INTERNATIONAL STANDARD

ISO 11979-6

First edition
2002-06-01

Ophthalmic implants — Intraocular lenses —

Part 6: Shelf-life and transport stability

Implants ophtalmiques — Lentilles intraoculaires —

Partie 6: Durée de conservation et stabilité pendant le transport

Reference number
ISO 11979-6:2002(E)

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Printed in Switzerland

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 3.

Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this part of ISO 11979 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 11979-6 was prepared by Technical Committee ISO/TC 172, *Optics and optical instruments*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

ISO 11979 consists of the following parts, under the general title *Ophthalmic implants — Intraocular lenses*:

- *Part 1: Vocabulary*
- *Part 2: Optical properties and test methods*
- *Part 3: Mechanical properties and test methods*
- *Part 4: Labelling and information*
- *Part 5: Biocompatibility*
- *Part 6: Shelf-life and transport stability*
- *Part 7: Clinical investigations*
- *Part 8: Fundamental requirements*

Annex A forms a normative part of this part of ISO 11979. Annexes B, C and D are for information only.

Introduction

The purpose of a stability study is to ascertain that the properties of the intraocular lens (IOL) remain within specified limits for a sufficiently long period of time under the influence of a variety of environmental conditions.

The storage stability of the intraocular lens material is an important factor in the overall investigation of a new lens material, a new combination of given lens materials, a new packaging material or a new manufacturing process. To assess this, a study of the ageing of the lenses in their containers is performed.

Changes in the composition and material, material suppliers, manufacturing conditions (including the sterilization process), or the package design or material may affect the shelf-life and may therefore necessitate renewed investigations.

The design of the stability tests should be based on the known properties of the material from which the intraocular lens is made and the recommendations for use of the intraocular lens. Knowledge of the quantity and identity of extractable substances found after storage or accelerated ageing studies is of importance in evaluating new intraocular lens materials.

On the basis of the information obtained, transport and storage conditions can be recommended that will maintain the quality of the intraocular lens in relation to its safety, efficacy and acceptability throughout the proposed shelf-life, i.e. during storage and distribution up until the moment of dispensing. The results obtained are also used to determine the expiration date.

In practical terms, it is the stability of the material from which the intraocular lens is made that is being tested, along with the integrity of the packaging that maintains the necessary environment of the intraocular lens. Stability studies for intraocular lenses are thus material specific, i.e. this type of study does not need to be performed for more than one intraocular lens model for a given combination of IOL material(s), packaging materials and manufacturing processes.

Stability studies of intraocular lenses will allow the determination of the shelf-life and package suitability, as well as recommendations for transport and storage conditions.

NOTE It always was and still is the intention of the Technical Committees ISO/TC 172/SC 7 and CEN/TC 170 to prepare identical ISO and CEN (European Committee for Standardization) Standards on intraocular lenses. However, during the preparation of Part 7 of this series, problems were encountered with normative references to the existing ISO 14155 and EN 540 horizontal standards on clinical investigation of medical devices, which are similar but not identical.

ISO and CEN principles concerning normative references made it impossible to continue the preparation of identical International and European Standards on the clinical investigation of intraocular lenses. As a result, two different standards series have had to be prepared. It is the intention of ISO/TC 172/SC 7 and CEN/TC 170 to revise these standards with the goal to ultimately have identical ones as soon as identical ISO and CEN horizontal standards on clinical investigations become available.

Ophthalmic implants — Intraocular lenses —

Part 6:
Shelf-life and transport stability

1 Scope

This part of ISO 11979 specifies tests by which the shelf-life of sterile intraocular lenses (IOLs) in their final packaging can be determined. These tests include procedures to establish the stability of IOLs in distribution and storage.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 11979. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 11979 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 2248:1985, *Packaging — Complete, filled transport packages — Vertical impact test by dropping*

ISO 8318:2000, *Packaging — Complete, filled transport packages and unit loads — Sinusoidal vibration tests using a variable frequency*

ISO 11607:1997, *Packaging for terminally sterilized medical devices*

ISO 11979-1:1999, *Ophthalmic implants — Intraocular lenses — Part 1: Vocabulary*

ISO 11979-3:1999, *Ophthalmic implants — Intraocular lenses — Part 3: Mechanical properties and test methods*

3 Terms and definitions

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

3.1
device history record
compilation of records containing the production history

3.2
finished intraocular lens lot
all units of an intraocular lens which have undergone a single series of manufacturing operations including the sterilization operation and which are identified on a single device history record

NOTE Some definitions of ISO 11979-1, relevant to this part of ISO 11979, are reproduced in annex D.

