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Ophthalmic implants — Ophthalmic viscosurgical devices

Implants ophtalmiques — Dispositifs ophtalmiques viscochirurgicaux

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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 International Standard may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 15798 was prepared by Technical Committee ISO/TC 172, *Optics and optical instruments*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

Annexes A and B form an integral part of this International Standard. Annexes C and D are for information only.

Ophthalmic implants — Ophthalmic viscosurgical devices

1 Scope

This International Standard applies to ophthalmic viscosurgical devices (OVDs), a class of non-active surgical implants with viscous and/or viscoelastic properties, intended for use during surgery in the anterior segment of the human eye. OVDs are designed to create and maintain space, to protect intra-ocular tissues and to manipulate tissues during surgery. OVDs are not designed to have any pharmacological effect.

This International Standard defines requirements with regard to safety for the intended performance, design attributes, preclinical and clinical evaluation, sterilization, product packaging, product labelling and information supplied by the manufacturer of these devices.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this International Standard. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this International Standard 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 10993-1:1997, *Biological evaluation of medical devices — Part 1: Evaluation and testing.*

ISO 10993-2:1992, *Biological evaluation of medical devices — Part 2: Animal welfare requirements.*

ISO 10993-6:1994, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation.*

ISO 10993-9:1999, *Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products.*

ISO 10993-16:1997, *Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables.*

ISO 11134:1994, *Sterilization of health care products — Requirements for validation and routine control — Industrial moist heat sterilization*.

ISO 11135:1994, *Medical devices — Validation and routine control of ethylene oxide sterilization*.

ISO 11137:1995, *Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization*.

ISO 11607:—[1)], *Packaging for terminally sterilized medical devices*.

ISO 13408-1:1998, *Aseptic processing of health care products — Part 1: General requirements*.

1) To be published. (Revision of ISO 11607:1997)

ISO 14155:1996, *Clinical investigation of medical devices*.

ISO 14630:1997, *Non-active surgical implants — General requirements*.

ISO 14971-1:1998, *Medical devices — Risk management — Part 1: Application of risk analysis*.

ISO 15223:2000, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied*.

EN 868-1:1997, *Packaging materials and systems for medical devices which are to be sterilized — Part 1: General requirements and test methods*.

EN 1041:1998, *Information supplied by the manufacturer with medical devices*.

EN 12442-1:2000, *Animal tissues and their derivates utilized in the manufacture of medical devices — Part 1: Analysis and management of risk*.

EN 12442-2:2000, *Animal tissues and their derivates utilized in the manufacture of medical devices — Part 2: Controls on sourcing, collection and handling*.

EN 12442-3:2000, *Animal tissues and their derivates utilized in the manufacture of medical devices — Part 3: Validation of elimination and/or inactivation of viruses and other transmissible agents*.

USP 24 <85>, United States Pharmacopoeia, 24th revision, <85> *Bacterial endotoxins test*.

3 Terms and definitions

For the purposes of this International Standard, the following terms and definitions apply.

3.1
delivery system
sealed container in which the product is supplied and any additional components provided to introduce the product into the eye

3.2
elasticity
tendency of a body to return to its original shape after being deformed in some way

NOTE Elasticity is quantitatively defined as stress (the force generated within the body) divided by strain (the change in dimensions of the body).

3.3
lost to follow-up patient
subject in the clinical trial for whom the final post-operative case report is overdue and who cannot be contacted despite extensive written and telephone follow-ups to determine their final clinical outcome

3.4
ophthalmic viscosurgical device
OVD
generic term that includes a variety of materials with viscous and/or viscoelastic properties, that are designed to create and maintain space, to protect intra-ocular tissues and to manipulate tissues during surgery in the anterior segment of the human eye

3.5
primary container
vial or syringe that contains the OVD

NOTE This container forms part of the delivery system

3.6
rheologically active component
compound or mixture of compounds in the finished OVD giving the product viscous and/or viscoelastic properties

3.7
serious adverse event
intra-operative or post-operative adverse event that is potentially sight-threatening

NOTE Adapted from ISO 14155.

3.8
shear viscosity
tendency of a substance to resist deformation when subjected to stress

NOTE 1 Quantitatively, shear viscosity is the quotient of shear stress divided by shear rate in steady shear flow.

NOTE 2 It is expressed in millipascal seconds (mPa·s) [previously expressed in centipoise (cP)].

3.9
sterile barrier
pouch containing the product and delivery system that maintains sterility during transport and storage

3.10
storage container
that part of the packaging intended to protect the device during transport and storage, containing a package insert and a sealed, sterile pouch within which is the product and delivery system

3.11
viscoelastic
having both viscous and elastic properties

3.12
zero shear viscosity
steady state shear viscosity at vanishing shear rate

NOTE It is expressed in millipascal seconds (mPa·s) [previously measured in centipoise (cP)].

4 Intended performance

The general requirements for the intended performance of non-active surgical implants outlined in ISO 14630 shall apply. In addition, the manufacturer shall describe and document the functional characteristics of the OVD in terms of its:

a) chemical composition;

b) rheological properties;

c) effectiveness in protecting the corneal endothelium.

