TECHNICAL REPORT

ISO TR 10993-9

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Biological evaluation of medical devices —

Part 9:
Degradation of materials related to biological testing

Évaluation biologique des dispositifs médicaux —
Partie 9: Dégradation des matériaux relative à l'évaluation biologique

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Contents

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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 main task of technical committees is to prepare International Standards, but in exceptional circumstances a technical committee may propose the publication of a Technical Report of one of the following types:

— type 1, when the required support cannot be obtained for the publication of an International Standard, despite repeated efforts;

— type 2, when the subject is still under technical development or where for any other reason there is the future but not immediate possibility of an agreement on an International Standard;

— type 3, when a technical committee has collected data of a different kind from that which is normally published as an International Standard ("state of the art", for example).

Technical Reports of types 1 and 2 are subject to review within three years of publication, to decide whether they can be transformed into International Standards. Technical Reports of type 3 do not necessarily have to be reviewed until the data they provide are considered to be no longer valid or useful.

ISO/TR 10993-9, which is a Technical Report of type 2, was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This document is being issued in the type 2 Technical Report series of publications (according to subclause G.4.2.2 of part 1 of the ISO/IEC Directives, 1992) as a "prospective standard for provisional application" in the field of degradation of materials because there is an urgent need for guidance on how standards in this field should be used to meet an identified need.

This document is not to be regarded as an "International Standard". It is proposed for provisional application so that information and experience of its use in practice may be gathered. Comments on the content of this document should be sent to the ISO Central Secretariat.

A review of this type 2 Technical Report will be carried out not later than two years after its publication with the options of: extension for another two years; conversion into an International Standard; or withdrawal.

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

— *Part 1: Guidance on selection of tests*

— *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 cytotoxicity: in vitro methods*

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

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 9: Degradation of materials related to biological testing* [Technical Report]

— *Part 10: Tests for irritation and sensitization*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymers*

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

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

— *Part 16: General guidance on toxicokinetic study design for degradation products and leachables from medical devices*

— *Part 17: Glutaraldehyde and formaldehyde residues in industrially sterilized medical devices*

Annexes A, B and C of this part of ISO 10993 are for information only.

Introduction

Attention is drawn to the definition of "medical device" (see 3.1).

When the material of an implanted device experiences a decrease in its mechanical properties and/or mass, it is referred to as degradation for polymers and ceramics, and corrosion for metals and alloys. For those medical devices and materials which experience repeated stress cycles during use, the biological environment may reduce their anticipated fatigue life or endurance limit.

The stability of materials and devices in the biological environment is influenced by the conditions of the service environment as well as the chemical composition, additives, processing aides, impurities, manufacturing processes and decontamination/sterilization.

In addition to the principal components, most polymers contain additives such as antioxidants and stabilizers and all materials contain either minor components or impurities which may be leachable and enter the biological environment and induce a tissue response even if the principal component is stable. Most devices rely upon their stability to ensure safe and efficacious performance. Others, such as resorbable sutures, are designed intentionally to degrade.

While the ability to predict the stability of materials and medical devices *in vivo* is of great importance, the extrapolation of *in vitro* data to the clinical service environment remains a difficult, yet-to-be resolved problem. *In vitro* methods for assessing degradation of materials and medical devices range from the very simple, e.g. exposure to 0,9 % isotonic saline solution, to more complex exposure to solutions containing enzymes, phospholipids, etc. In addition, the material/device can be subjected to external mechanical stress/load during testing. A sequential approach to *in vitro* degradation testing of medical devices and materials involving both accelerated and real-time testing techniques is shown in figure 0.1.

Selection of methods for accelerating degradation testing in a manner which is representative of the service environment remains the responsibility of the designers of the *in vitro* test schemes used. Currently, there are no standard practices, methods or guidelines for the assessment of the degradation of medical devices and materials, and of the degradation products formed, from degradation of these materials and devices in the biological environment. There are, however, methods used for extracting leachable fractions from materials and devices to be used in biological response testing (see, for example, ISO 10993-3, ISO 10993-5, ISO 10993-6 and ISO 10993-7).

The extraction media used may be selected to be compatible with the biological test and may not necessarily represent an adequate extraction of the material. There is a need for additional research to develop accelerated methods for evaluating materials degradation in the human body.

