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Utgåva 1

Ögonimplantat – Intraokulära linser –
Del 5: Biokompatibilitet
(ISO 11979-5:1999, modifierad)

Ophthalmic implants – Intraocular lenses –
Part 5: Biocompatibility
(ISO 11979-5:1999, modified)

ICS 11.040.70; 11.100
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The European Standard EN 13503-5:2001 has the status of a Swedish Standard. This document contains the official English version of EN 13503-5:2001.

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ICS 11.040.70; 11.100

English version

Ophthalmic implants - Intraocular lenses - Part 5: Biocompatibility (ISO 11979-5:1999, modified)

Implants ophtalmiques - Lentilles intraoculaires - Partie 5: Biocompatibilité (ISO 11979-5:1999, modifié)

Ophthalmische Implantate - Intraokularlinsen - Teil 5: Biokompatibilität (ISO 11979-5:1999, modifiziert)

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This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the Management Centre has the same status as the official versions.

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

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Foreword

This document has been prepared by Technical Committee CEN /TC 170, "Ophthalmic optics" the secretariat of which is held by DIN.

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of an identical text or by endorsement, at the latest by September 2001, and conflicting national standards shall be withdrawn at the latest by September 2001.

EN 13503 was developed by CEN/TC 170, *Ophthalmic optics*, in cooperation with ISO/TC 172/SC 7, *Ophthalmic optics and instruments*, and is published in several parts under the general title *Ophthalmic implants - Intraocular lenses*:

Part 1: Vocabulary

Part 2: Optical properties and test methods

Part 3: Mechanical properties and test methods

Part 4: Labelling and information

Part 5: Biocompatibility

Part 6: Shelf-life and transport stability

Part 7: Clinical investigations

Part 8: Fundamental requirements

EN 13503 is the modified ISO 11979. The main difference between both series of standards is that ISO 11979 is based on the reference to ISO 14155 *Clinical investigation of medical devices* while EN 13503 is based on the reference to EN 540 *Clinical investigation of medical devices for human subjects*.

Modifications of this part of EN 13503 compared with ISO 11979-5 are indicated as follows:

- text which has been deleted is striked out;
- text which has been changed or added is underlined.

This Part 5 of EN 13503 contains four normative annexes, A to D, and one informative annex, Annex E.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom.

Endorsement notice

The text of the International Standard ISO 11979-5:1999 was approved by CEN as a European Standard with agreed commun modifications as given in the Foreword and indicated in the text by strike-out and underlining.

NOTE A-deviations are given in Annex ZA (informative).

Introduction

EN ISO 10993-1 indicates the fundamental principles governing the biological evaluation of medical devices, the definition of categories based on the nature and duration of contact with the body, and selection of appropriate tests. Other parts of EN ISO 10993 present biological test methods, tests for ethylene oxide residues, tests for degradation and principles for sample preparation.

NOTE It always was and still is the intention of the Technical Committees ISO/TC 172/SC 7 and CEN/TC 170 to prepare identical ISO and CEN (European Committee for Standardization) Standards on intraocular lenses. However, during the preparation of part 7 of this series, problems were encountered with normative references to the existing ISO 14155 and EN 540 horizontal standards on clinical investigation of medical devices, which are similar but not identical.

ISO and CEN principles concerning normative references made it impossible to continue the preparation of identical International and European Standards on the clinical investigation of intraocular lenses. As a result, two different standards series have had to be prepared. It is the intention of ISO/TC 172/SC 7 and CEN/TC 170 to revise these standards with the goal to end up with identical ones as soon as identical ISO and CEN horizontal standards on clinical investigations become available.

1 Scope

This part of EN 13503 ~~ISO 11979~~ specifies particular requirements for the the biological evaluation of intraocular lenses (IOLs) which are in addition to the requirements outlined in the relevant parts of EN ISO 10993. It also gives guidance on conducting an ocular implantation test.

2 Normative references

This European Standard incorporates by dated or undated references, provisions from other publications. These normative references are cited at the appropriate places in the text and the publications are listed hereafter. For dated references, subsequent amendments to or revisions of any of these publications apply to this European Standard only when incorporated in it by amendment or revision. For undated references the latest edition of the publication referred to applies (including amendments).

