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Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals (ISO/DIS 10993-7:2006)

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This draft European Standard is submitted to CEN members for parallel enquiry. It has been drawn up by the Technical Committee CEN/TC 206.

If this draft becomes a European Standard, CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration.

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EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

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Foreword

This document (prEN ISO 10993-7:2006) has been prepared by Technical Committee ISO/TC 194 "Biological evaluation of medical devices" in collaboration with Technical Committee CEN/TC 206 "Biocompatibility of medical and dental materials and devices", the secretariat of which is held by NEN.

This document is currently submitted to the parallel Enquiry.

This document will supersede EN ISO 10993-7:1995.

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 Directive(s).

Endorsement notice

The text of ISO 10993-7:2006 has been approved by CEN as prEN ISO 10993-7:2006 without any modifications.

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Biological evaluation of medical devices —

Part 7:
Ethylene oxide sterilization residuals

Évaluation biologique des dispositifs médicaux —

Partie 7: Résidus de stérilisation à l'oxyde d'éthylène

[Revision of first edition (ISO 10993-7:1995)]

ICS 11.100.20

ISO/CEN PARALLEL ENQUIRY

The CEN Secretary-General has advised the ISO Secretary-General that this ISO/DIS covers a subject of interest to European standardization. **In accordance with the ISO-lead mode of collaboration as defined in the Vienna Agreement, consultation on this ISO/DIS has the same effect for CEN members as would a CEN enquiry on a draft European Standard.** Should this draft be accepted, a final draft, established on the basis of comments received, will be submitted to a parallel two-month FDIS vote in ISO and formal vote in CEN.

In accordance with the provisions of Council Resolution 15/1993 this document is circulated in the English language only.

Conformément aux dispositions de la Résolution du Conseil 15/1993, ce document est distribué en version anglaise seulement.

To expedite distribution, this document is circulated as received from the committee secretariat. ISO Central Secretariat work of editing and text composition will be undertaken at publication stage.

Pour accélérer la distribution, le présent document est distribué tel qu'il est parvenu du secrétariat du comité. Le travail de rédaction et de composition de texte sera effectué au Secrétariat central de l'ISO au stade de publication.

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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 10993-7 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*, Subcommittee SC , and by Technical Committee CEN/TC 206, *Biocompatibility of medical and dental materials and devices* in collaboration.

This second edition cancels and replaces the first edition (EN ISO 10993-7:1995), 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*

— *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 the identification and quantification of potential degradation products*

— *Part 10: Tests for irritation and delayed-type hypersensitivity*

— *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: Method for the establishment of allowable limits for leachable substances*

— *Part 18: Chemical characterization of materials*

— *Part 19: Physico-chemical, morphological and topographical characterization of materials*

— *Part 20: Principles and methods for immunotoxicology testing of medical devices*

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

Annexes A and B form an integral part of this part of ISO 10993. Annexes C to K are for information only

Introduction

Requirements for the quality system for validation and routine monitoring of sterilization of medical products with gaseous ethylene oxide are given in International Standards developed by ISO/TC 198. Certain requirements relating to medical devices for biological testing, selection of tests, and the allocation of devices to categories are dealt with in a variety of International Standards developed by ISO/TC 194. The specific requirement for ethylene oxide and other sterilization process residuals was referred to ISO/TC 194. Other international standards delineate particular requirements for biological testing for specific products.

When determining the suitability of ethylene oxide (EO) for sterilization of medical devices, it is important to ensure that the levels of residual EO, ethylene chlorohydrin (ECH) and ethylene glycol (EG) pose a minimal risk to the patient in normal product use. EO is known to exhibit a number of biological effects. In the development of this standard, consideration was given to these effects, which include: irritation, organ damage, mutagenicity and carcinogenicity in humans and animals; and reproductive effects in animals. Similar consideration was given to the harmful effects of ECH and EG. In practice, for most devices, exposure to EO and ECH is considerably lower than the maximum values specified in this part of ISO 10993.

Product development and design should have considered the use of alternative materials and sterilization processes with the aim of minimizing exposure to residuals. Requirements herein are in addition to the biological testing requirements for each individually designed medical device as indicated in ISO 10993 Part 1. The biological testing requirements, combined with the EO-sterilization process residue limits, form the justification that an EO-sterilized device is acceptable for use.

Biological evaluation of medical devices —

Part 7:
Ethylene oxide sterilization residuals

1 Scope

This part of ISO 10993 specifies allowable limits for residual ethylene oxide (EO) and ethylene chlorohydrin (ECH) in individual EO-sterilized medical devices; procedures for the measurement of EO and ECH; and methods for determining compliance so that devices may be released. Additional background and guidance and a flowchart showing how the standard is applied are also included in informative annexes.

EO-sterilized devices that have no patient contact (e.g., *in vitro* diagnostic devices) are not covered by this standard.

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: Guidance on selection of tests*

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

ISO 10993-10, *Biological evaluation of medical devices - Part 10: Tests for irritation and delayed type hypersensitivity*

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: Method for the establishment of allowable limits for leachable substances using health-based risk assessment*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 10993-1, ISO 10993-17 and the following apply.

