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Ophthalmic implants — Intraocular lenses —

Part 5: Biocompatibility

Implants ophtalmiques — Lentilles intraoculaires —

Partie 5: Biocompatibilité

Reference number
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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 11979-5 was prepared by Technical Committee ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

This second edition cancels and replaces the first edition (ISO 11979-5:1999), which has been technically revised.

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*

— *Part 9: Multifocal intraocular lenses*

— *Part 10: Phakic intraocular lenses*

Introduction

This part of ISO 11979 follows the general principles given in ISO 10993-1. ISO 10993-1 describes the principles governing the biological evaluation of medical devices, the definitions 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.

Ophthalmic implants — Intraocular lenses —

Part 5:
Biocompatibility

1 Scope

This part of ISO 11979 specifies particular requirements for the biocompatibility evaluation of materials for intraocular lenses (IOLs) including the processing conditions to produce them. These requirements include evaluation of physicochemical properties that are relevant to biocompatibility. It also gives guidance on conducting an ocular implantation test.

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: Evaluation and testing*

ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

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

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

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

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

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

ISO 14971, *Medical devices — Application of risk management to medical devices*

3 Terms and definitions

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

4 General requirements applying to biocompatibility evaluation of intraocular lenses

The evaluation of the biocompatibility of the test material shall start with an initial assessment of risk in accordance with ISO 14971. The physicochemical tests described in Clause 5 shall first be considered. The evaluation of the material for biological safety shall then be undertaken in accordance with the principles and requirements of ISO 10993-1 and ISO 10993-2, taking into consideration the results from the physicochemical tests.

Furthermore, the risk assessment shall include an assessment of the potential for material changes such as calcification. This risk assessment should consider the history of clinical use of the material, and animal models to test the long-term stability of the material.

Carry out the biocompatibility testing in accordance with ISO 10993-1, ISO 10993-3, ISO 10993-5, ISO 10993-6 and ISO 10993-10 and as noted in this part of ISO 11979.

The pre-existing information on the material and all the information obtained in the evaluation process shall be integrated in an overall risk benefit assessment in accordance with ISO 14971.

5 Physicochemical tests

5.1 General

5.1.1 The following physicochemical tests shall be considered:

a) exhaustive extraction;

b) leachables;

c) hydrolytic stability;

d) photostability against ultraviolet/visible (UV/Vis) irradiation;

e) stability against Nd-YAG laser exposure;

f) insoluble inorganics.

5.1.2 The objectives of this group of tests are:

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

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.

5.1.3 The results of the tests given in 5.1.1 and 5.1.2 shall be recorded and included in the assessment for risk in accordance with ISO 14971. If any of the above tests was not performed, a rationale justifying this decision shall be documented.

5.2 Exhaustive extraction test

The test material shall be tested for extractables under exhaustive extraction conditions in accordance with the method described in Annex A, which describes several extraction conditions, including the extraction media, temperature and duration. Alternate methods can be used provided that they have been validated.

The following shall be observed.

a) The reasons for selecting each solvent shall be justified and documented.

b) The extraction media shall be qualitatively and quantitatively analysed at the end of extraction for possible extractable components of the material, such as process contaminants, residual monomers, additives, and other extractable components. The detection limit for the extractables shall be established based on a risk assessment of the total exposure to the patient and it shall be expressed as µg/g of material.

c) The test material shall be weighed before and after extraction and any change in mass shall be calculated.

The results shall be evaluated to assess the risk for potentially harmful effects due to extractable components and they shall be recorded.

5.3 Test for leachables

The test material shall be tested for leachables under simulated physiological conditions in accordance with the method described in Annex B, which specifies several extraction conditions including the extraction media, temperature and duration.

The following shall be observed.

a) The reasons for selecting each solvent shall be justified and documented.

b) The extraction media shall be qualitatively and quantitatively analysed at the end of extraction for possible extractable components of the material, such as process contaminants, residual monomers, additives, and other extractable components. The detection limit for the extractables shall be established based on a risk assessment of the total exposure to the patient and it shall be expressed as µg/g of material.

The results shall be evaluated to assess the risk for potentially harmful effects from extractable components and they shall be recorded.

