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Ophthalmic implants — Intraocular lenses —

Part 5: Biocompatibility

Implants ophtalmiques — Lentilles intraoculaires —

Partie 5: Biocompatibilité

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Contents

Page

Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 170, *Ophthalmic optics*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This third edition cancels and replaces the second edition (ISO 11979-5:2006), which has been technically revised.

The main changes compared to the previous edition are as follows:

— correction and addition of references throughout the document;

— added more specific guidance on risk-based approach throughout the document;

— added requirement to use state of the art analytical methods;

— update of apparatus lists where applicable;

— clarification of test material in Tables 1 and 2, reference to ISO/TR 22979 when the IOL is a modification of a parent IOL and requirement for a biological evaluation plan added to Clause 4;

— combination and re-writing of physicochemical test methods and their objectives in Table 3 of 5.1;

— added requirement for physical/chemical description and contaminants in 5.2;

— revised order of tests in 6.1 for alignment with ISO 10993 and added subclauses for every test;

— clarification of ratio for material and extraction medium in biological tests in 6.1;

— principle and procedure of exhaustive extraction is explained in more detail (Annex A);

— in hydrolytic stability, products are their own control for spectral transmittance and dioptric power (Annex C);

— removed the allowance of representative test material for photostability testing, added the requirement to measure lens power and image quality (Annex D);

— Annex F change from informative to normative;

— duration of subcutaneously or intramuscularly implantation increased from 4 weeks to 3 months (Annex F);

— duration of ocular implantation test in rabbits reduced from 6 months to 3 months (Annex G).

A list of all parts in the ISO 11979 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

This document 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 document 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 documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 within a risk management process*

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 10993-5, *Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity*

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 skin sensitization*

ISO 10993-12, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

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*

ISO 18369-4, *Ophthalmic optics — Contact lenses — Part 4: Physicochemical properties of contact lens materials*

ISO/TS 21726, *Biological evaluation of medical devices — Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents*

ISO/TR 22979, *Ophthalmic implants — Intraocular lenses — Guidance on assessment of the need for clinical investigation of intraocular lens design modifications*

3 Terms and definitions

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

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

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. Refer to Table 1, Table 2 and ISO 11979-1 for definition of test material and allowance of representative samples. At a minimum, independent from the initial risk assessment outcome, the tests described in Clause 5 shall be performed to characterize the physicochemical properties of the intraocular lens. The evaluation of the material for biological safety shall then be undertaken per biological evaluation plan, 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 10993-2, ISO 10993-3, ISO 10993-5, ISO 10993-6, ISO 10993-10, ISO 10993-12, ISO 10993-17 and ISO/TS 21726 and as noted in this document.

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. ISO 10993-1 describes the content of such evaluation.

Refer to ISO/TR 22979 when the IOL is a modification of a parent IOL.

Table 1 — Allowance of representative samples for physicochemical tests

Test	Test material	
	Sterile finished IOL	Representative sample[a]
Exhaustive extraction	X	X
Leachables	X	X
Hydrolytic stability	X	X
Photostability against UV/Vis irradiation	X	
Stability against Nd-YAG laser exposure	X	
Insoluble inorganics	X	

[a] Sample, manufactured and processed, including intended sterilization, using a procedure equivalent to that used for the intraocular lens, that has the same central thickness as the final product (typically 20,0 D IOL).

Table 2 — Allowance of representative samples for biological tests

Test	Test material	
	Sterile finished IOL	Representative sample[a]
Cytotoxicity	X	X
Sensitization	X	X
Genotoxicity	X	X
Local effects after implantation	X	X
Ocular implantation test	X[b]	

[a] Sample, manufactured and processed, including intended sterilization, using a procedure equivalent to that used for the intraocular lens, that has the same central thickness as the final product (typically 20,0 D IOL).

[b] To allow for dimensional differences between human and animal eyes, the IOL could require scaling to fit the anatomical placement site of the animal.

5 Physicochemical tests

5.1 General

The physicochemical tests listed in Table 3 shall be performed to characterize the physicochemical properties of the IOL and to facilitate an analysis of any risk introduced by chemical compounds which may result from processing, treatment in use, or (simulated) ageing of the test material. The results of the tests in Table 3 should be used as input for the risk assessment in accordance with ISO 14971.

The outcomes of the physicochemical tests should be subjected to systemic toxicologically evaluation according to ISO 10993-17 and ISO/TS 21726.