4 Requirements

4.1 General

A study protocol shall be developed prior to initiation of the study.

The study shall demonstrate that the parameters assessed with regard to efficacy, safety and product acceptability are within the original manufacturing specifications at the conclusion of the study.

NOTE In view of the fact that sufficiently long experience of storage of a new intraocular lens may not have been accumulated by the time it is brought to the market, the results of accelerated tests are acceptable. A test in real-time should be carried out under certain conditions (see 4.3.2) to confirm the accelerated shelf-life study.

A maximum of five years of shelf-life should be claimed by a real-time study or an accelerated study regardless of material used in the intraocular lens. In the case where a manufacturer wishes to maintain the possibility to resterilize finished intraocular lens lots, the finished intraocular lens lot(s) used in the stability study shall have undergone the maximum number of sterilization cycles allowed under the manufacturer's procedures.

4.2 Materials and methods

4.2.1 Test samples

The manufacturing lot(s) used for the stability study shall be representative for normally produced manufacturing lots, and be packaged in the manner intended for marketing.

NOTE 1 The number of finished intraocular lens lots and the dioptre range of the test samples depend on whether the intraocular lenses under study are made of new or known materials (see annex A).

The number of intraocular lens lots to be studied shall be in accordance with the provisions of annex A.

NOTE 2 In certain cases, more than one of the tests listed in annex A may be performed on a single IOL (e.g. dioptric power, imaging quality and spectral transmission may all be measured on the same IOL), thereby reducing the total number of intraocular lenses required.

4.2.2 Analytical methods

Suitable analytical methods shall be chosen for the tests indicated in annex A and for any additional tests contained in the study protocol. The methods selected shall be recorded. If a method is selected that is not included among those listed in annex C, the method and the details of its validation, demonstrating the capability of the method, shall also be documented.

4.3 Product stability studies

4.3.1 Real-time shelf-life and package integrity study

Annex A lists tests that shall be performed depending on intraocular lens type.

For new intraocular lens types, additional parameters shall be considered for testing, depending upon the nature of the intraocular lens. In the case where a specific test listed in annex A has not been carried out, the reasons for that shall be stated.

Testing for changes due to interaction with the packaging material shall be considered, as shall testing for changes in the concentration of additives and coatings in addition to those listed in annex A.

For one of the finished intraocular lens lots, the tests chosen shall be carried out initially and at intervals in accordance with the protocol up to and including the manufacturer's desired expiration date (maximum five years). The other finished intraocular lens lots shall be tested, at least initially and at the desired expiration date.

The following is the procedure for real-time stability studies. Intraocular lenses to be tested shall, if applicable, at each instance be evenly distributed among the different power groups (see annex A).

— Assign a unique identification to each individual intraocular lens in the total sample and put that identification on the intraocular lens packaging.

— Collect the intraocular lenses to be tested initially and carry out the tests of the protocol. Record the unique identifications, the results and measurement conditions.

— Transfer the remaining packages to storage under controlled conditions (25 °C ± 3 °C at 60 % ± 20 % relative humidity). Record actual temperature, relative humidity and date.

— Monitor temperature and relative humidity regularly during the course of the study in a manner that fluctuations in temperature and relative humidity are also recorded.

— In accordance with the protocol, periodically remove a sufficient number of intraocular lenses for testing. Allow the intraocular lenses to equilibrate, within the original packaging, to the initial measurement conditions. Then carry out the tests of the protocol. Record the unique identifications, the results and measurement conditions.

— Collect the intraocular lenses to be tested at the expiration date. Allow the intraocular lenses to equilibrate, within the original packaging, to the initial measurement conditions. Then carry out the tests of the protocol. Record the unique identifications, the results and measurement conditions.

The parameters measured shall remain within the specified limits of the applicable parts of ISO 11979. In the case where there are no limits specified in ISO 11979, the parameters measured shall remain within the manufacturer's internal finished product release specifications. If, during the course of the study, a parameter is no longer found to conform to the specifications at two or more consecutive time intervals, the maximum shelf-life of the intraocular lens under study has been reached at the last conforming measurement point.

4.3.2 Accelerated shelf-life study

Studies under accelerated conditions are likely to speed up any degradation processes, and may therefore permit extrapolation of intervals under accelerated conditions to intervals at normal storage conditions. Accelerated testing shall be accepted under the following conditions.

a) Accelerated conditions have been validated for the test materials.

b) For microbial barrier testing, the accelerated conditions should involve storage at a specified temperature and with a relative humidity of at least 40 %. If a manufacturer wishes to perform sterility testing in lieu of microbial barrier testing, the storage temperature should be no higher than 45 °C.

