relevant aspects of biological evaluation.

Introduction

This part of ISO 10993 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 causes mostly particulate debris, whereas the release of substances from surfaces due to leaching, chemical breakdown of structures or corrosion can lead to 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, no further investigation may be necessary.

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

Biological evaluation of medical devices —

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

1 Scope

This part of ISO 10993 provides general principles for the systematic evaluation of the potential and observed biodegradation of medical devices and for the design and performance of biodegradation studies. Information obtained from these studies can be used in the biological evaluation described in the ISO 10993 series. This part of ISO 10993 considers both non-resorbable and resorbable materials.

This part of ISO 10993 is not applicable to:

a) 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 1 Purely mechanical degradation causes mostly particulate matter. Although this is excluded from the scope of this part of ISO 10993, such degradation products can evoke a biological response and thus need to 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.

NOTE 2 This part of ISO 10993 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.

2 Normative references

The following referenced documents are indispensable for the application 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.

3.1
degradation
decomposition of a material

3.2
biodegradation
degradation (3.1) due to the biological environment

3.3
bioresorbable medical device
medical device intended for **degradation** (3.1) and resorption in the biological environment of the body

3.4
leachable
extractable component from a material that is not a product of degradation

3.5
corrosion
attack on metallic materials by chemical or electrochemical reactions

NOTE The term is sometimes used in a general sense for the deterioration of other materials but is in this part of ISO 10993 reserved for metallic materials.

3.6
substance
single chemical element or compound, or a complex structure of compounds

3.7
device component
one of the different parts of which a device is composed

3.8
degradation product
any particle or chemical compound that is derived from the chemical breakdown of the original material

3.9
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 models chosen for evaluation shall be representative of the service environment of the device. The studies to be conducted do not require a biological environment, but one that simulates the conditions of the biological environment.

Experience has shown that in some degradation processes, *in vitro* models do not reflect all aspects of the service environment, e.g. mechanical processes can influence biodegradation, and should be taken into account when defining the model service environment.

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 biodegradation studies.

It is neither necessary nor practical to conduct degradation studies for all medical devices. Consideration of the need for degradation studies is provided in Annex A. 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 a study can result in the conclusion that no further testing is needed if the product under consideration has a demonstrated history of acceptable clinical experience, new data, published data and analogies with known devices, materials and degradation products.

Guidance on the biological evaluation of degradation products and leachables is given in ISO 10993-1, ISO 10993-16 and ISO 10993-17. See ISO 10993-12 for guidance on the extraction of leachables from medical devices and ISO 10993-18 for guidance on the chemical characterization of materials and their leachables used in medical devices. See ISO 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 leachables from degradation products.

NOTE Despite the difference between leachables and degradation products, it might be possible to combine a study on degradation products with a study on leachable components. Distinguishing between degradation products and other types of leachable is not 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.

4.3 Study design

A biodegradation 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 and physicochemical properties;

b) surface morphology;

c) biochemical properties.

The approved study plan shall also describe the methods used to generate degradation products. The methods should be optimized for detection of degradable substances and justified.

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 the degradation products.

NOTE Biodegradation can be modelled by *in vitro* tests.

4.4 Characterization of degradation products from medical devices

The degradation products produced in the study may be particulate or soluble compounds or ions. Appropriate analytical methods to characterize these products shall be used, validated and reported in the study report. If particles are generated, they need to be characterized with regard to size, shape, surface area and other relevant characteristics.

NOTE 1 Because the physical and chemical properties of particulate materials can change at the nanoscale, this can affect their toxicological properties.

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 biodegradation 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.

NOTE 2 The extent and rate of release of degradation products depends on variables such as manufacturing processes which 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 Clause B.2), including intended use and nature of body contact;

b) assessment of degradation and rationale for the assessment of degradation;

c) description of degradation test methods, test conditions, test materials and procedures, including controls;

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;

h) interpretation and discussion of results.

Annex A
(normative)

Consideration of the need for degradation studies

A.1 Degradation studies shall be considered if

a) the device is designed to be bioresorbable 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 substances can be released during body contact.