Table 3 — Physicochemical tests and their objectives

Test		Objectives
a)	Exhaustive extraction	To identify and quantify the total amount of extractable material that is present in the IOL, possible residues from synthesis and additives or impurities from manufacturing and packaging and to be used for performing the risk assessment.
b)	Leachables	To identify and quantify the substances that are released from IOL under simulated physiological conditions and to be used for determining the risk during the clinical use.
c)	Hydrolytic stability	To identify and quantify possible degradation products due to hydrolysis to determine the stability of an IOL in an aqueous environment and to assess the risk for potentially harmful effects due to hydrolytic degradation products.
d)	Photostability against ultraviolet/visible (UV/Vis) irradiation	To characterize the effect of UV/Vis irradiation on the optical, mechanical and chemical properties of the IOL and to assess the risk for potentially harmful effects of degradation products due to irradiation.
e)	Stability against Nd-YAG laser exposure	To identify the effect of Nd-YAG laser treatment on the chemical properties of the IOL and to assess the risk for potentially harmful effects of degradation products due to Nd-YAG laser exposure.
f)	Insoluble inorganics	To quantify the levels of insoluble inorganics which may result from manufacturing processing and packaging and to assess the risk from insoluble inorganics.

5.2 Physical/Chemical description

The manufacturer shall provide a description of each of the components in the formulation to facilitate the interpretation of physical and chemical test results.

For description of each component the manufacturer shall provide, if available:

a) Name — Provide the chemical name and Chemical Abstracts Service (CAS) registry number;

b) Structure formula — Provide the chemical structure and molecular formula;

c) If the component material is derived from biological sources, the organism from which it is obtained shall be stated along with its source.

For the finished polymer the manufacturer shall provide, if available:

d) Structure formula — Provide the chemical structure and molecular formula.

5.3 Exhaustive extraction test

The test material shall be tested for extractables under exhaustive extraction conditions in accordance with the method specified in Annex A. Alternative methods can be used, provided that they have been validated and are reflective of the current state of the art.

The following shall be observed:

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

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

c) 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 results shall be evaluated to assess the risk for potentially harmful effects due to extractable components.

5.4 Test for leachables

The test material shall be tested for leachables under simulated physiological conditions in accordance with the method specified in Annex B. Alternative analytical methods can be used that are reflective of the current state of the art in common use.

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 leachables of the material, such as process contaminants, residual monomers, additives, and other leachables.

The results shall be evaluated to assess the risk for potentially harmful effects due to leachable components.

5.5 Test for hydrolytic stability

Hydrolytic stability testing shall be conducted in accordance with the method specified 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.

NOTE Five years is considered sufficiently long to show changes when the product is not hydrolytically stable and is considered appropriate since only limited test acceleration is possible.

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

$$F = 2{,}0^{(Ta\text{-}To)/10}$$

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.

f) 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 average absolute change in dioptric power greater than 0,25 D for a 20 D lens or a corresponding change in refractive index comparing before testing and after exposure to the simulated time of at least 5 years.

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

5.6 Photostability test

Photostability testing shall be conducted in accordance with Annex D.

The following shall be observed:

a) There shall be no changes in appearance of the irradiated test material when compared with non-irradiated test material, such as bulk and surface defects induced by photo irradiation.

b) No significant change shall be detected between the UV/Vis spectra, dioptric power and image quality of the test material exposed to UV radiation and controls receiving no radiation.

c) The exposure medium shall be qualitatively and quantitatively analysed for any chemical entities after irradiation and compared to non-irradiated controls.

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.

The results shall be evaluated to assess the risk for potentially harmful effects due to instability of the material from exposure to UV/Vis irradiation.

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.

5.7 Nd-YAG laser exposure test

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

The exposure medium shall be qualitatively and quantitatively analysed for any chemical entities after laser exposure.

NOTE Nd-YAG laser treatment can lead to a higher concentration of released chemicals during the laser treatment, which can cause a local effect.

The results shall be evaluated to assess the risk for potentially harmful effects, due to instability of the material from exposure to Nd-YAG laser.

Additionally, the exposure medium is subjected to a cytotoxicity test according to ISO 10993-5 using an elution or direct contact method for the detection of cell cytotoxic substances after laser exposure.

5.8 Evaluation of insoluble inorganics

The manufacturing process shall be assessed for the presence of insoluble inorganics that may remain on the lens at the end of the manufacturing process (e.g., manufacturing materials, processing aids, etc.). The IOL shall be evaluated for all detectable insoluble inorganics, with emphasis on determining the specific levels of the potential manufacturing residues. The test methods used for this evaluation shall be identified, validated and justified. Consideration shall be given to methods with a detection limit of 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.