5.4 Test for hydrolytic stability

Hydrolytic stability testing shall be conducted in accordance with the method described in Annex C. The following shall be observed.

a) The study shall be designed to evaluate the stability of the material in an aqueous environment at 35 °C ± 2 °C for a period of at least five years or at an elevated temperature for a simulated exposure time of at least five years.

b) The simulated exposure time is to be determined by multiplying the actual study time with the following factor F:

$$F = 2{,}0^{(T_a - T_o)/10}$$

where

T_a is the accelerated temperature;

T_o is the temperature of the inside of the eye (35 °C).

c) The exposure medium shall be qualitatively and quantitatively analysed for any chemical entities at the end of the exposure period.

d) The test material shall be examined by light microscopy at 10× or higher and by scanning electron microscopy (SEM) at 500× or higher before and after testing. The test material shall be compared with the untreated material and there shall be no significant difference in surface appearance (e.g. bubbles, dendrites, breaks and fissures).

e) Optical transmittance spectra of the test material in the ultraviolet and visible spectral regions (UV/Vis) shall be recorded before and after testing. By comparison of the spectra, assurance shall be obtained that there are no significant changes in spectral transmittance. The dioptric power shall be determined before and after testing if finished IOLs are used in the testing. The refractive index shall be determined instead if a facsimile material is used. There shall be no significant change in dioptre power (± 0,25 D for a 20 D lens) or refractive index before and after testing.

The results shall be evaluated to assess the risk for potentially harmful effects due to instability of the material in an aqueous environment and they shall be recorded.

5.5 Photostability test

Photostability testing shall be conducted in accordance with Annex D.

Furthermore, when performing the testing for anterior chamber IOLs, it shall be shown that no significant change in mechanical properties of the irradiated test material has occurred when compared with non-irradiated test material.

No significant change shall be detected between the UV/Vis spectra of the test material exposed to UV radiation and controls receiving no radiation.

NOTE 1 The loops of implanted anterior chamber IOLs are exposed to radiation, hence the rationale for requiring mechanical testing after irradiation.

NOTE 2 The following parameters have been found to be relevant to *in situ* exposure of an IOL to UV radiation:

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): 0,3 mW/cm^2;

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 300 nm to 400 nm range 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. Assuming that the cornea and the aqueous humour absorb 50 % of the UV-A, the IOL is exposed to an irradiation of 3,25 mW/cm^2 in the 300 nm to 400 nm range 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.

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).

The *in vitro* test period (T_2, in days) can be calculated using the following equation (see Reference [1]), with (I_2) being the *in vitro* intensity of the radiation source in the 300 nm to 400 nm range,

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

EXAMPLE If I_2 = 10 mW/cm^2, T_2 = 27,4 d.

The results shall be evaluated to assess the risk of potential harmful effects due to degradation products identified in the photostability test and they shall be recorded.

5.6 Nd-YAG laser exposure test

The effect of Nd-YAG laser exposure shall be evaluated in accordance with Annex E.

There shall be no cytotoxic substances released due to Nd-YAG laser exposure.

5.7 Evaluation of insoluble inorganics

The IOL material shall be assessed for the presence of residual insoluble inorganics on and in the lens arising from manufacturing materials and process aids. Where possible residues have been identified, the lens shall be evaluated for such residuals. The test methods used for this evaluation shall be identified, validated and justified. Consideration shall be given to methods with a detection limit of 0,2 µg/lens or 10 µg/g, and in which the solvents will dissolve the material.

The results shall be evaluated to assess the risk of potentially harmful effects due to the presence of residual insoluble inorganics on and in the lens and they shall be recorded.

6 Biological tests

6.1 General

An evaluation of biological safety shall be undertaken in accordance with the principles and requirements of ISO 10993-1 taking into consideration the results of the physicochemical tests. The following biological endpoints shall be considered:

— the effects on cell growth and cell damage;

— genotoxicity;

— local effects after implantation;

— sensitization potential.

Where testing is deemed necessary, the appropriate parts of ISO 10993 shall apply. Supplements to these parts are described in 6.2 and 6.3. Sample preparation shall be performed in accordance with ISO 10993-12 taking into consideration the supplemental requirements. In addition, an ocular implantation test shall also be considered in accordance with 6.4.

If the risk assessment has identified the potential for material change when exposed to an *in vivo* environment, a test shall be performed to assess the reciprocal tolerance of the test material and local tissue. An example of such a test is the test for local effects after implantation as described in ISO 10993-6 supplemented as indicated in informative Annex F.