The real-time shelf-life is calculated by multiplying the studied time period with the factor of $1{,}8^{(T_a - T_0)/10}$, where T_a is the accelerated temperature and T_0 is the typical storage temperature (usually room temperature).

NOTE There are no published data to support the requirements for the accelerated conditions above. They have been established by the US FDA, based on experience with accelerated studies.

Accelerated studies shall be carried out in the same way as real-time studies with the exception of the conditions chosen. It is important that intraocular lenses to be measured are allowed to equilibrate to the same conditions as at the initial measurements before being tested.

4.4 Transport stability

In view of the temperature fluctuations that can occur during transport, the manufacturer shall consider the maximum and minimum temperatures which the IOL is designed to withstand. The manufacturer shall obtain data and records that demonstrate that the IOL remains within its specifications after having been exposed to the maximum temperature for 24 h and, similarly, after having been exposed to the minimum temperature for 24 h. Alternatively, the manufacturer may study the intraocular lenses at the temperatures and durations given in ASTM D 4169-94.

The tests to be performed in these transport studies are listed in annex A.

The complete, filled intraocular lens transport containers shall also be able to withstand drops and vibration in accordance with the methods described in ISO 2248 and ISO 8318. Both the package and the product shall be inspected following these tests and the packaged product shall be considered to have satisfactorily passed the test if, upon examination, the product is free from damage and the container still affords functional protection to the content.

4.5 Results

A report comprising the following information shall be available:

a) summary of the results;

b) copy of the labelling of the intraocular lens;

c) manufacturing lot numbers, lot sizes, dates of manufacture and name of the manufacturer of the intraocular lens;

d) details of the packaging, including the materials used and descriptions of the container and the closure;

e) description of conceivable changes of the product, the materials used and the product's mechanical and optical properties;

f) interpretation of the results in terms of shelf-life, storage and shipping recommendations;

g) name of the test laboratory, dates of testing and an approval signature.

For each finished intraocular lens lot, the initial results, as well as the results during storage and at the end of the proposed shelf-life, should be presented in tabular form for easy interpretation.

5 Test methods and sampling

The appropriate tests specified in the normative references listed in clause 2 shall be applied.

Unless the method description specifies the sample size, a minimum of 10 intraocular lenses shall be used for each test at every testing occasion.

Annex A
(normative)

Shelf-life and transport stability test table

Table A.1 — Surface and bulk homogeneity

IOL material		No. of finished IOL lots[a]	IOL dioptric power range	Tests per study type (minimum 10 IOLs per lot)		
Body (optic)	Loop (haptic)			Product stability	Package integrity[b]	Transport stability[c]
Polymethyl-methacrylate (PMMA)	Polymethyl-methacrylate (PMMA)	1	Medium	• Dimensions • Surface and bulk homogeneity	• Labelling • Seal/closure integrity • Microbial barrier[d] or Whole package physical integrity	• Labelling • Surface and bulk homogeneity • Drop and vibration test • Seal/closure integrity • Microbial barrier[d] or Whole package physical integrity
Polymethyl-methacrylate (PMMA)	Polypropylene, polyimide or polyvinylidene-fluoride (PVDF)	1	Medium	• Dimensions • Surface and bulk homogeneity • Extractables[e] • Cytotoxicity[f]	• Labelling • Seal/closure integrity • Microbial barrier[d] or Whole package physical integrity	• Dimensions • Surface and bulk homogeneity • Drop and vibration test • Seal/closure integrity • Microbial barrier[d] or Whole package physical integrity
Cross-linked polydimethyl-siloxane (silicone)	Cross-linked polydimethyl-siloxane (silicone)	2	Low Medium High	• Dimensions • Haptic pull test • Retention of properties (for foldable IOLs[g])	None	None
	polypropylene polyimide polymethyl-methacrylate (PMMA), or polyvinylidene-fluoride (PVDF)		Medium (in addition)	• Surface and bulk homogeneity • Dioptric power • Imaging quality • Spectral transmission • Extractables[e] • Cytotoxicity[f]	• Labelling • Seal/closure integrity • Microbial barrier[d] or Whole package physical integrity	• Labelling • Surface and bulk homogeneity • Drop and vibration test • Seal/closure integrity • Microbial barrier[d] or Whole package physical integrity