INTERNATIONAL STANDARD

ISO 11979-5

First edition
1999-11-15

Ophthalmic implants — Intraocular lenses —

Part 5: Biocompatibility

Implants ophtalmiques — Lentilles intraoculaires —

Partie 5: Biocompatibilité

Reference number
ISO 11979-5:1999(E)

Contents

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Printed in Switzerland

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 3.

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 11979-5 was developed by Technical Committee ISO/TC 172, *Optics and optical instruments*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

ISO 11979 consists of the following 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*

Annexes A to D form a normative part of this part of ISO 11979. Annex E is for information only.

Introduction

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 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.

Ophthalmic implants — Intraocular lenses —

Part 5:
Biocompatibility

1 Scope

This part of 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 ISO 10993. It also gives guidance on conducting an ocular implantation test.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 11979. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 11979 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

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

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

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

ISO 11979-2:—[1)], *Ophthalmic implants — Intraocular lenses — Part 2: Optical properties and test methods*.

ISO 11979-3:1999, *Ophthalmic implants — Intraocular lenses — Part 3: Mechanical properties and test methods*.

ISO 14971-1:1998, *Medical devices — Risk management — Part 1: Application of risk analysis*.

3 Terms and definitions

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

NOTE Some definitions from 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 ISO 10993-1. The evaluation of the biological safety of the test material shall include an assessment for risk in accordance with 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 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 from 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 10× and by scanning electron microscopy (SEM) at 500× 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 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 for 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 glassware.

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 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 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.

A.4.3.2 **Glass vials,** of hydrolytic class I according to EP and USP.

A.4.3.3 **Laboratory glassware**.

A.4.3.4 Syringes.

A.4.3.5 Analytical balance.

A.4.3.6 Shaker.

A.4.3.7 Incubator.

A.4.3.8 Centrifuge.

A.4.3.9 High pressure liquid chromatograph (HPLC).

A.4.3.10 Gas chromatograph (GC).

A.4.3.11 UV/Visible spectrophotometer.

A.4.3.12 Optical microscope.

A.4.3.13 Scanning electron microscope (SEM).

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

A.4.4 Test procedure

A.4.4.1 Extraction

Extract the test material at 37 °C ± 2 °C and 50 °C ± 2 °C using an aqueous extraction medium selected with relevance to the test material.

Divide the test material into four equal parts. Determine the mass of each part.

For each temperature, extract one part for 30 d ± 2 d, and one for 90 d ± 2 d. 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 per combination of temperature and duration of hydrolysis. 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 hydrolysis.

A.4.4.2 Analysis of hydrolysates

Carry out analysis of the hydrolysate 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 of products of hydrolysis.

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 hydrolysates of the test material to those of the solvent blank and interpret the findings in the context of possible material changes.

A.4.4.3 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 for each treatment condition.

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

Examine the test material from the four test conditions and the control material, and photograph by light microscopy at 10× magnification and thereafter by SEM at 500× magnification. If necessary, dehydrate the test material prior to microscopy to allow comparison with the control material. Compare the observations and photos of test material and control material to detect any changes in appearance, e.g. bubbles, dendrites, breaks and fissures. Record the results.

Annex B
(normative)

Test of photostability

B.1 Purpose

The purpose of this test is to determine the photostability of IOL materials if irradiated in the wavelenth range 300 nm to 400 nm.

B.2 General remarks

The following parameters have been found to be relevant:

a) *in vivo* UV-A radiation intensity in the range 300 nm to 400 nm at the position of the IOL at diffuse light conditions (I_1): 0,5 mW/ cm^2;

b) daily exposure time to sunlight (t): 3 h;

c) *in vivo* exposure time (T_1): 20 years;

d) intensity factor (n): 1 (i.e. maximum intensity under consideration of sunny regions);

e) *in vitro* test period (T_2, in days): this factor is calculated using the following equation (see reference [10] in Bibliography) depending on the *in vitro* density (I_2) of the radiation source in the spectral range 300 nm to 400 nm,

$$T_2 = 365 \cdot T_1 \cdot \left[\left(\frac{I_2}{I_1} \right)^n \cdot \left(\frac{24}{t} \right) \right]^{-1}$$

EXAMPLE If I_2 = 10 mW/cm^2, and the other parameters take the values above, T_2 = 45,6 days.

Estimating the cornea and the aqueous humour to absorb 50 % of the UV-A, the IOL is exposed to an irradiation of 3,25 mW/cm^2 in the range 300 nm to 400 nm at full intensity of sunlight. The diffuse, reflected light intensity is estimated to be one-tenth of the above value. The irradiation of an intraocular lens *in vivo* is therefore approximately 0,3 mW/cm^2.

NOTE The internationally accepted estimation for full intensity of sunlight is an average of 1 kW/m^2 = 100 mW/cm^2 in sunny areas close to the Tropic of Cancer. The portion of near ultraviolet wavelengths in the range 300 nm to 400 nm is approximately 6,5 % of the total intensity, i.e. about 6,5 mW/cm^2.

Intraocular lenses are exposed to sunlight which reaches behind the cornea and the aqueous humour. Within the spectrum of sunlight, that part of the near ultraviolet radiation which is not absorbed by the cornea and the aqueous humour, and which can potentially damage IOLs by photochemical degradation, amounts to approximately 40 % to 50 % of the total UV-A radiation.

B.3 Test material

Use 15 pieces of test material to be exposed to UV radiation.

B.4 Control material

Use 15 pieces of unexposed material.