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

6.2 Tests for genotoxicity

Testing for genotoxicity shall be performed in accordance with ISO 10993-3 supplemented with the following:

— Two separate extractions of the material shall be performed, one with physiological saline, and the other with a lipophilic or dipolar solvent. The lipophilic or dipolar solvent shall not dissolve or degrade the material.

— Extraction shall be performed with agitation at 37 °C ± 2 °C for 72 h ± 2 h at a ratio of 1 g of material per 10 ml of extracting medium.

6.3 Tests for sensitization

Testing for sensitization shall be performed in accordance with ISO 10993-10 supplemented with the following.

— Either the maximization sensitization test or the local lymph node assay (LLNA) can be used for testing.

— The test material shall be extracted with two different extractants, one of which is physiological saline, and the second a lipophilic or dipolar solvent. The lipophilic or dipolar solvent should not dissolve or degrade the test material. The solvent itself should also not be a known irritant, adjuvant or sensitizer.

6.4 Ocular implantation test

An intraocular implantation test shall be performed when the manufacturer has no documented evidence on the safety of the material in the intraocular environment. Testing shall be conducted in accordance with the general principles in ISO 10993-6, supplemented as described in Annex G. When this test is deemed not necessary, the risk assessment shall provide reasonable assurance that the risks arising from the new use of the material are deemed acceptable based on information from previous clinical use and other relevant literature.

Annex A
(normative)

Exhaustive extraction test

A.1 Purpose

The purpose of this test is to detect and quantify extractable additives and other leachables from intraocular lens material under exhaustive extraction conditions.

A.2 General considerations

Select analytical methods that are justified in terms of being well established and of sufficient sensitivity to detect significant concentrations.

A.3 Principle

The method of extraction described in this annex employs the normal Soxhlet apparatus. This annex also describes the particular precautions necessary when handling intraocular lenses; it also gives guidance on the range of solvents that may be employed. In selecting the solvent, give consideration to the ability of the solvent to swell the material to enable extraction without destroying the polymeric structure or dissolving the material and the solubility of the potential residual monomers in the solvent to obtain complete extraction. Use water or a suitable organic solvent for the extraction. Extraction of some materials such as hydrophilic IOLs can require both aqueous and organic solvent extraction to insure extraction of both hydrophilic (salts) and hydrophobic components (monomers, UV absorbers, etc).

The material extracted from the intraocular lenses should be examined by appropriate chromatographic, spectrophotometric and wet analysis methods to identify residual monomers, cross-linking agents, catalysts etc. employed in the manufacturing process.

The following method can be utilized when the solvent swells the material enough to ensure complete extraction.

A.4 Test samples

Sterile finished IOLs weighing no less than 200 mg.

A.5 Reagents

A.5.1 **Water**, distilled or deionized.

A.5.2 **Organic solvent**, of analytical grade or purer.

A.5.3 **Boiling stones** or **anti-bumping granules**.

A.5.4 **Active desiccant**.

A.6 Apparatus

The following list is advisory. Other suitable means can be used.

A.6.1 Soxhlet extraction apparatus, including condenser, round-bottom flask and heating mantle with glass components of standard borosilicate laboratory glassware.

A.6.2 Extraction thimble, made from perforated stainless steel, sintered glass, paper or equivalent, fitted with a glass wool plug or other suitable closure.

A.6.3 Drying apparatus, vacuum oven, or other suitable drying apparatus.

A.6.4 Analytical balance, precise to 0,1 mg or better.

A.6.5 High-pressure liquid chromatography (HPLC).

A.6.6 Gas chromatography (GC).

A.6.7 Gas chromatography/mass spectroscopy (GC/MS).

A.6.8 Rotary evaporator.

A.7 Test procedure

CAUTION — When using a volatile or flammable solvent the equipment should be placed in a fume-hood.

Dry the intraocular lenses to constant mass preferably under vacuum at 60 °C ± 5 °C. Allow the intraocular lenses to cool to room temperature under vacuum before weighing. If they are hygroscopic, transfer the intraocular lenses from the oven to a desiccator and allow to cool over active desiccant.

Weigh the dry intraocular lenses to the nearest 0,1 mg.

Put the intraocular lenses into the extraction thimble. Place the boiling stones in the flask if necessary, and partly fill the flask (to about 70 % of its capacity) with the appropriate solvent. Place the extraction thimble into the Soxhlet apparatus and assemble the flask, the Soxhlet extractor and the condenser. Place the flask in the heating mantle.