EN 1441 : 1997, *Medical devices – Risk analysis* ~~ISO 14971-1:1998, *Medical devices - Risk management - Part 1: Application of risk analysis.*~~

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

EN 30993-6 ~~ISO 10993-6~~ : 1994, *Biological evaluation of medical devices - Part 6: Tests for local effects after implantation*.

EN ISO 11979-1: 1999, *Ophthalmic implants - Intraocular lenses - Part 1: Vocabulary.*

EN ISO 11979-2 : 1999, *Ophthalmic implants - Intraocular lenses - Part 2: Optical properties and test methods*.

EN 13503-3 ~~ISO 11979-3: 1999~~ *Ophthalmic implants - Intraocular lenses - Part 3: Mechanical properties and test methods*.

3 Terms and definitions

For the purposes of this part of EN 13503 ~~ISO 11979~~, the terms and definitions given in EN ISO 11979-1 apply.

NOTE Some definitions from EN ISO 11979-1 are reproduced for information in Annex E.

4 General requirements applying to the biological evaluation of intraocular lenses

An evaluation of biological safety shall be undertaken in accordance with the principles and requirements of EN ISO 10993-1. The evaluation of the biological safety of the test material shall include an assessment for risk in accordance with EN 1441 ~~ISO 14971-1~~. The results of the tests described in clause 5 shall be included in the risk assessment.

The material shall be either the final product or representative sample material which has undergone the same processing steps, including sterilization. Where representative sample material is used, the shape and size shall be justified.

In addition, for each test material the results of the following physicochemical evaluations (see clause 5) shall be available. All extractions shall be performed using an aqueous solvent and a lipophilic solvent, unless otherwise stated in the test method:

a) extractables and hydrolytic stability;

b) photostability against ultraviolet/visible (UV/Vis) irradiation; and

c) stability against Nd-YAG laser exposure.

Consideration of the need for an ocular implantation test shall be documented and justified. Where necessary, an ocular implantation test shall be conducted in line with the general principles in EN 30993-6 ~~ISO 10993-6~~, supplemented as described in annex D.

NOTE As the mass of an intraocular lens is typically only about 20 mg, in general no systemic or chronic toxicity testing is required.

5 Physicochemical tests

5.1 General

The objectives of this group of tests are:

a) to quantify possible residues of synthesis and additives or impurities from manufacturing;

b) to quantify possible degradation products due to hydrolysis;

c) to quantify leachable chemical components; and

d) to facilitate an analysis of any risks introduced by toxic products which may result from processing, treatment in use, or ageing of the test material.

5.2 Test for extractables and hydrolytic stability

The material shall be tested for extractables and hydrolytic stability in accordance with annex A, which specifies several different extraction conditions, including the extraction media, temperature and duration. For all conditions the following shall be observed.

— The manufacturer shall be required to justify and document the reasons for selecting each solvent.

— The extraction media shall be qualitatively and quantitatively analysed for possible extractable components of the material, such as process contaminants, residual monomers, additives of any kind, and other extractable components.

— Before and after extraction, the test material shall be weighed and any change in mass shall be calculated.

The test material underdoing hydrolysis testing shall be examined by light microscopy at 10x and by scanning electron microscopy (SEM) at 500x before and after extraction. The test material shall be compared with nonhydrolysed material and shall exhibit no difference in surface appearance (e.g. bubbles, dendrites, breaks and fissures).

Optical transmittance curves of the test material in the ultraviolet and visible spectral regions (UV/Vis) shall be recorded before and after hydrolysis testing. By comparison of the spectra, assurance shall be obtained that no significant changes in spectral transmittance have occurred due to the testing.

The results shall be evaluated to assess the risk for potentially harmful effects due to extractable components. The results of the tests described in annex A shall be recorded and included in the assessment for risk in accordance with EN 1441 ~~ISO 14971-1~~ as discussed in clause 4.

5.3 Degradation tests

5.3.1 Test for photostability

The test material shall be assessed for photostability in accordance with annex B.

The saline solution surrounding the test material during exposure shall be analysed for migrated components.

