Meditsiiniseadmete bioloogiline hindamine. Osa 13: Polümeersetest meditsiiniseadmetest pärit mittetäisväärtuslike saaduste kuuluvuse ja koguse kindlakstegemine

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

EESTI STANDARDIKESKUS
ESTONIAN CENTRE FOR STANDARDISATION

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NATIONAL FOREWORD

Käesolev Eesti standard EVS-EN ISO 10993-13:2010 sisaldab Euroopa standardi EN ISO 10993-13:2010 ingliskeelset teksti.	This Estonian standard EVS-EN ISO 10993-13:2010 consists of the English text of the European standard EN ISO 10993-13:2010.
Standard on kinnitatud Eesti Standardikeskuse 30.09.2010 käskkirjaga ja jõustub sellekohase teate avaldamisel EVS Teatajas.	This standard is ratified with the order of Estonian Centre for Standardisation dated 30.09.2010 and is endorsed with the notification published in the official bulletin of the Estonian national standardisation organisation.
Euroopa standardimisorganisatsioonide poolt rahvuslikele liikmetele Euroopa standardi teksti kättesaadavaks tegemise kuupäev on 15.06.2010.	Date of Availability of the European standard text 15.06.2010.
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English Version

Biological evaluation of medical devices - Part 13: Identification and quantification of degradation products from polymeric medical devices (ISO 10993-13:2010)

Évaluation biologique des dispositifs médicaux - Partie 13: Identification et quantification de produits de dégradation de dispositifs médicaux à base de polymères (ISO 10993-13:2010)

Biologische Beurteilung von Medizinprodukten - Teil 13: Qualitativer und quantitativer Nachweis von Abbauprodukten in Medizinprodukten aus Polymeren (ISO 10993-13:2010)

This European Standard was approved by CEN on 5 June 2010.

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Foreword

This document (EN ISO 10993-13:2010) has been prepared by Technical Committee ISO/TC 194 "Biological evaluation of medical devices" in collaboration with Technical Committee CEN/TC 206 “Biological evaluation of medical devices” the secretariat of which is held by NEN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by December 2010, and conflicting national standards shall be withdrawn at the latest by December 2010.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN [and/or CENELEC] shall not be held responsible for identifying any or all such patent rights.

This document supersedes EN ISO 10993-13:2009.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directives.

For relationship with EU Directives, see informative Annex ZA and ZB, which are integral parts of this document.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland and the United Kingdom.

Endorsement notice

The text of ISO 10993-13:2010 has been approved by CEN as a EN ISO 10993-13:2010 without any modification.

Annex ZA
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 93/42/EEC on Medical devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 93/42/EEC on Medical devices.

Once this European Standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this European Standard given in Table ZA.1 confers, within the limits of the scope of this Intenational Standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZA.1 — Correspondence between this European Standard and Directive 93/42/EEC on Medical devices

Clause(s)/subclause(s) of this European Standard	Essential Requirements (ERs) of Directive 93/42/EEC on Medical devices	Qualifying remarks/notes
4, 5 and 6	7.1 and 7.5	These relevant Essential Requirements are only partly addressed in this standard.

General note: Presumption of conformity depends on also complying with all relevant clauses/subclauses of ISO 10993-1.

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this European Standard.

Annex ZB
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 90/385/EEC on Active Implantable Medical Devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 90/385/EEC on Active Implantable Medical Devices.

Once this European Standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this European Standard given in Table ZB.1 confers, within the limits of the scope of this European Standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZB.1 — Correspondence between this European Standard and Directive 90/385/EEC on Active Implantable Medical Devices

Clause(s)/subclause(s) of this European Standard	Essential Requirements (ERs) of Directive 90/385/EEC on Active Implantable Medical Devices	Qualifying remarks/notes
4, 5 and 6	9 (first and second indents only)	The first and second indents of this relevant Essential Requirement are only partly addressed in this standard.

General note: Presumption of conformity depends on also complying with all relevant clauses/subclauses of ISO 10993-1.

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this European Standard.

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Introduction

Degradation products covered by this part of ISO 10993 are formed primarily by chemical bond scission due to hydrolytic and/or oxidative processes in an aqueous environment such as the human body. It is recognised 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 can contain residuals and leachables such as monomers, oligomers, solvents, catalysts, additives, fillers and processing aids. These components which, if present, can interfere with the identification and quantification of the degradation products need to be considered and accounted for. It should be recognised that residual monomers can generate the same degradation products as the polymer itself. If the reader is solely interested in using the results from a degradation test as input to further biological evaluation tests, the reader might not be interested in distinguishing between a leachable and a degradation product. If this is the case, then the care taken to separate the leachable from the degradation product may not be needed.

Because of the generalized nature of this part of ISO 10993, product standards, when available, that address degradation product formation under more relevant conditions of use, may be considered as an alternative. This part of ISO 10993 is suitable for screening new polymeric materials and/or modified polymeric materials with unknown degradation behaviour in body contact. This part of ISO 10993 does not reproduce degradation *in vivo*. The user of this part of ISO 10993 can consider running additional degradation tests addressing *in vivo* degradation issues.

Long-term implants might not degrade within the time frame of the tests shown in this part of ISO 10993. The intention of this part of ISO 10993 is to help determine the biological hazards from potential degradation products from polymer components of medical devices. As noted above, those products might come from a variety of degradation mechanisms. This part of ISO 10993 is not intended to be a complete analysis of the degradation of the medical device and the impact on its performance. The interested user is referred to the relevant product standards.

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 10993-17 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 general requirements for the design of tests in a simulated environment 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 in a simulated environment. For materials that 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 non-resorbable polymers. Similar but appropriately modified procedures may be applicable for resorbable polymers.

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 or biological factors such as enzymes, other proteins and cellular activity.

NOTE An informative text discussing environmental stress cracking (ESC) of polymers is included as a potential aid to the design of degradation studies (see Annex B).

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, ISO 10993-16 and ISO 10993-17.

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 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 3696, *Water for analytical laboratory use — Specification and test methods*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

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

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

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
residual monomer
unreacted chemical compound(s) used to build the polymeric chains, which is 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 can have a neutral, acidic or alkaline pH value and can contain additional chemical compounds or ions.

3.5
oxidative degradation
scission of chemical bonds in a polymer by the attack of one or more oxidizing agents

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 can provide sufficient information for risk analysis. If identification and quantification of degradation products from the accelerated test do not provide sufficient information for the risk analysis, real-time testing shall be performed. The sequence of steps that shall be followed is described in detail in this part of ISO 10993.

NOTE The accelerated degradation test can 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.