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Ophthalmic implants — Intraocular lenses —

Part 6: Shelf-life and transport stability testing

Implants ophtalmiques — Lentilles intraoculaires —

Partie 6: Durée de conservation et stabilité pendant le transport

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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).

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For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

This third edition cancels and replaces the second edition (ISO 11979-6:2007), which has been technically revised.

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 testing*

— *Part 7: Clinical investigations*

— *Part 8: Fundamental requirements*

— *Part 9: Multifocal intraocular lenses*

— *Part 10: Phakic intraocular lenses*

Introduction

The purpose of a stability study is to ascertain that the properties of a product, in this case an 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 could affect the shelf-life and could therefore necessitate renewed investigations. The need for studies of product stability, package integrity, and transport stability can be assessed using ISO 14971.

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 are 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 need not be performed for more than one intraocular lens model for a given combination of IOL material(s), packaging materials, and manufacturing processes.

Ophthalmic implants — Intraocular lenses —

Part 6:
Shelf-life and transport stability testing

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 documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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

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

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

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 11607-2, *Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes*

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 Requirements

4.1 General

If, following a risk analysis in accordance with ISO 14971, it is found that a product stability study, a package integrity study, and/or a transport stability study are needed, this part of ISO 11979 shall apply to the planning and conduct of these studies.

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

The study results shall demonstrate that the parameters measured with regard to performance, safety, and product acceptability are within the finished product specifications, when available. In cases where there are no finished product specifications, then the parameters measured shall remain within the limits of the applicable parts of ISO 11979. If there exists neither finished product specifications nor applicable limits specified within ISO 11979, then a comparison to time zero product shall be performed.

In view of the fact that an intraocular lens may not have sufficient storage assessments accumulated by the time it is brought to the market, the results of accelerated tests (see 4.3.2) are acceptable for initial labelling purposes, i.e. to establish a shelf-life to be indicated on the product labelling. A maximum of five years of shelf-life can be claimed by a real-time study or an accelerated study regardless of material used in the intraocular lens. However, an accelerated study shall always be verified by a real-time study, and the real-time study results shall always take precedence over the accelerated study results. The same product or a Level A modification of it (see ISO/TR 22979) shall be used in the real-time study, and the real-time study shall be started before the release of the new intraocular lens into the market.

In case a manufacturer wishes to maintain the possibility of resterilizing 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 studies shall be performed using IOLs from finished intraocular lens lots. The proposed sample sizes are described in Annex A.

4.2.2 Methods

Suitable methods shall be chosen for any tests contained in the study protocol. The methods selected shall be recorded. Annex B contains suggested tests. Due to the variation in product and package materials and design, other tests could be more appropriate. The methods selected, other than those specified in Annex B, shall be recorded and the details of validation for each test method, demonstrating the capability of the method, shall also be documented.

In certain cases, more than one of the tests listed in Annex B can be performed on a single IOL, thereby reducing the total number of IOLs required.

4.3 Product stability

4.3.1 General

If the risk analysis in accordance with ISO 14971 shows a need for a shelf-life study, the following shall apply. The rationale for choice of tests shall be documented in the risk management plan.

For both real-time and accelerated testing, finished IOLs (or finished injector systems with IOLs) shall be used. For test parameters that can be affected by optical power, at least three groups, comprising lenses from one or more finished intraocular lens lots, shall be tested, one each from low, medium, and high dioptric power ranges, each group comprising one or more dioptric powers. For test parameters not affected by optical power, at least one group of lenses shall be used. See Annex A for guidance.

4.3.2 Real-time shelf-life study

4.3.2.1 Test parameters

The following parameters shall be considered:

a) dimensions;

b) dioptric power;

c) imaging quality;

d) surgical manipulation;

e) recovery of properties following simulated surgical manipulation (for IOLs intended to be folded or otherwise deformed as part of the surgical procedure);

f) surface and bulk homogeneity;

g) compression force (samples from one or more dioptric power lots);

h) dynamic fatigue (samples from one or more dioptric power lots);

i) spectral transmission;

j) exhaustive extraction (samples from one or more dioptric power lots);

k) cytotoxicity (if an increase is seen in the content of extractables and/or if a new substance is present); it is sufficient to perform cytotoxicity testing on IOL samples from one dioptric power group. For this testing, an extraction of the IOL using culture medium with serum needs to be performed in accordance with ISO 10993-5. The ratio of surface area to volume of extraction medium is specified in ISO 10993-12 and the extraction conditions are defined in ISO 10993-5;

l) specific surface tests (if warranted).