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.

At the minimum, the following biological endpoints shall be considered:

— cytotoxicity (the effects on cell growth and cell damage);

— sensitization potential;

— genotoxicity;

— local effects after implantation;

— ocular implantation.

The appropriate parts of ISO 10993 shall apply. Supplements to these parts are described in 6.2 to 6.6. Sample preparation shall be performed in accordance with ISO 10993-12 using surface area to volume for the extraction ratio and taking into consideration the supplemental requirements.

After collecting all biologically relevant data, an interpretation of biological evaluation data and overall biological risk assessment according to ISO 10993-1 shall be performed.

6.2 Test for cytotoxicity

Testing for cytotoxicity shall be performed in accordance with ISO 10993-5 by using an extract or direct contact test.

6.3 Tests for sensitization

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

— The maximization sensitization test can be used for testing. Local Lymph Node Assay (LLNA) test may be used with adequate justification.

— 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 shall not dissolve or degrade the test material. The solvent itself shall also not be a known irritant, adjuvant or sensitizer.

6.4 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. When additional dilution is required to use the extract in the genotoxicity testing, the dilution factor shall be within the selected extraction ratio.

NOTE According to ISO 10993-3 genotoxicity testing has to be performed using a testing battery as one single genotoxicity test is not able to describe all genotoxic risks.

6.5 Test for local effects

The test for local effects after implantation shall be conducted as described in ISO 10993-6 and supplemented as specified in Annex F.

6.6 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, identify and quantify extractable additives and other extractables from IOLs under exhaustive extraction conditions.

A.2 General considerations

Select analytical methods that are reflective of current state of the art in common use and of sufficient sensitivity to detect significant concentrations.

A.3 Principle

The method of extraction described in this annex uses 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 used. 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. Depending on the material, 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 chemical substances extracted from the intraocular lens material should be examined by appropriate chromatographic, spectrophotometric and/or wet analysis methods to identify residual monomers, cross-linking agents, catalysts, impurities, degradation products etc. used in the manufacturing process.

Exhaustive extraction is defined in ISO 10993-12 as “extraction conducted until the amount of extractable material in a subsequent extraction is less than 10 % by gravimetric analysis of that detected in the initial extraction”. The concept of an exhaustive extraction is discussed in ISO 10993-12:2012, Annex D. An exhaustive extraction establishes the absolute maximum amounts of extractables that can be removed (extracted) from the medical device or material and thus defines the upper bound on the amount of leachables that could potentially be released by the device or material during clinical use/ lifetime.

As noted in ISO 10993-12:2012, Annex D, exhaustive extraction involves sequential extraction of the test article under relevant extraction conditions with a relevant extraction vehicle and is achieved when the level of extracted substance(s) by gravimetric (or other analysis) in an individual extraction step is less than 10 % of the level of the extracted substance(s) in the initial extract. Achieving the required 10 % level for each individual extractable may be analytically and practically challenging [e.g., when the 10 % level is below the method’s Limit of Quantification (LOQ)]; thus, it might be necessary to establish that the 10 % level of extraction has been established by alternate means [e.g., total peak area, Total Organic Carbon (TOC), non-volatile residue]. Such alternate means should be justified.

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

A.4 Test material

Sterile finished IOLs or representative sample material weighing no less than 200 mg per extraction media.

A.5 Control material

Solvent blanks that have undergone the procedures described in A.8.1 are used as control for comparison with the solvent used in testing.

A.6 Reagents

A.6.1 Water, distilled or deionized.

A.6.2 Organic solvent, of analytical grade or purer.

A.6.3 Boiling stones or **anti-bumping granules**.

A.6.4 Active desiccant.

A.7 Apparatus

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

A.7.1 Soxhlet extraction apparatus, including condenser, round-bottom flask and heating mantle with glass components of standard borosilicate laboratory glassware.

A.7.2 Extraction thimble, made from perforated stainless steel, sintered glass, paper or equivalent, fitted with a glass wool plug or other suitable closure.

A.7.3 Drying apparatus, vacuum oven, or other suitable drying apparatus.

A.7.4 Analytical balance, precise to 0,1 mg or better.

A.7.5 High-pressure liquid chromatograph (HPLC).

A.7.6 Gas chromatograph (GC).

A.7.7 Gas chromatography/Mass spectroscope (GC/MS).

A.7.8 Rotary evaporator.

A.7.9 Desiccator with desiccant.