Set the extraction rate at about 4 to 6 thimble flushes per hour and extract the intraocular lenses for at least 4 h. The extraction apparatus could need to be insulated by wrapping with foil to achieve the desired extraction rate when using some solvents such as water.

Allow the solvent to cool to room temperature.

A.8 Analysis of the test material

Remove the intraocular lenses from the extraction thimble. Dry the intraocular lenses to constant mass as described in A.7. Determine the total mass of the intraocular lenses after extraction and calculate the change in mass from the extraction.

In the case of intraocular lenses being marketed in a hydrated state, correct for the salt content of the hydrating medium by adding the mass of salt in the hydrating solution to the extracted material.

It is common for hydrophilic lenses to be hydrated and supplied in a solution containing inorganic salts. In order for the effect of the salt content on the calculated result to be accurately determined, the water content of the lenses will have to be known or measured in accordance with ISO 10339. Alternatively, the lenses could be equilibrated in at least two changes of water for 24 h at room temperature prior to testing.

A.9 Analysis of extracts

Remove the extraction medium from the Soxhlet apparatus and allow to equilibrate at room temperature. Concentrate the extract to about 10 ml using a rotary evaporator or equivalent apparatus. Perform qualitative and quantitative analyses for leachable substances such as UV-absorbers, additives, degradation products and other impurities from manufacturing by HPLC, GC, GC/MS or other appropriate methods.

Carry out corresponding qualitative and quantitative analyses on solvent blanks that have undergone the same extraction 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.10 Test report

The test report shall include the following at a minimum:

a) all information necessary for identification of the samples tested;

b) a reference to this part of ISO 11979 (ISO 11979-5:2006);

c) the extraction medium;

d) the results of the test, including the results of the individual determinations and their means, where applicable;

e) any deviations from the procedure specified;

f) any unusual features (anomalies) observed during the test;

g) the date of extraction and the dates of subsequent analyses.

Annex B
(normative)

Test for leachables

B.1 Purpose

The purpose of this test is to detect and quantify extractable additives and other leachables from intraocular lens material under physiological conditions.

B.2 General considerations

Select analytical methods that are justified in terms of being well established and of sufficient sensitivity to detect significant concentrations.

B.3 Test material

Either sterile finished IOLs or representative sample material weighing approximately 4 g are used.

B.4 Control material

Solvent blanks that have undergone the same procedures described in B.6.1 are used for comparison with extracts of test material.

B.5 Apparatus

The following list is advisory. Other suitable means can be used.

B.5.1 Glass vials, of hydrolytic Class I in accordance with the European Pharmacopoeia (Ph. Eur.) and the US Pharmacopoeia (USP).

B.5.2 Laboratory glassware.

B.5.3 Syringes.

B.5.4 Analytical balance.

B.5.5 Shaker.

B.5.6 Incubator.

B.5.7 Centrifuge.

B.5.8 High-pressure liquid chromatograph (HPLC).

B.5.9 Gas chromatograph (GC).

B.5.10 UV/visible (UV/Vis) spectrophotometer.

B.6 Test procedure

B.6.1 Extraction

Choose 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.

Place the test material in glass vials containing 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. Agitate to ensure that all surfaces of the test material are available for extraction during the entire period of extraction.

Extract the test material at 35 °C ± 2 °C for 72 h ± 1 h.

B.6.2 Analysis of extracts

Remove the vials from the incubator and allow them to equilibrate at room temperature. Remove the test materials from the vials and examine them as specified in B.6.3. Perform qualitative and quantitative analyses for leachable substances such as UV-absorbers, additives, and degradation products by HPLC, GC, and/or UV/Vis spectrophotometry as appropriate. Analyse the extract in each vial separately.

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

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.

B.6.3 Analysis of the test material

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

B.7 Test report

The test report shall include the following at a minimum:

a) all information necessary for identification of the samples tested;

b) a reference to this part of ISO 11979 (ISO 11979-5:2006);

c) the extraction media;

d) the results of the test, including the results of the individual determinations and their means, where applicable;

e) any deviations from the procedure specified;

f) any unusual features (anomalies) observed during the test;

g) the date of extraction and the dates of subsequent analyses.

Annex C
(normative)

Hydrolytic stability

C.1 Purpose

The purpose of this test is to determine the stability of an IOL material in an aqueous environment through detection and quantification of possible degradation products from hydrolysis and changes in physical appearance, optical properties, and chromatographic characteristics.