References to suggested test methods are found in Annex B.

Testing for changes due to interaction with the packaging material shall also be considered, as shall testing for changes in surface treatments as well as the concentration of additives in the IOL or additives in a solution in which the IOL is stored.

An example of a calculation of the number of IOLs to be used in a shelf-life and transport stability study for an IOL made from a new material can be found in Annex A.

4.3.2.2 Combination lens-injector systems

In cases of preloaded or combined IOL delivery systems, the following additional parameters shall be considered for inclusion:

a) stability of injector system materials;

b) chemical interactions between delivery system and IOL;

c) mechanical interactions between delivery system and IOL;

d) cytotoxicity testing of any potential degraded materials;

e) lens delivery system performance.

Additional samples beyond those listed in Table A.1 might need to be required for shelf-life testing based on the results of the considerations.

4.3.2.3 Study procedure

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

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

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

c) Transfer the remaining packages to storage under controlled conditions at the maximum recommended storage condition. Record actual temperature, relative humidity, and date.

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

e) In accordance with the protocol, periodically remove a sufficient number of intraocular lenses for testing. Carry out the tests of the protocol. Record the unique identifications, the results, and the measurement conditions.

f) Collect the intraocular lenses to be tested at the expiration date. Carry out the tests of the protocol. Record the unique identifications, the results, and the measurement conditions.

The parameters measured shall remain within the limits of the finished product specifications. In cases where there are no finished product specifications, then the parameters measured shall remain within the limits of the applicable parts of ISO 11979. If there exists neither finished product specifications nor applicable limits specified in ISO 11979, then a comparison to time zero product shall be performed. If a measured parameter is found to no longer conform, and this finding is confirmed by an investigation, then the maximum shelf-life is determined by the time point of the last conforming measurement.

4.3.3 Accelerated shelf-life study

Studies under accelerated conditions are likely to speed up any degradation processes, and can therefore permit extrapolation of intervals under accelerated conditions to intervals at normal storage conditions. The same parameters as for real-time studies [4.3.2.1 a) to l)] shall be considered for inclusion when an accelerated shelf-life study is planned. References to suggested test methods can be found in Annex B. The same study procedures (except temperature and humidity conditions) used for real-time studies [4.3.2.3 a) to f)] are also valid.

Storage humidity shall be at least 40 %.

The equivalent real-time shelf-life is calculated by multiplying the studied time period by a factor of $2^{(T_a - T_0)/10}$, where T_a is the accelerated temperature and T_0 is the recommended maximum allowed storage temperature for the intraocular lens investigated.

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 Package integrity

If the risk analysis in accordance with ISO 14971 shows that a package integrity study needs to be performed, the following shall apply. The rationale for choice of tests shall be documented in the risk management plan.

For information regarding forming, sealing, and/or assembly processes for the IOL sterile barrier system, follow ISO 11607-2.

For information regarding the stability testing of packaging systems (sterile barrier systems and protective packages), follow ISO 11607-1.

Packaging from three sterilization runs shall be used for the package integrity study. As the mass of an IOL is typically only about 20 mg, the interaction of the lens material upon the sterile barrier system can be evaluated as negligible. Therefore, sterile barrier systems without containing IOLs can be used for the evaluation of the package properties.

Package integrity studies can also be performed as accelerated studies, using the same conditions and interpretations as shown under 4.3.3, with the proviso that a real-time study is started prior to putting the product on the market.

For a package integrity study, a minimum of the following tests shall be performed:

a) legibility of labelling;

b) seal/closure integrity;

c) whole package physical integrity.

References to suggested test methods are found in Annex B.

4.5 Transport stability

If the risk analysis in accordance with ISO 14971 shows a need for a transport stability study, the following shall be considered. The rationale for choice of tests shall be documented in the risk management plan.

The complete, filled intraocular lens packages (in their normal transport package) shall be able to withstand extremes of the temperature and humidity (as expected in shipping), vibration, and being dropped. Both the packaging and the product shall be inspected following completion of the pretest conditioning. The IOL shall be considered to have satisfactorily passed the test if the IOL is free from physical damage when visually inspected under magnification. The packaging shall also continue to provide functional protection to the IOL.

