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Ophthalmic implants — Intraocular lenses —

Part 7: Clinical investigations

Implants ophtalmiques — Lentilles intraoculaires —
Partie 7: Investigations cliniques

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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 11979-7 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

This part of ISO 11979 provides fundamental requirements of a general nature for intraocular lenses. It refers to other standards applicable to intraocular lenses for specific methods and requirements.

It always was and still is the intention of 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 this part of ISO 11979, 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 end up with identical ones as soon as identical ISO and CEN horizontal standards become available.

Ophthalmic implants — Intraocular lenses —

Part 7:
Clinical investigations

1 Scope

This part of ISO 11979 specifies particular requirements for clinical investigation protocols for posterior and anterior chamber monofocal intraocular lenses (IOLs) for the correction of aphakia.

NOTE Any other type of IOL not directly covered by ISO 11979 and any IOL for which the sponsor wishes to investigate claims in addition to those defined in ISO 11979 may be clinically evaluated by reference to ISO 14155.

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 14155: 1996, *Clinical investigation of 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 14155 and ISO 11979-1 apply, together with the following.

For the convenience of users of this part of ISO 11979, some definitions from ISO 11979-1 are reproduced in annex A. Terms relating to the design of IOLs are given in ISO 11979-3.

3.1
serious adverse event
event which is potentially sight threatening

NOTE 1 The definition for serious adverse event given in the ICH *Harmonized tripartite guideline for good clinical practice* also applies (see reference [1] in the bibliography).

NOTE 2 Examples of potentially sight-threatening adverse events are included in Tables D.1 and D.2.

4 Ethical considerations

For clinical investigations of medical devices for human subjects, the requirements of ISO 14155 apply.

5 Requirements

5.1 General requirements

The requirements given in 5.1 to 5.7 of ISO 14155:1996 shall apply.

5.2 Additional requirements

5.2.1 In addition to the requirements given in 5.5 of ISO 14155:1996, the sponsor and the sponsor's investigators shall evaluate the rates of adverse events and visual acuity (VA) for the IOLs under clinical investigation on a continuing basis.

NOTE The published national study of cataract surgery in the United Kingdom may provide useful guidance on clinical performance of IOLs at periods corresponding with the early post-operative case report forms (see references [2] and [3]).

5.2.2 In addition to the requirements given in 5.6 of ISO 14155:1996, the safety and effectiveness of an IOL model shall be established through either:

— a clinical investigation conducted in accordance with this part of ISO 11979, or

— a comparison of the model characteristics that establish the model as a minor modification of a parent model for which the safety and effectiveness have been established through clinical investigation in accordance with this part of ISO 11979.

NOTE Annex B provides guidance in determining if a modification is minor by providing examples of modifications that have historically been considered minor.

For the IOL intended for correction of aphakia in a general adult population, a clinical investigation shall either be developed using the protocol elements provided in annex C or a sponsor shall develop an equivalent protocol that shall have a similar statistical power to detect differences in adverse event and visual acuity rates between the test population and a concurrent control population. Subjects implanted with a parent IOL that has met the requirements of all parts of ISO 11979 may be used as a control population.

In the case of IOLs designed for either chamber, a separate clinical investigation shall be performed to assess the clinical performance of the IOL in each chamber.

5.2.3 In addition to the requirements given in 5.7 of ISO 14155:1996, all subjects in a clinical investigation shall be monitored for the duration of the investigation. The clinical investigation shall be considered completed when all subjects that have been enrolled in the investigation, including those whose IOL was removed or replaced, have reached the final reporting period.

6 Methodology

6.1 Documentation

The requirements given in 6.1 of ISO 14155:1996 shall apply.

6.2 Access to information

The requirements given in 6.2 of ISO 14155:1996 shall apply.

6.3 Additional health care

The requirements given in 6.3 of ISO 14155:1996 shall apply.

6.4 Clinical investigation plan

6.4.1 General requirements

The requirements given in 6.4 of ISO 14155:1996 shall apply.

6.4.2 Additional requirements

The following additional requirements shall apply.

The investigational lens shall only be implanted in a single eye of each subject.

At least the minimum sample size required by the study shall be included in the clinical investigation for each reporting period. The sponsor shall ensure a sufficient number of subjects in the clinical investigation so that the minimum number required by the investigation at each reporting period is reached.

NOTE Examples of pre-operative, operative and post-operative case report forms are included in annex C.

6.5 Role of sponsor

The requirements given in 6.5 of ISO 14155:1996 shall apply.

6.6 Role of monitor

The requirements given in 6.6 of ISO 14155:1996 shall apply.

6.7 Role of clinical investigator

6.7.1 General requirements

The requirements given in 6.7 of ISO 14155:1996 shall apply.

6.7.2 Additional requirements

The following additional requirements shall apply.

Clinical investigators shall file adverse event reports of serious adverse events with the sponsor immediately after learning of their occurrence. Other adverse events shall be reported on the case report forms.

7 Presentation of results

The results shall be presented as specified in clause 7 of ISO 14155:1996.

Annex A
(normative)

Selected definitions

To facilitate the understanding of this part of ISO 11979, selected definitions are reproduced in this annex. In the case of discrepancy, the definitions of ISO 11979-1 take precedence over those given here.

A.1
best-case subject
subject with no pre-operative pathology

A.2
cumulative adverse events
total number of adverse events which have occurred at any time up to a specified point in time post-operatively

A.3
intraocular lens model
identification by which the features of an intraocular lens, including those of its body and its loops, and the material(s) used in its construction, have been fully specified

NOTE 1 Examples of body features are body diameter, optic diameter, optic shape factor; examples of loop features are configuration, calibre, angulation.