A.8 Test procedure

A.8.1 Treatment

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. While in the oven, allow the intraocular lenses to cool to room temperature under vacuum. Transfer the intraocular lenses from the oven to a desiccator and allow to further cool over active desiccant. Weigh the dry intraocular lenses to the nearest 0,1 mg.

Perform the exhaustive extraction of the test samples as follows:

a) 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 a known amount of 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.

b) 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 might need to be insulated by wrapping with foil to achieve the desired extraction rate when using some solvents such as water.

c) Remove the extraction medium from the Soxhlet apparatus and allow to equilibrate at room temperature. Transfer a sufficiently large aliquot of the extraction medium into a pre-weight container and evaporate the extraction medium. Weigh the container until constant mass. Calculate the non-volatile residue for the first extraction step.

   If there is reliable evidence (e.g., internal experimental data, publications, etc.) that the extraction method used is capable of extracting more than 90 % of the total amount of extractable substances from the IOL material after the first extraction step, no further extraction steps as described in Steps d) and e) shall be performed.

d) For subsequent extractions, add the appropriate solvent to the same volume as used for the first extraction [refer to Step a)] into the flask. Repeat Steps b) and c).

e) As long as the non-volatile residue of a particular extraction step is above the level of 10 % of the initial non-volatile residue [Step c)], perform a further extraction step as described per Step d).

Instead of determining the non-volatile residue as a basis for the evaluation of reaching the exhaustive extraction, it is also acceptable to use analytical methods.

A.8.2 Analysis of the test material

Remove the intraocular lenses or representative test material from the extraction thimble. Dry the intraocular lenses to constant mass as described in A.8.1. 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 shall be known or measured in accordance with ISO 18369-4. Alternatively, the lenses may be equilibrated in at least two changes of water for 24 h at room temperature prior to testing.

A.8.3 Analysis of extracts

Combine the remaining extraction media of the individual extraction steps [see A.8.1, Step c)]. Concentrate the extract to about 10 ml using a rotary evaporator or equivalent apparatus. In case substances with a low boiling point (up to a temperature shortly above the boiling temperature of the extraction medium) can be expected, care shall be taken avoiding an evaporation of these substances during the pre-concentration step. It shall be considered if the analytical detection limits are sufficient to analyse the extracts without pre-concentration. Perform qualitative and quantitative analyses for extractable 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.

A.9 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 document, i.e. ISO 11979-5:2020;

c) the extraction medium;

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

NOTE If internal experimental data, publications, etc. are used demonstrating that the extraction method used is capable of extracting more than 90 % of the total amount of extractable substances from the IOL material after the first extraction step, this source has to be referred to within the report.

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, identify and quantify leachable additives and other leachables from IOLs under physiological conditions.

B.2 General considerations

Select analytical methods that are reflective of current state of the art in common use and of sufficient sensitivity to detect significant concentrations.

B.3 Test material

Either sterile finished IOLs weighing approximately 4 g 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.

A set of 5 untreated test material is used as negative controls for transmittance spectra testing in B.6.3.

B.5 Apparatus and materials

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/Mass spectroscope (GC/MS).

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 material 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/MS, 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.

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 document, i.e. ISO 11979-5:2020;

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 in an aqueous environment through detection, identification 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 reflective of current state of the art in common use 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 20 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.6.2 are used as control for comparison with the solvent used in testing.

The treated test material will be its own control material for spectral transmittance, refractive index or dioptric power testing.

Five untreated IOLs will be the negative control material for comparison of microscopy examination described in C.6.4.

C.5 Apparatus and materials

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

C.5.1 Aqueous solvent, used as an extraction medium.

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 / Mass spectroscope (GC/MS).

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 Pre-treatment testing

Take at random five IOLs from the test material and ensure they can be individually identified after treatment. Determine their spectral transmittance and dioptric power as described in ISO 11979-2. If a representative sample material is used for testing, determine the refractive index instead of dioptric power of the five samples using a validated method.

C.6.2 Treatment

Place the test material in glass vials containing a sufficient volume of a suitable aqueous solvent 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.6.3 Analysis of the aqueous solvent after incubation

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.6.4. Perform qualitative and quantitative analyses on the solvent by HPLC, GC/MS and/or UV/Vis spectrophotometry as appropriate in accordance with the experimental design. The solvent 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 test solvent to that of the solvent blank.

NOTE 1 Additional analysis to assess the effects of temperature could be necessary if extraction is done at an elevated temperature.