A minimum of the following tests shall be performed:

a) legibility of labelling;

b) physical damage assessment by visual inspection for surface and bulk homogeneity of the IOLs (sealed packages shall be used) including, where applicable, an evaluation of haptic-optic junctions, geometry, and loop pull strength;

c) seal/closure integrity;

d) whole package physical integrity;

e) in cases of preloaded systems, a test of delivery function and conformity of injected IOLs.

For a), c), and d) above, the complete package including any storage solution, but without the IOL, may be used.

References to suggested test methods can be found in Annex B.

For transport stability studies where complete packages with IOLs are needed, it is adequate to use only one intraocular lens lot of the medium dioptric power for all tests.

4.6 Results

A report comprising the following information shall be kept on file:

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 the descriptions of the container and the closure;

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

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

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

5 Test methods and sampling

Suggested test methods are referenced in Annex B.

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
(informative)

Shelf-life study example

A.1 Assumptions

A manufacturer has a foldable IOL made from a new material (without any surface modification) that will undergo shelf-life testing. The IOL is packaged in a new container. The manufacturer wants to ultimately validate a five-year shelf-life but intends to enter the market with a one-year shelf-life and then increase that expiration dating by one year at a time as the data supporting the shelf-life dating becomes available.

The manufacturer intends to perform an accelerated shelf-life study and therefore includes three groups to be tested under accelerated conditions and three groups that are stored under real-time conditions to validate the acceleration conditions for the test material.

A.2 Sample requirements

A.2.1 General

There are five evaluation time points for the test samples (one, two, three, four, and five years).

The power range of the manufacturer's IOL is 6 D to 30 D. The manufacturer makes the following designations:

— low dioptric power: e.g. 8 D;

— medium dioptric power: e.g. 18 D;

— high dioptric power: e.g. 27 D.

See 4.3.1 as well as Tables A.1 and A.2 for additional guidance.

The three groups are evaluated at each of the time points for both real-time and accelerated package integrity testing.

One group of IOLs is evaluated once for transport stability testing (of medium dioptric power). Some of the units for transport stability testing can be complete packages without IOLs.

A single sample of an IOL can be used in more than one test in the evaluation of product stability.

A.2.2 Product stability and package integrity testing (for each time point)

A.2.2.1 Product stability

a) 30 packages, with IOL: 10 each of low, medium, and high dioptric power, for imaging quality, spectral transmittance, dimensions, surface and bulk homogeneity, and surgical manipulation tests

b) 10 packages, with medium dioptric power IOL, for compression force

c) 10 packages, with medium dioptric power IOL, for dynamic fatigue

d) 30 packages, with IOL: 10 each of low, medium, and high dioptric power, for recovery of properties following simulated surgical manipulation

e) 10 packages, with medium dioptric power IOL, for exhaustive extraction testing (if more than one extraction medium is used, additional samples will be required, and all media containing extractables should be used for further testing)

f) 30 packages, with medium dioptric power IOL, for cytotoxicity tests (if, as in this example, an increase in the content of extractables was seen together with a new substance in the extract)

A.2.2.2 Package integrity

a) 30 packages (10 per sterilization run), with or without IOL, for whole package physical integrity tests

b) 30 packages (10 per sterilization run), with or without IOL, for legibility of labelling and seal integrity tests

The number of packages might need to be adjusted depending on the test design.

A.2.3 Transport stability (tested only once)

Based on how the IOLs are expected to be transported, the manufacturer determines the worst case environmental conditioning and handling necessary.

A total of 60 samples (20 packages with IOL and 40 with or without IOL) need to be conditioned and evaluated at one time point:

a) 20 packages, with any dioptric power IOL, for assessment of physical damage [refer to 4.5 b)];

b) 30 packages, with or without IOL, for whole package physical integrity tests;

c) 10 packages, with or without IOL, for legibility of labelling and seal/closure integrity tests.

The number of packages might need to be adjusted depending on the test design.

A.3 Total sample size

In this example, the manufacturer has chosen to perform the cytotoxicity test. As can be seen from Table A.1, the accelerated test programme then requires 600 packages with IOLs and 300 packages with or without IOLs. Another 600 packages with IOLs and 300 packages with or without IOLs will be required for the subsequent real-time test programme. The transport stability testing (see Table A.2) requires 20 packages with IOLs and 40 packages with or without IOLs. Therefore, a total of 1 220 packages with IOLs and 640 packages with or without IOLs are needed for all the necessary studies.

