INTERNATIONAL STANDARD

ISO 10993-13

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Biological evaluation of medical devices —

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

Évaluation biologique des dispositifs médicaux —
Partie 13: Identification et quantification de produits de dégradation de dispositifs médicaux à base de polymères

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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.

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.

International Standard ISO 10993-13 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices.*

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

— *Part 1: Evaluation and testing*

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

— *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 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*

Annex A of this part of ISO 10993 is for information only.

Introduction

This part of ISO 10993 was developed from ISO/TR 10993-9. Degradation products covered by this standard are formed primarily by chemical bond scission due to hydrolytic and/or oxidative processes in an aqueous environment. It is recognized that additional biological factors, such as enzymes, other proteins and cellular activity, can alter the rate and nature of degradation.

It should be kept in mind that a polymeric device may contain residuals and leachables such as monomers, oligomers, solvents, catalysts, additives, fillers and processing aids. These components which, if present, may interfere with the identification and quantification of the degradation products, need to be considered and accounted for. It should be recognized that residual monomers may generate the same degradation products as the polymer itself.

The identified and quantified degradation products form the basis for biological evaluation in accordance with ISO 10993-1, for risk assessment in accordance with ISO 14538 and, if appropriate, for toxicokinetic studies in accordance with ISO 10993-16.

Biological evaluation of medical devices —

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

1 Scope

This part of ISO 10993 provides guidance on general requirements for the design of tests for identifying and quantifying degradation products from finished polymeric medical devices ready for clinical use.

This part of ISO 10993 describes two test methods to generate degradation products, an accelerated degradation test as a screening method and a real-time degradation test. For materials which are intended to polymerize *in situ*, the set or cured polymer is used for testing. The data generated are used in the biological evaluation of the polymer.

This part of ISO 10993 considers only those degradation products generated by a chemical alteration of the finished polymeric device. It is not applicable to degradation of the device induced during its intended use by mechanical stress, wear or electromagnetic radiation.

The biological activity of the debris and soluble degradation products is not addressed in this part of ISO 10993, but should be evaluated according to the principles of ISO 10993-1 and ISO 14538.

Because of the wide range of polymeric materials used in medical devices, no specific analytical techniques are identified or given preference. No specific requirements for acceptable levels of degradation products are provided in this part of ISO 10993.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this part of ISO 10993. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this part of ISO 10993 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 3696:1987, *Water for analytical laboratory use — Specification and test methods.*

ISO 10993-1:1997, *Biological evaluation of medical devices — Part 1: Evaluation and testing.*

ISO 10993-9:—[1)], *Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products.*

ISO 10993-12:1996, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials.*

[1)] To be published.

ISO 10993-16:1997, *Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables.*

ISO 13781:1997, *Poly(L-lactide) resins and fabricated forms for surgical implants — In vitro degradation testing.*

ISO 14538:—[1)] *Biological evaluation of medical devices — Establishment of permissible limits for sterilization and process residues using health-based risk assessment.*

3 Definitions

For the purposes of this part of ISO 10993, the definitions given in ISO 10993-1, ISO 10993-9, ISO 13781 and the following definitions apply.

3.1 residual monomer
unreacted chemical compound(s) used to build the polymeric chains and still present in the final polymeric material

3.2 degradation product
chemical compound derived from the breakdown of the polymeric material, including any compound produced by consecutive chemical reactions

3.3 polymeric material
materials consisting of long-chain and/or crosslinked molecules composed of units called monomers

3.4 hydrolytic degradation
scission of chemical bonds in a polymer by the attack of water

NOTE The water may have a neutral, acidic or alkaline pH value and may contain additional chemical compounds or ions.

3.5 oxidative degradation
scission of chemical bonds in a polymer by the attack of oxidizing agent(s)

3.6 debris
particulate material produced by the degradation of a polymeric material

4 Degradation test methods

4.1 General procedures

4.1.1 Test design

In accordance with ISO 10993-9, degradation tests shall be used to generate, identify and/or quantify degradation products. If degradation is observed in an accelerated test, identification and quantification of the degradation products may provide sufficient information for risk analysis. Where this information is insufficient or absent, real time testing shall be performed. The sequence of steps which shall be followed is described in detail in this part of ISO 10993.

NOTE The accelerated degradation test may be used as a screening test. If no degradation is observed in the accelerated test, no real-time degradation test should be necessary.

4.1.2 Sample preparation

When not specifically addressed by the selected method(s), the general aspects of sample preparation shall be in accordance with ISO 10993-12.

4.1.3 Initial material characterization

The analytical methods used for the initial material characterization shall be appropriate for the polymeric material under investigation. The analytical techniques used shall be reported and justified.

Annex A of this part of ISO 10993 presents a list of analytical methods and their application range for the characterization of polymeric materials.

4.1.4 Reagents and apparatus

4.1.4.1 Test solutions

All test solution(s) used shall be described and justified in the test report.

4.1.4.1.1 Reagents for hydrolytic degradation

For hydrolytic degradation the following solutions are suggested:

a) water for analytical laboratory use, grade 2, in accordance with ISO 3696;

b) buffer, e.g. in accordance with ISO 13781.

4.1.4.1.2 Reagents for oxidative degradation

For oxidative degradation the following solutions are suggested:

a) water and hydrogen peroxide, e.g. 3 % hydrogen peroxide solution, Pharmacopoeia grade;

b) Fenton´s reagent [mixture of dilute hydrogen peroxide solution and iron(II) salts, e.g. 100 µmol Fe^{2+} and 1 mmol H_2O_2].

These oxidative solutions may not be stable at elevated temperatures or for a prolonged time. Therefore the oxidative capacity shall be maintained in an appropriate range.

This stability range shall be specified, justified and reported.

4.1.4.1.3 Other test solutions

Other test solutions for a specific polymer or a specific application site may be chosen.

NOTE If a biological assay of the debris or the degradation solution is to be made, then the use of antibacterial or antifungal additives will interfere with these assays and it may be necessary to maintain a sterile environment for the duration of the real-time degradation test.

4.1.4.2 Container

Depending on the test solution, chemical grade glassware, polytetrafluoroethylene or polypropylene containers in an enclosed system shall be used. Controls shall be used in order to assess contaminants from the container. Evidence shall be provided that containers do not interfere with the analysis.

4.1.4.3 Balance

The balance used to determine mass loss shall be capable of weighing the initial sample mass with the precision required. For materials designed to be resorbed, a precision of 1 % is appropriate, for materials designed to resist degradation, a precision of at least 0,1 % shall be used. The accuracy of the balance for resorbable polymers shall be 0,1 %, and for stable polymers 0,01 %,of the total sample mass.

The precision and standard deviation of the method of the determination of mass loss shall be stated in the test report.