5 Design attributes

5.1 General

The general requirements for non-active surgical implants outlined in ISO 14630 shall apply.

All testing requirements described below shall be performed with the finished, sterilized product.

NOTE Tests described herein are intended to apply when qualifying materials but not necessarily apply as a routine quality assurance/control programme.

The purity of water used shall be Water for Injection (in accordance with Pharmacopoeia Europe/USP 24/JP).

5.2 Characterization of the rheologically active components

5.2.1 Chemical description

The manufacturer shall provide a description of each rheologically active component in the product. The raw materials used in its manufacture shall be listed, along with their quality specifications. These shall comply with recognized compendial standards wherever possible. If the rheologically active component is derived from animal sources the requirements of EN 12442-1, EN 12442-2, and EN 12442-3 shall apply.

If the rheologically active component is a high-molecular mass organic polymer, the repeating subunits that comprise it shall be chemically identified and the linkages between them described. Any crosslinking shall also be described.

The nature of the mixture of the rheologically active component in the finished product shall be described (e.g. dissolved, dispersed, etc.). If in solution, the solubility of the rheologically active component in the solvent at the storage temperature and at 25 °C ± 2 °C shall be stated.

5.2.2 Concentration

The concentration of each rheologically active component material in the finished product shall be reported as weight of material per unit volume of solution. Since the testing methodology may affect the actual concentration reported, the standard physical or chemical techniques utilized shall be described.

5.2.3 Molecular mass distribution

If the rheologically active component of the OVD is a polymer, the average molecular mass shall be reported.

It is recognized that many OVDs contain high molecular mass polymers that are polydispersed and that the molecular mass distribution may be complex. In these circumstances the manufacturer shall conduct and report such additional tests as are necessary to provide an adequate description of the molecular mass distribution of the components in the finished product. Standard methods shall be used wherever possible.

5.3 Characterization of the finished product

5.3.1 General

The rheological and optical properties of OVDs are physical characteristics that determine their performance in ophthalmic surgery. It is therefore imperative that the physical properties of OVDs identified below are fully and accurately described. The rheological properties shall be measured at the conditions expected and relevant at the time of use.

5.3.2 Shear viscosity

The shear viscosity of the product as provided to the end-user shall be measured over the range of shear rates that are likely to be encountered during routine use of the device. Measurements shall be made at 25 °C ± 2 °C. The test equipment and other conditions of measurement shall be documented.

NOTE The suggested shear rate range is from 0,001 s^{-1} at one extreme, approximate to zero shear, when the viscoelastic material is stationary within the anterior chamber, to a shear rate of approximately 1 000 s^{-1} at the other extreme, approximate to the conditions when the viscoelastic material is being injected into the eye though a cannula. It is recognized that, for products of low viscosity, it is impossible to measure the shear viscosity at very low shear rates. In such circumstances the viscosity can be measured at shear rates from 1 000 s^{-1} to the lowest shear rate at which the viscosity can be practically determined. For products of very high viscosity ($\geqslant 2 \times 10^6$ mPa·s), shear rates below 0,001 s^{-1} may be required to determine the zero shear viscosity.

The viscosity-shear rate relationship shall be graphically presented on a standard plot of log viscosity vs. log shear rate. The viscosity shall be measured using a rotational viscometer under standard conditions. The zero shear viscosity is determined as the steady-state shear viscosity at vanishing shear rate. For highly viscous solutions, measurement with a constant-stress rheometer is preferred.

5.3.3 Elasticity

The elasticity of the OVD shall be measured at frequencies from 0,01 Hz to 20 Hz. Measurements shall be made at 25 °C ± 2 °C. The test equipment and other conditions of measurement shall be documented. Both the log viscous and elastic moduli shall be plotted against the log frequency. Data can also be presented as a plot of percent elasticity against log frequency.

5.3.4 Chemical description of the components

The manufacturer shall document the general nature of the solvent, accompanied by a detailed list of each component, the rationale for its inclusion, and its molar concentration in the finished product. Wherever possible components shall comply with compendial standards.

5.3.5 pH

The pH of the finished product shall be measured with a calibrated pH meter at 25 °C ± 2 °C. The pH of the product shall be between 6,8 and 7,6.

The pH of the product should be close to that of the aqueous humor (pH 7,38) in order to prevent damage to the corneal endothelial cells. *In vitro* studies have shown that the pH range tolerated by the endothelium narrows as exposure time increases.

5.3.6 Chemical and biological contaminants

The identification of potentially hazardous chemical or biological contaminants shall be determined by a risk analysis. For raw materials of biological origin, these contaminants can include proteins, nucleic acids, or other biological materials. Contaminants of the finished product derived from the source materials or from the manufacturing process (e.g. crosslinking agents and antioxidants) that are potentially hazardous to the tissues of the eye or systemically hazardous shall be identified, whenever possible, and their concentrations in the finished product reported.

NOTE Droplets of silicone lubricant, derived from the syringe, are frequent contaminants, often misinterpreted as air bubbles or particulates. Contamination of the product from this source should be considered in the risk assessment.