C.2 General considerations

Select analytical methods that are justified in terms of being well established and of sufficient sensitivity to detect significant concentrations.

C.3 Test material

Either sterile finished IOLs or representative sample material are used. A minimum of 15 pieces of test material is needed for each combination of temperature and duration.

C.4 Control material

Solvent blanks that have undergone the procedures described in C.6.1 are used as control for comparison with the solvent used in testing.

C.5 Apparatus and materials

The following list is advisory. Other suitable means can be used.

C.5.1 Incubation medium (an aqueous solvent).

C.5.2 Glass vials, of hydrolytic Class I in accordance with the European Pharmacopoeia (Ph. Eur.) and the US Pharmacopoeia (USP).

C.5.3 Laboratory glassware.

C.5.4 Syringes.

C.5.5 Analytical balance.

C.5.6 Shaker.

C.5.7 Incubator.

C.5.8 Centrifuge.

C.5.9 High-pressure liquid chromatograph (HPLC).

C.5.10 Gas chromatograph (GC).

C.5.11 UV/Visible (UV/Vis) spectrophotometer.

C.5.12 Optical microscope.

C.5.13 Scanning electron microscope (SEM).

C.6 Test procedure

C.6.1 Treatment

Place the test material in glass vials containing a sufficient volume of a suitable aqueous medium to achieve a ratio of 10 g of test material per 100 ml of medium and then incubate at a temperature that is appropriate for the test material. Prepare at least two vials for each combination of temperature and duration. Agitate to ensure that all surfaces of the test material are available for extraction during the entire testing period.

C.6.2 Analysis of the solvent after exposure to incubation medium

Remove the vials from the incubator and allow to equilibrate to room temperature. Remove the test material from the solvent and examine it as specified in C.6.3. Perform qualitative and quantitative analyses on the supernatant by HPLC, GC and/or UV/Vis spectrophotometry as appropriate in accordance with the experimental design. The supernatant from each vial shall be analysed separately.

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 incubation medium to that of the solvent blank and interpret the findings in the context of possible material changes.

NOTE Additional analysis to assess the effects of temperature could be necessary if extraction is done at an elevated temperature.

C.6.3 Analysis of the test material

After incubation, rinse the test material and allow it to dry.

Take at random five pieces of test material and determine their spectral transmittance as described in ISO 11979-2. Compare the transmittance spectra of the treated samples with those of untreated samples and record any changes.

Take at random five IOLs from and determine their dioptric power as described in ISO 11979-2. If a representative sample material is used for testing, determine instead the refractive index of the five samples using a validated method. Compare the dioptric power or refractive index of the treated material with that of the control material and record any changes.

Examine and photograph the test material and the untreated material 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 untreated material. Compare the observations and photos of test material and untreated material to detect any changes in appearance, e.g. bubbles, dendrites, breaks and fissures.

NOTE Additional analysis to assess the effects of temperature could be necessary if extraction is done at an elevated temperature.

C.7 Test report

The test report shall include the following at a minimum:

a) all information necessary for identification of the samples tested;

b) a reference to this part of ISO 11979 (ISO 11979-5:2006);

c) hydrolysis temperature and duration;

d) hydrolysis medium;

e) the results of the test, including the results of the individual determinations and their means, where applicable;

f) any deviations from the procedure specified;

g) any unusual features (anomalies) observed during the test;

h) the date of exposure to the hydrolysis medium and the dates of subsequent analyses.

Annex D
(normative)

Photostability test

D.1 Purpose

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

D.2 Test material

Ten finished IOLs or 10 pieces of representative sample material with a thickness similar to that of the IOL.

D.3 Control material

Ten finished IOLs or 10 pieces of representative sample material with a thickness similar to that of the IOL, which will remain unexposed to UV radiation.

D.4 Reagents

D.4.1 Physiological saline, used as exposure medium.

D.5 Apparatus

D.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 in accordance with the European Pharmacopoeia (Ph. Eur.) and the US Pharmacopoeia (USP)].

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

D.6 Test procedure

Immerse the test material in the vial containing 2 ml physiological saline. Expose the vial to the Xenon arc lamp for the required length of time (see 5.5), ensuring that during exposure the temperature of the test material in the vial is maintained at 35 °C $\pm$ 2 °C.