NOTE 2 Any significant change in the specification of the materials (including their formulation or synthesis procedures) results in it being considered a new model.

A.4
level A modification of a parent intraocular lens model
modifications of a parent model which are considered minor and are not expected to result in any safety hazards or loss in effectiveness when compared to the parent model

A.5
level B modification of a parent intraocular lens model
modifications of a parent model which are greater than level A modifications

NOTE Level B modifications may present a safety hazard or loss of effectiveness concerns which result in a new model that is significantly different from the parent model.

A.6
lost to follow-up
describing a subject for whom the final post-operative case report form is overdue and who cannot be contacted despite extensive written and telephone follow-ups to determine the final clinical outcome

NOTE This category does not include subjects who have died.

A.7
optic shape factor
term describing the curvatures of the refracting surfaces of the optic (e.g. plano-convex, bi-convex)

A.8
parent intraocular lens model
intraocular lens model that a sponsor has qualified based on a clinical investigation of at least 100 subjects and which has met the requirements of all parts of ISO 11979

A.9
persistent adverse event
adverse event which is present at the conclusion of a clinical investigation

Annex B
(informative)

Examples of modifications of a parent IOL model

B.1 Design/material modifications of an IOL model

B.1.1 General

Modifications to an IOL that has previously undergone a clinical investigation by the sponsor have different requirements depending on the magnitude of the modifications. Two levels of modifications have historically been associated with a parent IOL: Level A and Level B. Examples of Level A and Level B modifications are given in B.2.

B.1.2 Level A

Level A modifications of a parent model in almost all cases do not require a clinical investigation. A case where a clinical investigation of a Level A modification of a parent model should be performed is if the modified model poses additional clinical questions which cannot be adequately addressed by preclinical testing, such as potential tissue damage associated with a modification in implantation technique necessitated by the modified design.

A Level A modification of a parent IOL usually does not itself become a parent IOL for subsequent modifications. The only case where it may is described below.

If a model is still under clinical investigation, Level A modified versions of that model may be introduced into the clinical investigation of the model and the data from the original investigational model and the Level A modified model(s) may be combined, except in the case of those Level A changes that involve material substitutions from parent models (i.e. modifications described in B.2.2.12).

A Level A modified IOL which was added to the clinical investigation of the investigational model may only itself be considered a parent IOL at the conclusion of the study if that Level A modified model was investigated in a minimum of 100 subjects at each case report form, if it met the requirements of all parts of ISO 11979 and if the results of a clinical analysis indicate that there is no significant difference between its clinical performance and the clinical performance of the other investigational models in the clinical investigation.

B.1.3 Level B

The clinical investigation of new IOLs that are Level B modifications of a parent model should include a minimum of 100 subjects monitored up to case report form 4 (case report forms are given in annex C).

The minimum number of case report forms for each visit should be 100. The sponsor should anticipate needing to enrol 125 subjects to take into account the subjects that are lost or die in the course of the clinical investigation.

The sample size required for the Level B clinical investigation is the minimum number necessary to detect a clinically significant difference in adverse event and visually acuity rates between the IOL under investigation and the rates associated with the historical control population. If the sponsor chooses to compare the performance of their IOL to a concurrently run control population, the sponsor should enrol sufficient subjects such that the ability of the study to detect changes in visual acuity and adverse event rates are equivalent to the ability associated with the study which compares the IOL to the historical control population.

The loss to follow-up subjects in the Level B investigation should be less than 10 %. Each investigator should have a minimum of 20 subjects, and no more than 25 % of the subjects in the investigation. The Level B clinical investigation should be considered completed when all subjects that have been enrolled in the investigation have reached case report form 4.

A Level B modified IOL may only itself be considered a parent IOL at the conclusion of the study if it was investigated in a minimum of 100 subjects at each case report form (therefore the model could not have been combined with Level A modifications of itself in the clinical study), and if it met the requirements of all parts of ISO 11979.

B.2 Examples of IOL modifications

B.2.1 General

Modifications to an IOL that has undergone a clinical investigation can be classified in one of two categories depending on the level of modification: Level A or Level B. The criteria that are to be used to determine what level of modification has occurred to the parent model are described below.

The applicability column indicates the type of IOL that the modification is allowed with:

P designates polymethylmethacrylate (PMMA) posterior chamber IOLs;

A designates PMMA anterior chamber IOLs;

SP designates posterior chamber IOLs made from soft materials that are of a one-piece, plate design (no loops);

SS designates multi-piece, posterior chamber IOLs with optics made of soft materials and loops made from standard material (PMMA, polypropylene, or polyimide);

SN designates multi-piece, posterior chamber IOLs with optics made of soft materials and loops made from non-standard materials.

A modified model may have various combinations of the modifications listed below, as long as all the required criteria are met (e.g. the modified model may have a larger optic with a slightly modified loop configuration and a larger overall diameter than the parent model). Modification B.2.2.12 differs from the other modifications in that it involves material/design substitutions of parent models only.

B.2.2 Level A modifications (see B.2.1 for P, A etc.)

B.2.2.1 Mirror-image version of a model

Applicability is P/A/SP/SS/SN.

B.2.2.2 Change in overall diameter

Applicability in the case of the addition of a size specific to patients with a certain anterior chamber width range is A.

B.2.2.3 Changes in loop features

Applicability in the case of changes, such as the addition of notches or the addition of small loops or rounded ends to loops is P/A/SS/SN.

B.2.2.4 Change in loop angulation

Applicability in the case of a change from planar to a design with the body angulated posterior to loops resulting in an increase in the sagitta value up to a maximum of 1,6 mm for the 20 D version of the model is P/SS/SN.