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Ögonimplantat – Intraokulära linser –
Del 5: Biokompatibilitet (ISO 11979-5:2006)

Ophthalmic implants – Intraocular lenses –
Part 5: Biocompatibility (ISO 11979-5:2006)

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Ophthalmic implants - Intraocular lenses - Part 5: Biocompatibility (ISO 11979-5:2006)

Implants ophtalmiques - Lentilles intraoculaires - Partie 5: Biocompatibilité (ISO 11979-5:2006)

Ophthalmische Implantate - Intraokularlinsen - Teil 5: Biokompatibilität (ISO 11979-5:2006)

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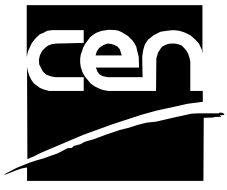

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Foreword

This document (EN ISO 11979-5:2006) has been prepared by Technical Committee ISO/TC 172 "Optics and optical instruments" in collaboration with Technical Committee CEN/TC 170 "Ophthalmic optics", the secretariat of which is held by DIN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by December 2006, and conflicting national standards shall be withdrawn at the latest by December 2006.

This document supersedes EN 13503-5:2001.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland and United Kingdom.

Endorsement notice

The text of ISO 11979-5:2006 has been approved by CEN as EN ISO 11979-5:2006 without any modifications.

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.