Contaminants shall be determined using standard analytical methods when available, and all methods shall be described. Limits for identified contaminants shall be set and included. Testing for the biological effects of these contaminants during evaluation of biological safety may be required if the risk analysis determines it necessary.

5.3.7 Osmolality

The manufacturer shall determine and document the osmolality range of the OVD. Osmolality of the finished product shall not be less than 200 mOsm/kg or greater than 400 mOsm/kg. Osmolality shall be determined using either a vapour pressure or cryoscopic osmometer under standard conditions.

5.3.8 Spectral transmittance

The spectral transmittance of the finished product shall be recorded over the range 200 nm to 1 200 nm. Results shall be presented graphically, plotting percent transmission against wavelength.

5.3.9 Particulates

There is potential for adverse events [such as an excessive or prolonged elevation in intra-ocular pressure (IOP)] arising as a result of particles of certain sizes and characteristics in the finished product.

A risk assessment shall evaluate the potential for contamination by, or formation of, particulates in the product during manufacture, the conditions expected during transport and storage and during use of the product. In particular the potential for aggregation, polymerization and adhesion of particles to ocular tissues shall be taken into account.

NOTE 1 OVDs containing synthetic polymers are likely to be at significantly higher risk of formation of microgels, which are difficult to identify and quantify either by light scattering or by microscopic methods.

The manufacturer shall identify the potential hazards associated with each type of particle identified by the risk assessment.

The manufacturer shall characterize the types, range of sizes, and levels of particulates present in the finished product. A limit for each type of particle present shall be set and an adequate justification for the limit shall be documented.

NOTE 2 A method for the determination of particulate counts is contained in annex C.

5.3.10 Refractive index

The refractive index between air and the OVD shall be measured with a refractometer at 25 °C ± 2 °C stating at which wavelength it was determined.

6 Design evaluation

6.1 General

The requirements for evaluation of non-active implants outlined in ISO 14630 shall apply.

6.2 Evaluation of biological safety

6.2.1 General

The procedure for evaluation of biological safety of an OVD shall commence with an assessment of risk, carried out and documented in accordance with ISO 14971-1. The results of the risk analysis shall determine the tests required to evaluate the biological safety of the OVD.

For OVDs containing material of animal origin, the risk analysis and management requirements outlined in EN 12442-1, EN 12442-2 and EN 12442-3 shall apply.

For all OVDs the requirements for evaluation of biological safety specified in ISO 10993-1 shall apply, together with the following particular requirements.

In addition to the biocompatibility tests identified in ISO 10993-1 and by the risk analysis, all of the following tests shall be considered in the selection of tests to evaluate the biological safety of an OVD.

NOTE 1 Based upon the typical clinical applications in the anterior segment of the eye, OVDs are categorized as "Implant devices, tissue/bone". The tests for this and other categories of devices identified in Table 1 of ISO 10993-1 are for guidance only; they do not represent maximum or minimum test requirements.

NOTE 2 It may be possible to combine biocompatibility tests, thereby reducing the number of animals required for testing. Two tests can be conducted simultaneously in a single animal provided that the test animal is not subjected to undue pain or distress.

6.2.2 Intra-ocular implantation test

An intra-ocular implantation site, either in the anterior chamber or vitreous cavity, shall be used for this test. The general requirements for implantation tests outlined in ISO 10993-6 shall apply. The particular requirements for the intra-ocular implantation test are outlined in annex A.

If the test OVD causes a significantly greater ocular reaction or inflammatory response than the OVD used as the control, a risk/benefit evaluation shall be performed.

6.2.3 Bacterial endotoxins test

The OVD shall be evaluated for the presence for bacterial endotoxins using the limulus amoebocyte lysate (LAL) test, in accordance with the procedure described in USP 24, or equivalent validated test procedure. Any product that exceeds a bacterial endotoxin limit of 0.5 endotoxin units (EU) per millilitre fails the test.

6.2.4 Evaluation of the intra-ocular pressure increase

A test for IOP shall be performed in accordance with the procedure outlined in annex B.

If the test OVD causes a significantly higher or more prolonged IOP increase than the OVD used as the control, a risk/benefit evaluation shall be performed.

The results of the test shall be used to determine the likely size and duration of the post-surgical IOP rise. This will influence the design of the clinical trial and may necessitate additional post-surgical measurements of the IOP to those listed in 6.3.3.

6.2.5 Clearance of residual OVD from the anterior chamber

Where no adequate literature exists, the rate at which residual product is cleared from the anterior chamber through the trabecular meshwork shall be determined using an appropriate test method, such as fluorescence or radioisotope labelling, and then reported.

6.2.6 Degradation and toxicokinetics

Where no adequate literature exists concerning the fate of the OVD, the manufacturer shall provide evidence of the route of elimination, biotransformation and catabolic products of the components. With regard to degradation and toxicokinetics, the requirements of ISO 10993-9 and ISO 10993-16 shall apply.

6.3 Clinical evaluation

6.3.1 General

This subclause specifies requirements for clinical evaluation of OVDs in the anterior segment of the eye. The general requirements concerning the clinical investigations of medical devices for human subjects specified in ISO 14155 shall apply, together with the following particular requirements.