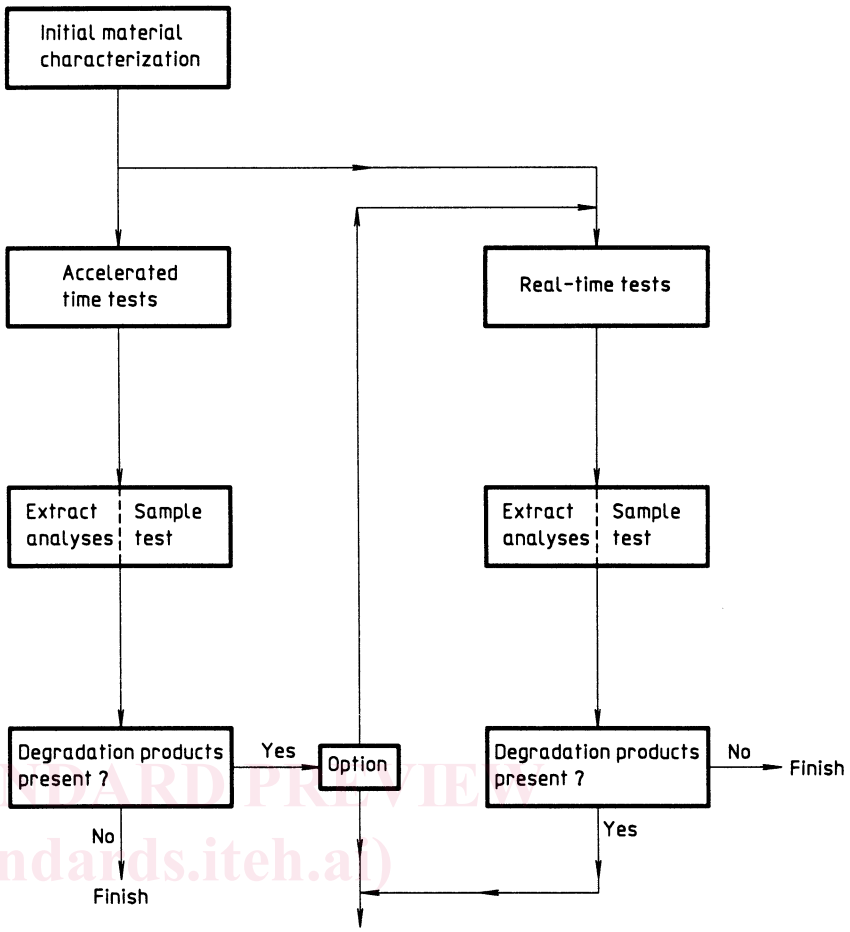

Figure 0.1 — Degradation product evaluation scheme

Biological evaluation of medical devices —

Part 9:
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1 Scope

This Technical Report aims to facilitate the design of test procedures which are used to evaluate the biological responses to degradation products released from medical devices. Following brief descriptions of each major class of material used for medical devices, this Technical Report focuses on the likely mechanisms of degradation of these materials when they are used in a biological service environment. Accelerated time and real-time degradation testing environments for devices and materials are suggested along with characterization techniques for the degradation products. Finally, an approach for identifying and quantifying degradation products obtained from explanted devices and tissues is proposed.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this Technical Report. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this Technical Report are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 10993-1:1992, *Biological evaluation of medical devices — Part 1: Guidance on selection of tests.*

ISO 10993-3:1992, *Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.*

ISO 10993-5:1992, *Biological evaluation of medical devices — Part 5: Tests for cytotoxicity: in vitro methods.*

ISO 10993-6:1994, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation.*

ISO 10993-7:—[1], *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals.*

ISO 10993-12:—[1], *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials.*

3 Definitions

For the purposes of this Technical Report, the definitions in ISO 10993-1, ISO 10993-3 and 10993-5, and the following definitions apply.

3.1 medical device: Any instrument, apparatus, appliance, material or other article, including software, whether used alone or in combination, intended by the manufacturer to be used for human beings solely or principally for the purposes of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease, injury or handicap;

— investigation, replacement or modification of the anatomy or of a physiological process;

1) To be published.

— control of conception;

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means. (Repeated for convenience from ISO 10993-1:1992, definition 3.1.)

3.2 accelerated time test: Laboratory test designed to speed up the degradation of a material/device which would normally take place in the service environment.

3.3 aluminium oxide ceramic: High density, high purity Al_2O_3 which may be a fine-grained polycrystalline, semicrystalline, amorphous or single crystal material.

3.4 amorphous polymer: Macromolecules which do not form crystalline structures.

3.5 antistatic agent: Additive which increases surface conductivity of the material and thus reduces the buildup of charge on the surface.

3.6 bioabsorption: Dynamic process involving the interaction of the body with a biomaterial which results in the breakdown and dissolution or uptake of the material in the physiological environment.

3.7 bioadsorption: Deposition of components of tissue and body fluids on the surface of a material/device.

3.8 bioceramic: Ceramic which upon implantation is transformed into less soluble minerals.

3.9 biodegradation: Alteration undergone by the biomaterial or medical device involving loss of their integrity or performance when exposed to a physiological or simulated environment.

3.10 bioerosion: Dissolution or fragmentation of a biomaterial implanted in the body occurring as a result of surface reactions.

3.11 bioglass; bioglass ceramic: Glass based on SiO_2 which has a specific surface reactivity that enhances the interaction with surrounding tissue due to the action of additives, primarily alkali oxides.