A.2 Degradation studies need not be necessary if

a) the probable degradation products are the same substances, in the predicted quantities, and produced at a similar rate and in comparable location to those that are produced by devices that have a history of safe clinical use and/or

b) the probable degradation products are particulate and are in a physical state, i.e. size, distribution and shape, and in the predicted quantities, and produced at a similar rate and in comparable location to those that are produced by devices that have a history of safe clinical use or

c) sufficient degradation data relevant to the substances and degradation products in the intended use already exist.

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 animal welfare (see 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.

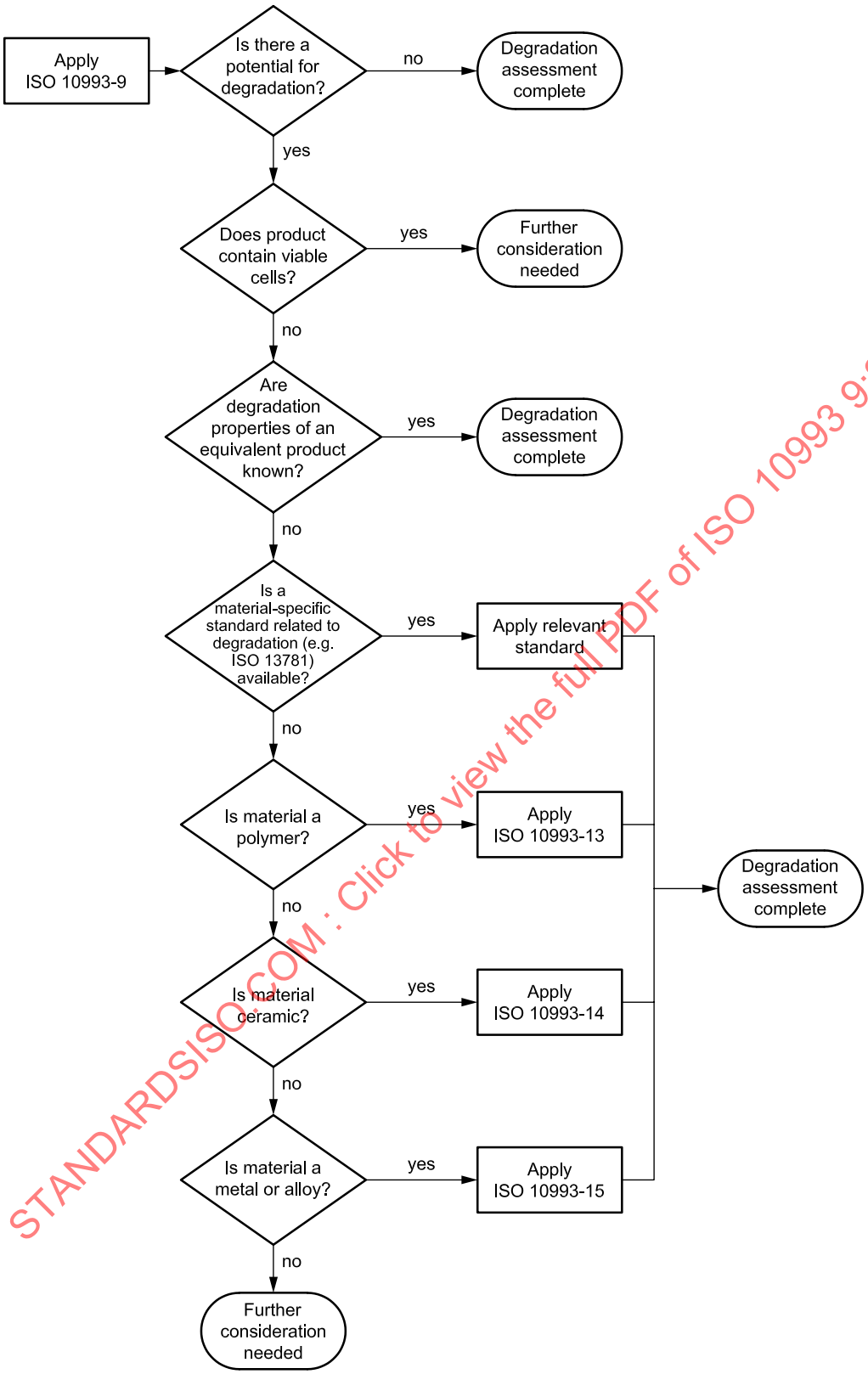

Figure A.1 — Flowchart illustrating consideration of the need for degradation studies