A.4 Results

In this example, the manufacturer performs the study under accelerated conditions, and when testing at the one-year time period, no failures are observed. The IOL is then labelled for a one-year shelf-life. At the simulated two-year time point, there are also no failures and the shelf-life is extended to two years. At the simulated three-year time point, a seal integrity failure of the test samples is observed and confirmed by an investigation. Therefore, the final shelf-life is two years.

The manufacturer uses the results of the real-time testing to confirm the study results of the accelerated study. If the real-time study is continued beyond two years and there are no failures in coming years, the shelf-life can be extended based on the real-time results.

Table A.1 — Real-time or accelerated shelf-life study of IOL and packaging
(number of IOLs and packages needed)

Study	Test	Example text ref.	Number of samples per testing occasion[a]														
			Low dioptric power					Medium dioptric power					High dioptric power				
			1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Product stability	Dioptric power	A.2.2.1 a)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Imaging quality																
	Spectral transmittance																
	Dimensions																
	Surface/bulk homogeneity																
	Surgical manipulation																
	Compression force	A.2.2.1 b)	—	—	—	—	—	10	10	10	10	10	—	—	—	—	—
	Dynamic fatigue	A.2.2.1 c)	—	—	—	—	—	10	10	10	10	10	—	—	—	—	—
	Recovery of properties	A.2.2.1 d)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Exhaustive extraction[c]	A.2.2.1 e)	—	—	—	—	—	10	10	10	10	10	—	—	—	—	—
	Cytotoxicity	A.2.2.1 f)	—	—	—	—	—	30	30	30	30	30	—	—	—	—	—
Total packages with IOL per study: 600			**20**	**20**	**20**	**20**	**20**	**80**	**80**	**80**	**80**	**80**	**20**	**20**	**20**	**20**	**20**
Package integrity[b]	Whole package physical integrity	A.2.2.2 a)	—	—	—	—	—	30*	30*	30*	30*	30*	—	—	—	—	—
	Label legibility	A.2.2.2 b)															
	Seal/closure integrity		—	—	—	—	—	30*	30*	30*	30*	30*	—	—	—	—	—
Total packages with or without IOL: 300			—	—	—	—	—	**60***	**60***	**60***	**60***	**60***	—	—	—	—	—

a Numbers with asterisks indicate packages that can be with or without IOL.

b The 30 samples represent 10 samples each from three sterilization lots.

c The number of samples will need to be doubled if two extraction media are used.

Table A.2 — Transport stability testing of IOL and packaging
(number of IOLs and packages needed)

Pretest conditioning	Tests on IOLs	Tests on packaging (with or without IOLs)
Selected temperatures and humidity(ies) Vibration test Drop test	Physical damage assessment [see 4.5 b)] 20 samples needed [see A.2.3 a)]	Whole package physical integrity 30 samples needed [see A.2.3 b)]
		Label legibility Seal/closure integrity 10 samples needed [see A.2.3 c)]
NOTE 1 Total packages with IOL: 20 samples. NOTE 2 Total packages with or without IOL: 40 samples.		

Annex B
(informative)

Tests for shelf-life studies

Table B.1 — Tests that can be considered for shelf-life studies

Type of test	Standard	Test
Optical properties	ISO 11979-2	Dioptric power
		Imaging quality
		Spectral transmittance
Mechanical properties	ISO 11979-3	Dimensions
		Compression force
		Dynamic fatigue durability
		Surgical manipulation
		Surface and bulk homogeneity
		Recovery of properties following simulated surgical manipulation (foldable IOLs)
Biocompatibility	ISO 11979-5	Exhaustive extraction test
	ISO 10993-5	Tests for *in vitro* cytotoxicity
	ISO 10993-12	Sample preparation and reference materials
Surface properties	None: test method and specification to be developed and validated by manufacturer	Specific surface characteristics tests (surface modified intraocular lenses)
Package integrity	ISO 11607-1	Whole package physical integrity
	ISO 11979-4	Label legibility
	ASTM F1929-12	Seal/closure integrity
Transport properties	ISO 2233	Conditioning for testing
	ISO 2248	Drop test
	ISO 8318	Vibration test

Bibliography

[1] ISO 2233:2000, *Packaging — Complete, filled transport packages and unit loads — Conditioning for testing*

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

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

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

[5] ASTM F1929-12, *Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration*

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