3.12 biomaterial: Synthetic, natural or modified natural material intended to be in contact and interact with the biological system.

3.13 bioresorption: Process by which biomaterials are degraded in the physiological environment and the byproducts eliminated or completely bioabsorbed.

3.14 biostability: Quality of a biomaterial or a medical device of which the physical, chemical and mechanical or other changes are not modified with respect to its behaviour, function or performance within the biological environment.

3.15 biotransformation: Any change which a biomaterial undergoes in the body due to the interaction between the material and the physiological constituents.

3.16 branched polymer: Long-chain molecules with side chains attached to the backbone of the polymer. Often soluble in the same solvents as the corresponding linear polymers.

3.17 calcium phosphate ceramic: Ceramic based on calcium and phosphorus oxide containing one or more calcium phosphate phases.

3.18 coating: Deposited layer or covering on a biomaterial or medical/dental device which is intended to protect or enhance the performance of the device or biomaterial.

3.19 [random] [regular] [block] [graft] copolymer: Polymer consisting of different repeating units (made from two or more different monomers), having different degrees of order.

3.20 corrosion: Chemical reaction of a solid material (usually a metal or alloy) with the environment which causes measurable material property changes.

3.21 crevice corrosion: Usually accelerated chemical reaction in a small fissure, pit or crack of a metal or alloy within a corrosive environment.

3.22 crosslinked [network] polymer: Polymer with chemical linkages between the chains.

3.23 degradation product: Byproduct of a material which is generated by the breakdown or decomposition of the material.

3.24 depolymerization: Reversion of a polymer to its monomer(s) or to a polymer of lower relative molecular mass.

3.25 deposit: Layer or covering laid down on a biomaterial or medical device.

3.26 elastomer: Polymer which maintains its elastic properties in the temperature range between glass

transition temperature and the temperature at which the elastomer begins to flow.

3.27 electrolyte: Substance, usually in solution, which will transmit an electric current by ions.

3.28 environmental stress-cracking: Cracking of stressed materials subjected to certain conditions: the stress may be externally applied, or internally introduced during processing.

3.29 enzymatic degradation: Degradation of materials enhanced and/or initiated by enzymes.

3.30 extraction medium: Liquid which does not dissolve a material or device, but does induce the release of one or more extractable components.

3.31 fatigue corrosion: Combined effect of dynamic loads and chemical attack on metal or alloy properties within a corrosive environment.

3.32 fretting corrosion: Combined interaction of wear and chemical attack on a metal or alloy within a corrosive environment.

3.33 fibre: Arrangement of molecules into a long tubular shape where the length is of the order of 100 times the diameter. Fibre can be continuous or specific lengths.

3.34 filler: Various forms of inorganic or organic materials added to alter material properties.

3.35 final product: Medical device in its "as-used" state.

3.36 homopolymer: Polymer consisting of identical repeating units (made from a single monomer).

3.37 hydrolysis: Chemical bond-cleavage which involves attack by neutral or ionized water in acidic, neutral or basic aqueous media.

3.38 implant coating interface: Zone between the substrate and the coating.

3.39 implant tissue interface: Zone between the implant material and the tissue.

3.40 inert bioceramic: Bioceramic which undergoes no measurable chemical change during long-term contact with the biological environment.

3.41 interface: Zone of contact between two surfaces.

3.42 *in vitro* degradation: Changes in a material exposed to an environment simulating *in vivo* conditions.

3.43 *in vivo* degradation: Structural, physical, mechanical and chemical changes in a material that are induced by the organism.

3.44 leachable: Extractable component, such as additives, monomers and low relative molecular mass constituents in polymeric materials.

3.45 linear polymer: Long chains of uncrosslinked backbone atoms which form a macromolecule.

3.46 lubricant: Substance added to enhance material flow and handling characteristics (e.g. during injection-moulding, extrusion, etc.).

3.47 matrix: Embedding material for fibres or fillers.

3.48 monomer: Any molecule that can be converted into a polymer.

3.49 natural polymer: Macromolecules of natural origin, such as collagen, cellulose, polyaminoacids, rubber, etc.

3.50 oxidative degradation: Reaction occurring due to air (oxygen) or oxidizing agents leading to chain cleavage of chemical bonds.

3.51 pigment: Insoluble colorant added to a material.

3.52 plasticizer: Substance added to polymers which modifies their forming properties and increases the flexibility of products made from these polymers.

3.53 plastics: Synthetic polymers containing additives which enhance polymer processing and/or the final properties of the resulting products.

3.54 polymer blend: Two or more polymers mixed together or in solution to form a product which has properties very often different from those of individual polymers.

3.55 potentiostatic polarization method: Method equal to chronoamperometry with a constant potential: the time-dependent measurement of the current density going through a material/solution interface at a definite potential.

3.56 potentiodynamic polarization method: Method equal to voltamperometry with a linear variation of the potential: the potential-dependent