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ISO 11979-5

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Ophthalmic implants — Intraocular lenses —

Part 5: Biocompatibility

Implants ophtalmiques — Lentilles intraoculaires —

Partie 5: Biocompatibilité

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Contents

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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 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.

B.5 Apparatus

B.5.1 Vial, of capacity 5 ml, transparent to wavelengths of 300 nm to 800 nm, chemically inert and stable (e.g. glass of hydrolytic class I according to EP or USP).

B.5.2 Xenon arc lamp, provided with a filter capable of excluding light of wavelength less than 300 nm.

B.5.3 Physiological saline, used as extraction medium.

B.6 Test procedure

Immerse the test material in the vial containing about 2 ml physiological saline. Expose the vial to the xenon arc lamp light for the required length of time (T_2, see B.2), ensuring that during exposure the temperature of the test material in the vial is maintained at 37 °C ± 2 °C.

The intensity of the irradiation source may be selected individually, but should not be in excess of 30 mW/cm^2, and should not cause excessively rapid photodegradation of the material.

Care should be taken to avoid microbial contamination, in order to avoid growth of microorganisms in the vials during the irradiation period.

B.7 Test evaluation

At the end of the calculated exposure time, analyse the saline solution for migrated components.

Determine UV/Vis spectra as described in ISO 11979-2, on five irradiated and five non-irradiated samples. Examine the spectra for differences, and record any changes due to the UV exposure.

For anterior chamber lenses, determine the relevant mechanical properties after exposure to UV light on at least five lenses in accordance with ISO 11979-3. Compare the results with those of non-irradiated IOLs to ascertain that no significant deterioration has occurred.

Annex C
(normative)

Nd-YAG laser exposure test

C.1 Purpose

The purpose of this test is to determine the physical and chemical effects of Nd-YAG laser exposure on the test material in order to obtain assurance that the Nd-YAG laser treatment commonly given to patients with implanted IOLs does not cause leakage of toxic substances.

C.2 Test material

For the test, use five pieces of the sterile finished IOLs. Representative sample material is unsuitable for this test.

C.3 Apparatus

C.3.1 Optical cuvette, capacity 2 ml.

C.3.2 Nd-YAG laser.

NOTE A Nd-YAG laser mounted on a slit-lamp microscope, as used clinically for laser capsulotomy, is suitable.

C.3.3 Physiological saline, used as extraction medium.

C.4 Test procedure

Immerse the IOL in the optical cuvette containing 2 ml physiological saline and expose to 50 single pulses from the Nd-YAG laser, set at an energy level of 5 mJ. Focus the laser on the posterior surface of the IOL. For each pulse, refocus the laser; distribute the spots evenly over the central 3 mm of the IOL optic. Remove the IOL from the cuvette and collect the extraction media for analysis. Repeat the procedure for the remaining IOLs.

C.5 Test evaluation

Analyse the saline solutions for possible released substances.

Annex D
(normative)

Ocular implantation test

D.1 Purpose

The purpose of this test is to demonstrate the reciprocal tolerance of test material and ocular tissues after implantation into an animal eye. The implantation procedure shall mirror the intended clinical use as closely as possible, i.e. a posterior chamber IOL is normally implanted into the capsular bag after extraction of the natural lens.

D.2 Test material

The test material shall be in the form of an IOL. The same fabrication methods as intended for the product to be marketed shall be followed.

NOTE To allow for dimensional differences between human and animal eyes, the IOL may require custom design to fit the anatomical placement site of the animal.

D.3 Control material

As control material, an IOL which has already been proven in animal experiments to be well tolerated regarding material and geometry, and which has also been proven to be highly tolerated in clinical use for a minimum period of five years, shall be used.

D.4 Apparatus

D.4.1 Operating microscope.

D.4.2 Slit lamp.

D.4.3 Indirect ophthalmoscope.

D.4.4 Phacoemulsification unit.

D.4.5 Lid speculum.

D.4.6 Sutures.

D.4.7 Surgical instruments.

D.4.8 Physiological saline or balanced salt solution.

D.4.9 Anaesthetic.

D.4.10 Drugs for pre- and post-operative treatment.

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

D.5 Test procedure

Based on the estimated drop-out-rate and other health and welfare considerations for the species chosen, use a sufficient number of animals so that a minimum of six test eyes and six control eyes are available at the end of the follow-up period. The rabbit is the preferred species. Implant one eye of each of these animals with the test material. Implant the fellow eye with a control IOL

NOTE A bilateral implantation is preferred, but unilateral implantation is permissible, if local rules so require. For statistical reasons, unilateral implantation requires more animals.

Implantation shall be performed by a person who is experienced and skilled in IOL implantation techniques.

Monitor the eyes by slit lamp biomicroscopy during the follow-up period.

If the rabbit is not chosen as the test species, a justification shall be given (in accordance with ISO 10993-6).

D.6 Intraoperative observations

Intraoperative observations shall include but are not limited to the following:

a) contact between the test material and the corneal endothelium;

b) collapse of the anterior chamber;

c) anterior chamber bleeding;

d) iris damage;

e) placement of the lens haptics and location/centration of the optic; and

f) unusual surgical problems that are common to the group as a whole.

All observations shall be recorded.

D.7 Implantation period

If the rabbit is chosen for ocular implantation a test period of 4 months to 6 months should be used. This is because if the natural crystalline lens is removed, lenticular regeneration will start to occur after approximately 3 months.

D.8 Test evaluation

D.8.1 Post-operative evaluations

Perform and record the following.

a) Gross examinations of the operated eyes one day after implantation.

b) Slit lamp biomicroscopy after 7 days, 4 weeks, 3 months and 6 months.

Include, but do not limit the observations to, the following occurrences:

— fibrin,

— flare,

— cells,

— adhesions,

— neovascularization,

— corneal oedema,

— lens clarity,

— location of the haptic,

— centration of the lens.

Slit lamp photographs shall be taken at every occasion.

NOTE These examinations may be carried out more often if deemed necessary.

D.8.2 Evaluation of enucleated eyes

Sacrifice the animals at the end of the follow-up period, and enucleate the eyes. Also enucleate eyes of any animals that die during the study of causes not due to surgical trauma or surgical complations.

For evaluation of the enucleated eyes, two alternatives are possible:

a) the enucleated eyes are immediately immersed into a suitable fixative for storage and later examination,

or

b) the eyes are dissected equatorially immediately after enucleation and an internal examination is performed, after which the eye halves are immersed in a suitable fixative.

Carefully remove the IOL.

Note any visible abnormalities and the location/centration of the implant. Take photographs to support the observations. Perform histopathological evaluations on the anterior and posterior segments of the eye. Examine specifically the support and contact zones between the IOL and the tissue.

D.8.3 Evaluation of explanted lenses

Examine the explanted IOLs by microscopy for cells (giant cells, macrophages, etc.), cell debris and fibrinous deposits, especially at the fixation points of the loops and on the inside of any positioning holes.

If the optic surfaces can be cleaned without being damaged, subject at least two IOLs to optical testing in accordance with ISO 11979-2.

Report all results. If some data are missing or could not be obtained, state the reasons.