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

NOTE Only the intensity of the Xenon arc lamp at a wavelength between 300 nm to 400 nm is used in the calculation of UV intensity.

Take care to avoid microbial contamination in order to avoid growth of microorganisms in the vials during the irradiation period.

Perform the same procedure on the control material ensuring that the material is prevented from being exposed to light.

D.7 Post exposure 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. Measure the lens power and resolution.

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.

D.8 Test report

The test report shall include the following:

a) all information necessary for identification of the samples tested;

b) a reference to this part of ISO 11979 (ISO 11979-5:2006);

c) the light intensity used in the exposure;

d) the duration of the light exposure;

e) the results of the test, including the results of the individual determinations and their means, where applicable;

f) any deviations from the procedure specified;

g) any unusual features (anomalies) observed during the test;

h) the date of light exposure and the dates of subsequent analyses.

Annex E
(normative)

Nd-YAG laser exposure test

E.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 assure that the Nd-YAG laser treatment commonly given to patients with implanted IOLs does not cause leakage of toxic substances.

E.2 Test material

Five sterile finished IOLs.

E.3 Reagents

E.3.1 Physiological saline, used as exposure medium.

E.4 Apparatus

E.3.1 Optical cuvette, capacity 2 ml.

E.3.2 Nd-YAG laser.

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

E.5 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 exposure media for analysis. Repeat the procedure for the remaining IOLs.

E.6 Post treatment evaluation

Pool the exposure medium for the IOLs for chemical analysis and for cytotoxicity testing.

Test the physiological saline solution for cytotoxicity after Nd-YAG laser treatment.

E.7 Test report

The test report shall include the following at a minimum:

a) all information necessary for identification of the samples tested;

b) a reference to this part of ISO 11979 (ISO 11979-5:2006);

c) the laser energy level used in the treatment;

d) the results of the test, including the results of the individual determinations and their means, where applicable;

e) any deviations from the procedure specified;

f) any unusual features (anomalies) observed during the test;

g) the date of laser exposure and the dates of subsequent analyses.

Annex F
(informative)

Supplemental conditions of test for local effects after implantation

F.1 Supplemental conditions to testing in accordance with ISO 10993-6

F.1.1 Testing for local effects of IOL material after implantation is performed in accordance with ISO 10993-6 supplemented with the conditions given in F.1.2 to F.1.5.

F.1.2 The test material is implanted subcutaneously or intramuscularly.

F.1.3 The test material is either finished IOLs with a central thickness of 0,8 mm to 1,0 mm or slabs of a representative sample material that are of an appropriate size to allow the required post-retrieval evaluations to be performed.

F.1.4 The duration of the implantation is four weeks.

F.1.5 The IOL material is retrieved at the end of the implantation period and evaluated for material changes and integrity. It is evaluated by light microscopy at appropriate magnifications for haze and surface abnormalities. Half of the samples are subsequently evaluated by SEM/EDX at appropriate magnifications for surface changes and by EDX for surface deposits. Light microscopy is used if the material does not lend itself to SEM. The other half of the samples is evaluated for UV/Vis transmittance.

F.2 Test report

The test report shall include the following at a minimum:

a) all information necessary for identification of the samples tested;

b) a reference to this part of ISO 11979 (ISO 11979-5:2006);

c) the animal model;

d) the implantation method (subcutaneous or intramuscular);

e) the results of the test, including the results of the individual determinations and their means, where applicable;

f) any deviations from the procedure specified;

g) any unusual features (anomalies) observed during the test;

h) the in-life study date and the dates of subsequent analyses.

Annex G
(normative)

Ocular implantation test

G.1 Purpose

This test is designed to evaluate the biocompatibility of an IOL material by surgical implantation of the material in the eye of an appropriate animal model for an appropriate period of time. The reciprocal tolerance of the test material and ocular tissues after implantation is evaluated.

G.2 Test material

The test material is in the form of a sterile finished IOL, whenever possible. A representative sample material can be implanted when justified. The same fabrication methods as intended for the product to be marketed are followed. The representative sample material has a mass equivalent to that of a finished IOL or greater and is of a shape and size that will allow the required post-retrieval evaluations to be performed.

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

G.3 Control material

The control material is a sterile finished IOL of a similar design that has been widely marketed for at least the last five years, whenever possible, and has not been associated with significant material-related adverse events. A representative sample material can be used when justified. The representative sample material has a mass equivalent to that of a finished IOL or greater and is of a shape and size that will allow the required post-retrieval evaluations to be performed. For evaluation of phakic IOLs, an appropriate control IOL may not be available because the short clinical history of such lenses. The requirement for the use of a control material is determined on a case-by-case basis and is justified.