NOTE 2 Trending analysis and/or comparison to the results of the leachable testing as performed per Annex B can be used to better interpret the results of the hydrolytic stability test.

C.6.4 Analysis of the test material

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

Take the five pieces of test material that had been identified in C.6.1 and perform the following:

a) Examine and photograph the test material and the untreated material by light microscopy at ×10 or higher magnification and thereafter by SEM at ×500 or higher 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.

b) Determine their spectral transmittance as described in ISO 11979-2. Per individual sample, compare the transmittance spectra of the treated sample with the pre-treatment results and record any changes.

c) 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. Per individual sample, compare the dioptric power or refractive index of the treated material with the pre-treatment results and record any changes.

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 document, i.e. ISO 11979-5:2020;

c) hydrolysis temperature and duration;

d) aqueous solvent;

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 IOLs irradiated in the wavelength range 300 nm to 400 nm.

D.2 General considerations

Select analytical methods that are reflective of current state of the art in common use and of sufficient sensitivity to detect significant concentrations.

D.3 Test material

10 finished IOLs.

D.4 Control material

Solvent blanks that have undergone the procedures described in D.7 are used as control for comparison with the solvent used in testing.

10 finished IOLs which will remain unexposed to UV radiation.

D.5 Reagents

D.5.1 Sterile physiological saline, used as exposure medium.

D.6 Apparatus

D.6.1 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.6.2 Xenon arc lamp, provided with a filter capable of excluding light of wavelength less than 300 nm.

D.7 Test procedure

D.7.1 Treatment

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, ensuring that during exposure the temperature of the test material in the vial is maintained at 35 °C ± 2 °C.

The intensity of the irradiation source can be selected individually, but shall not be in excess of 30 mW/cm^2, and shall 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.7.2 Post exposure evaluation

At the end of the calculated exposure time, the exposure medium from irradiated IOLs shall be qualitatively and quantitively analysed for any migrated components and compared to saline extract from non-irradiated controls. Select analytical methods that are reflective of current state of the art in common use.

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 dioptric power and image quality.

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.

Examine and photograph the test material and the untreated material by light microscopy at ×10 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.

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 document, i.e. ISO 11979-5:2020;

c) the light intensity used in the exposure;

d) the duration of the light exposure;

e) the exposure medium;

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

g) any deviations from the procedure specified;

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

i) 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 chemical effects of Nd-YAG laser exposure on the test material to assure that the Nd-YAG laser treatment commonly given to patients with implanted IOLs does not cause the generation and/or release of toxic substances.

E.2 General considerations

Select analytical methods that are reflective of current state of the art in common use and of sufficient sensitivity to detect significant concentrations.

E.3 Test material

Five sterile finished IOLs.

E.4 Control material

Sterile solvent blanks are used as control for comparison with the solvent used in testing.

E.5 Reagents

E.5.1 Sterile physiological saline, used as exposure medium.

E.6 Apparatus

E.6.1 Optical cuvette, capacity 2 ml.

NOTE As a cytotoxicity test of the extract after laser exposure is performed, all used solvents, cuvettes and other handling tools have to be sterilized. The handling should be performed under aseptic conditions in order to avoid a microbial contamination of the extract. A sterile filtration of the received extract is not suggested as this procedure may remove toxic substances from the extract.

E.6.2 Nd-YAG laser, an Nd-YAG laser mounted on a slit-lamp microscope, as used clinically for laser capsulotomy, is suitable.

E.6.3 High-pressure liquid chromatograph (HPLC).

E.6.4 Gas Chromatograph/ Mass spectroscope (GC/MS).

E.6.5 UV/Visible (UV/Vis) spectrophotometer.

E.6.6 Appropriate setup for cytotoxicity testing in accordance with ISO 10993-5.

E.7 Test procedure

E.7.1 Treatment

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.7.2 Post exposure evaluation

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

Analyse the exposure medium for migrated components. Perform qualitative and quantitative analyses for migrated substances, such as monomers, UV-absorbers, additives, and degradation products by HPLC, GC/MS, and/or UV/Vis spectrophotometry as appropriate. Carry out the corresponding qualitative and quantitative analyses on solvent blanks that have undergone the same treatment.

Test the exposure medium and the solvent blank for cytotoxicity, using an elution or a direct contact method, after Nd-YAG laser treatment in accordance with ISO 10993-5.

E.8 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 document, i.e. ISO 11979-5:2020;

c) the laser energy level used in the treatment;

d) the exposure 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 laser exposure and the dates of subsequent analyses.