INTERNATIONAL STANDARD

ISO 11979-5

Third edition
2020-09

Ophthalmic implants — Intraocular lenses —

Part 5: Biocompatibility

Implants ophtalmiques — Lentilles intraoculaires —

Partie 5: Biocompatibilité

Reference number
ISO 11979-5:2020(E)

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

Contents

Page

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.

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).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

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.