No significant change shall be detected between the UV/Vis spectra of the test material before and after the exposure.

For anterior chamber IOLs, it shall in addition be shown that no significant change in mechanical properties of the irradiated test material has occurred, compared with non-irradiated test material.

NOTE The loops of implanted anterior chamber IOLs are exposed to radiation, hence the rationale for requiring mechanical testing after irradiation.

5.3.2 Nd-YAG laser exposure test

The effect of Nd-YAG laser exposure shall be tested in accordance with annex C.

The physiological saline surrounding the IOLs shall be analysed for released additives and, also, shall show no cytotoxicity.

The results of the tests described in annexes B and C shall be recorded and included in the assessment for risk as described in clause 4.

Annex A
(normative)

Test for extractables and hydrolytic stability

A.1 Purpose

The purpose of these tests is to quantify extractable additives and other leachables, as well as possible degradation products due to hydrolysis.

A.2 General remarks

The selected analytical methods should be justified in terms of being well established and of sufficient sensitivity to detect significant concentrations.

A.3 Test of extractables

A.3.1 Test materials

Use a total of 180 IOLs, if sterile finished IOLs are chosen as the test material.

If representative sample material is chosen, cut it into pieces to give about the same ratio of mass to surface area as would be obtained with finished IOLs.

A.3.2 Control materials

Use untreated sterile finished IOLs or representative sample material as control material.

Use solvent blanks that have undergone the same procedures as described in A.3.4, for comparison with extracts of test material.

A.3.3 Apparatus

A.3.3.1 Glass vials, of hydrolytic class I according to EP and USP.

A.3.3.2 Laboratory glass ware.

A.3.3.3 Syringes.

A.3.3.4 Analytical balance.

A.3.3.5 Shaker.

A.3.3.6 Incubator.

A.3.3.7 Centrifuge.

A.3.3.8 High pressure liquid chromatograph (HPLC).

A.3.3.9 Gas chromatograph (GC).

A.3.3.10 UV/Visible spectrophotometer.

NOTE This list is advisory. Other suitable means may be used.

A.3.4 Test procedure

A.3.4.1 Extraction

Extract the test material at 37°C ± 2°C for 72 h ± 1 h using two different extraction media, one aqueous and one lipophilic solvent, selected with relevance to the test material.

Divide the test material into two equal parts for incubation in the two extraction media. Determine the mass of each part.

Incubate the test material in glass vials with a sufficient volume of medium to achieve a ratio of 10 g of test material per 100 ml of medium. Use at least two vials for each medium. If necessary, use more vials and agitate to ensure that all surfaces of the test material are available for extraction during the entire period of extraction.

A.3.4.2 Analysis of extracts

Carry out the analysis of the extract of each vial separately.

Remove the vials from the incubator and allow to equilibrate at room temperature for 2 h ± 15 min. Then shake the vials and centrifuge at room temperature. Collect the clear supernatant with a syringe and transfer to a second vial for qualitative and quantitative analyses for leachable substances such as UV-absorbers, additives, and degradation products.

Carry out corresponding qualitative and quantitative analyses on solvent blanks that have undergone the same incubation procedures.

Compare the results of the qualitative and quantitative analyses of the extracts of the test material to those of the solvent blank, and interpret the findings in the context of possible material changes.

A.3.4.3 Analysis of the test material

After extraction, rinse the test material and allow to dry. Determine the total mass and calculate and record the change in mass in each medium.

Take at random five pieces of test material from each extraction condition and determine their spectral transmittance as described in EN ISO 11979-2. Compare transmittance spectra of treated test material with spectra of control material, and record any changes.

A.4 Test for hydrolytic stability

A.4.1 Test material

Use a total of 180 IOLs, if sterile finished IOLs are chosen as the test material.

If representative sample material is chosen, cut it into pieces to give about the same mass to surface area ratio as would be obtained with finished IOLs.

A.4.2 Control materials

Use untreated sterile finished IOLs or facsimile material.

Use solvent blanks that have undergone the same procedures as described in A.4.4, for comparison with hydrolysates of test material.

A.4.3 Apparatus

A.4.3.1 Hydrolysation medium.

Use aqueous solvent, e.g. physiological saline.