DRAFT INTERNATIONAL STANDARD

ISO/DIS 11979-5

ISO/TC **172**/SC **7** Secretariat: **DIN**

Voting begins on: **2019-05-31**

Voting terminates on: **2019-08-23**

Ophthalmic implants — Intraocular lenses —

Part 5: Biocompatibility

Implants ophtalmiques — Lentilles intraoculaires —

Partie 5: Biocompatibilité

ICS: 11.040.70

This document is circulated as received from the committee secretariat.

ISO/CEN PARALLEL PROCESSING

Reference number
ISO/DIS 11979-5:2019(E)

COPYRIGHT PROTECTED DOCUMENT

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
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 on 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 the following URL: 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*.

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

— Clarification of requirements throughout the document

— Added requirement to use state of the art analytical methods

— Update of apparatus lists where applicable

— Clarification of test material and parent IOLs, added the requirement for a biological evaluation plan (Section 4)

— Combination and re-write of physicochemical test methods and objectives (Section 5.1)

— Added requirement for physical/chemical description and contaminants (Section 5.2)

— Adjustment of ratio for material and extraction medium in genotoxicity testing (Section 6.2)

— 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 resolution (Annex D)

— Clarification of Nd-YAG post exposure test (Annex E.6)

— 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 to 3 months (Annex G).

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

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 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 18369-4:2006, *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 http://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 (refer to 11979-1 and Table 1 for definition of test material and allowance of representative samples) shall start with an initial assessment of risk in accordance with ISO 14971. The tests described in Clause 5 shall first be performed to characterize the physicochemical properties of the intraocular lens. 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. Following the risk assessment, establish a biological evaluation plan in accordance with ISO 10993-1 addressing the residual risk and execute the biocompatibility testing.

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, ISO 10993-10, ISO 10993-17 and ISO/TS 21726 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.

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

Table 1A — 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 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 1B — Allowance of representative samples for biological tests

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

[a] Sample, manufactured and processed 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 custom design to fit the anatomical placement site of the animal.

5 Physicochemical tests

5.1 General

The physicochemical tests listed in Table 2 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. A risk-based approach should be used; the results of the tests in Table 2 should be used as input for a risk assessment and further testing when deemed necessary, in accordance with ISO 14971. The risk assessment should evaluate the potential local and systemic effects.

5.2 Physical/Chemical description

To facilitate the explaining of physical and chemical test results, the manufacturer shall provide a description of each of the components in the formulation. 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:

a) Structure Formula — Provide the chemical structure and molecular formula.

Table 2 — 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 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 material 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.

5.3 Exhaustive extraction test

The test material shall be tested for extractables under exhaustive extraction conditions in accordance with the method described in Annex A. Alternate 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.

All extractables shall be evaluated toxicologically according to ISO 10993-17 and ISO/TS 21726.

5.4 Test for leachables

The test material shall be tested for leachables under simulated physiological conditions in accordance with the method described 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 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 leachable components.

All leachables shall be evaluated toxicologically according to ISO 10993-17 and ISO/TS 21726.

5.5 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.

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 factor F:

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

where

T_a is the accelerated temperature;

T_0 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 diopter 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.

All degradation products shall be evaluated toxicologically according to ISO 10993-17 and ISO/TS 21726.

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.