G.4 Reagents and materials

The following list is advisory. Other suitable means can be used.

G.4.1 Physiological saline or balanced salt solution.

G.4.2 Anaesthetic.

G.4.3 Drugs, for pre- and post-operative treatment.

G.5 Apparatus

The following list is advisory. Other suitable means can be used.

G.5.1 Operating microscope.

G.5.2 Slit lamp microscope.

G.5.3 Indirect ophthalmoscope.

G.5.4 Phacoemulsification unit.

G.5.5 Lid speculum.

G.5.6 Sutures.

G.5.7 Surgical instruments.

G.6 Animal model

The rabbit is first considered for use due to its extensive history of use in ophthalmic studies and the availability.

G.7 Test procedure

The number of animals used is kept to a minimum in accordance with ISO 10993-2 on animal welfare requirements.

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. Implant one eye of each of these animals with the test sample. Implant the fellow eye with a control sample.

A bilateral implantation is preferred, but unilateral implantation is permissible, if local rules so require.

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

The implantation procedure is as close as possible to the intended clinical use whenever possible. Anatomical differences between the human and the animal model and ocular geometry-related surgical difficulty could necessitate placement of an IOL or representative sample material in an alternate ocular site. If an IOL material is not evaluated in the intended placement site, justification is given and a risk analysis is performed to identify areas of potential concerns when the IOL is placed in the intended placement site in the human.

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

G.8 Intra-operative observations

Intra-operative observations 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;

f) unusual surgical problems.

All observations are recorded.

G.9 Implantation period

If the rabbit is chosen for ocular implantation, the study duration is six months. The rabbit is prone to fibrin formation and rapid lens regrowth, which makes a longer-term biocompatibility assessment difficult. Since the rabbit eye is generally known to be more reactive, a study duration of six months is deemed appropriate.

The study duration is one year if an animal model other than the rabbit is used. Any deviations from this one-year requirement necessitated by specific limitations of the model shall be justified.

G.10 Test evaluation

G.10.1 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, 6 months, and at the end of the follow-up period.

The observations include, but are not limited to, the following occurrences:

— fibrin;

— flare;

— cells;

— adhesions;

— neovascularization;

— corneal oedema;

— material clarity;

— location of the haptic, where applicable;

— centration of the lens, where applicable.

Take slit lamp photographs, if needed, for documentation at the time of the examination.

G.10.2 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 or are euthanized during the study because of problems that are not related to the eye.

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

a) the enucleated eyes are immediately immersed into a suitable fixative for storage to allow dissection of the eye and subsequent evaluation to be performed later as described in b); or

b) the eyes are dissected equatorially immediately after enucleation and an internal examination is performed. Note any visible abnormalities, the location of the implant, and centration, where applicable. Examine specifically the support and contact zones between the IOL and the tissue, where applicable. Take photographs to support the observations. Carefully remove the IOL or IOL material sample and then perform histopathological evaluations of the anterior and posterior segments of the eye.

NOTE Storage of the enucleated globe in a fixative can result in changes to the IOL material.

G.10.3 Evaluation of explanted lenses

Examine the explanted IOLs or IOL material samples obtained in G.9.2 b) by light 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, where applicable. Half of the samples are then thoroughly cleaned, if the optical surfaces can be cleaned without being damaged, and then assessed for optical properties in accordance with ISO 11979-2. The other half of the samples is then evaluated by SEM, where feasible, for surface deposits and changes, and by SEM/EDS for signs of calcification as evidenced by the concomitant presence of Ca and P.

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

G.11 Test report

The test report shall include the following at a minimum:

a) all information necessary for identification of the samples tested;

b) a reference to this part of ISO 11979 (ISO 11979-5:2006);

c) the intraocular lens placement site;

d) the results of the test, including the results of the individual determinations and their means, where applicable;

e) any deviations from the procedure specified;

f) any unusual features (anomalies) observed during the test;

g) the in-life study date and the dates of subsequent analyses.

Bibliography

[1] SLINEY, D.H. Estimating the solar ultraviolet radiation exposure to an intraocular lens implant. *J Cataract Refract Surg*, **13**, 1987, pp.297-301

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