3.1 simulated-use extraction

extraction to demonstrate compliance with the requirements of this standard, by evaluating residue levels available to the patient or user from devices during the routine use of a device using an extraction method using water that simulates product use

NOTE The analytical laboratory should work with the device manufacturer to demonstrate that the simulated-use extraction is carried out under conditions that provide the greatest challenge to the intended use. Product use simulation should be carried out assuming the device is assigned to the most stringent category probable for duration of exposure and should take into consideration both tissue(s) exposed and temperature of exposure.

3.2 exhaustive extraction
extraction until the amount of EO or ECH in a subsequent extraction is less than 10 % of that detected in the first extraction, or until there is no analytically significant increase in the cumulative residue levels detected

NOTE As it is not possible to demonstrate the exhaustive nature of residual recovery, the definition of exhaustive extraction adopted is as above.

4 Requirements

4.1 General

NOTE Information on the derivation of the limits in this part of ISO 10993 as well as other important background information and guidance relevant to the use of this standard are contained in informative Annexes.

This subclauses specifies maximum allowable residues for ethylene oxide (EO) for each individual medical device sterilized with EO. Maximum allowable residues for ethylene chlorohydrin (ECH) when ECH has been found to be present in medical devices sterilized with EO also are specified. Local effects (e.g., irritation) have been considered and are incorporated in the tolerable contact level (TCL) as discussed in 4.3.3.1 and Annex G for EO and 4.3.3.2 and Annex H for ECH.

No device limits are specified for ethylene glycol (EG) because a risk assessment (Annex I) indicates that calculated allowable levels are higher than those likely to occur on a medical device. However, the potential exists for acute hemodynamic and haemolytic effects to occur following rapid intravenous administration of hyperosmolar compounds like EG. Ethylene oxide sterilization of medical devices would not be expected to produce hyperosmolar solutions.

The requirements that are in this part of ISO 10993 are in addition to the biological testing requirements set out in 10993-1. For devices sterilized by ethylene oxide, attention shall be paid in particular to ISO 10993-3 and ISO 10993-10. All applicable requirements of 10993-1 shall take into account the EO residual level at time of release for each individually designed medical device.

Results of the biological assessment of the device may dictate more stringent limits than those specified in 4.3, which are designed to protect against systemic effects.

4.2 Categorization of devices

In establishing the maximum daily doses of EO and ECH that a medical device is allowed to deliver to patients, devices shall be categorized according to duration of contact.

Devices shall be placed into one of three exposure categories in accordance with 4.3 of ISO 10993-1:

a) limited exposure: devices whose single or multiple use or contact is likely to be up to 24 h;

b) prolonged exposure: devices whose single, multiple, or long-term use or contact is likely to exceed 24h but not 30 days; and

c) permanent contact: devices whose single, multiple, or long-term use or contact exceeds 30 days.

NOTE 1 If a material or device may be placed in more than one duration category, the more rigorous testing requirements should apply. With multiple exposures, the decision into which category a device is placed should take into account the potential cumulative effect, bearing in mind the period of time over which these exposures occur.

NOTE 2 As it is applied in this part of ISO 10993, "multiple use" is defined to mean repeated use of the same device type, e.g. dialyzer cartridges.

4.3 Allowable limits

For each medical device, the maximum allowable doses of EO and ECH that are delivered to patients shall not exceed the values given below for the exposure category that the device has been placed into in accordance with 4.2.

NOTE The limits for permanent contact and prolonged exposure devices are expressed as maximum average daily doses. These limits also carry additional constraints for the first 24 h of the exposure period and, in the case of the permanent contact devices, for the first 30 days. These constraints place limitations on the amount of EO and ECH that can be delivered to the patient during these early time periods. If data are available consideration should be given for proportioning the limits downward if multiple devices with the residue of concern are used at one time or proportioning the limits upward when device use is only for a part of the exposure period of concern. These concomitant exposure factors (CEF) and proportional exposure factors (PEF) are discussed in ISO 10993-17. The procedure that was used to establish the allowable limits is described in Annex G for EO; in Annex H for ECH and the rationale for considering the establishment of allowable limits for EG is described in Annex I.

4.3.1 Permanent contact devices

The average daily dose of EO to patient shall not exceed 0,1 mg/d. In addition, the maximum EO dose shall not exceed:

— 4 mg in the first 24 h;

— 60 mg in the first 30 d; and

— 2,5 g in a lifetime.

The average daily dose of ECH to patient shall not exceed 0,4 mg/d. In addition, the maximum ECH dose shall not exceed:

— 9 mg in the first 24 h;

— 60 mg in the first 30 d; and

— 10 g in a lifetime.

4.3.2 Prolonged exposure devices

The average daily dose of EO to patient shall not exceed 2 mg/d. In addition, the maximum EO dose shall not exceed:

— 4 mg in the first 24 h; and

— 60 mg in the first 30 d.

The average daily dose of ECH to patient shall not exceed 3,8 mg/d. In addition, the maximum ECH dose shall not exceed

— 9 mg in the first 24 h; and

— 60 mg in the first 30 d.

4.3.3 Limited exposure devices

The average daily dose of EO to patient shall not exceed 4 mg.

The average daily dose of ECH to patient shall not exceed 9 mg.