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Ophthalmic implants — Ophthalmic viscosurgical devices

Implants ophtalmiques — Dispositifs ophtalmiques viscoélastiques

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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 2.

The main task of technical committees is to prepare International Standards. 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 document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

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

This second edition cancels and replaces the first edition (ISO 15798:2001) which has been technically revised. It also includes the Technical Corrigendum ISO 15798:2001/Cor 1:2003.

Ophthalmic implants — Ophthalmic viscosurgical devices

1 Scope

This International Standard is applicable 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.

This International Standard specifies 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 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 within a risk management process*

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

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

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

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

ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

ISO 11137-3, *Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects*

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

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

ISO 14155-1, *Clinical investigation of medical devices for human subjects — Part 1: General requirements*

ISO 14155-2, *Clinical investigation of medical devices for human subjects — Part 2: Clinical investigation plans*

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

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 15223-1, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*

ISO 15223-2, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 2: Symbol development, selection and validation*

ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical device*s

ISO 22442-1, *Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management*

ISO 22442-2, *Medical devices utilizing animal tissues and their derivatives — Part 2: Controls on sourcing, collection and handling*

ISO 22442-3, *Medical devices utilizing animal tissues and their derivatives — Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents*

EN 980, *Symbols for use in the labelling of medical devices*

EN 1041, *Information supplied by the manufacturer of medical devices*

3 Terms and definitions

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

3.1
absolute complex viscosity
$|\eta^*| = [(\eta')^2 + (\eta'')^2]^{0,5}$
absolute value of complex viscosity (3.2)

NOTE Absolute complex viscosity is expressed in pascal seconds (Pa·s).

3.2
complex viscosity
$\eta^* = \eta' - i \cdot \eta''$
viscosity consisting of a viscous η' and an elastic η'' component where i is an imaginary number defined by $i = (-1)^{0,5}$

3.3
delivery system
sealed container in which the product is supplied and any additional components provided to introduce the product into the eye

3.4
elasticity
tendency of a body to return to its original shape after having been deformed

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

3.5
lost to follow-up subject
subject for which 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.

3.6
ophthalmic viscosurgical device
OVD
generic term that includes a variety of materials with viscous and/or viscoelastic properties, which 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

3.7
primary container
vial or syringe that contains the OVD

NOTE This container forms part of the delivery system.

3.8
rheologically active component
compound or mixture of compounds in the finished OVD giving the product viscous and/or viscoelastic properties

3.9
shear viscosity
tendency of a fluid to resist flow 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 Shear viscosity is expressed in pascal seconds (Pa·s), traditionally in millipascal seconds (mPa·s).

NOTE 3 Shear rate is the velocity gradient in a flowing fluid, expressed in s^{-1} (per second).

NOTE 4 The shear viscosity divided by the solution density gives the *kinematic viscosity,* which is a measure of the viscosity of a fluid influenced by inertia (e.g. gravity).

3.10
sterile barrier
sealed packaging, containing the product and delivery system, which maintains sterility during transport and storage

3.11
storage container
that part of the packaging intended to protect the device during transport and storage, containing the sterile barrier

3.12
viscoelasticity
characteristics of a fluid having both viscous and elastic properties

NOTE The viscous modulus, G'', is frequently called the loss modulus and the elastic modulus, G', is frequently called the storage modulus, both moduli are expressed in Pascal (Pa). The moduli can be combined to show the elasticity of the OVD (see 5.3.5).

3.13
zero shear viscosity
plateau viscosity at vanishing shear rate in a log-log plot of viscosity versus shear rate

NOTE Zero shear viscosity is expressed in pascal seconds (Pa·s), traditionally in millipascal seconds (mPa·s), or as a logarithm of the zero shear viscosity.

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) performance 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.

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.

A risk assessment shall be performed in accordance with ISO 14971.

5.2 Characterization of the components

The manufacturer shall provide a description of each rheologically active component, quantitatively and qualitatively, in the product.

The raw materials used in the manufacture of the product shall be listed qualitatively, 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 ISO 22442-1, ISO 22442-2, and ISO 22442-3 shall apply.

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

5.3 Characterization of the finished product

5.3.1 General

All testing requirements described in 5.3.2 to 5.3.12 shall be performed with the finished, sterilized product. 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 under the conditions expected and relevant at the time of use, and be reported.

5.3.2 Absolute complex viscosity

The logarithm of the absolute complex viscosity versus the logarithm of the oscillation frequency shall be graphed to simultaneously demonstrate the resistance to flow and deformation of the OVD formulation. At very low frequencies the absolute complex viscosity approaches the zero shear viscosity.

NOTE Complex viscosity should, if possible, be determined at frequencies between (10^{-3} to 10^{3}) Hz (s^{-1}). For products of very high viscosity (>2×10^{3} Pa·s), frequencies below 0,01 Hz will be required to show the zero shear viscosity.

5.3.3 Chemical and biological contaminants

All chemical or biological contaminants shall be identified and their potential ocular hazard shall be determined by risk analysis. For raw materials of biological origin, these contaminants can include proteins, nucleic acids or other biological materials. Contaminants derived from the source materials or from the manufacturing process, e.g. cross linking agents and antioxidants, shall be identified whenever possible, and their concentrations in the finished product shall be reported.

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 is required, if the risk analysis deems it necessary.

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.

5.3.4 Concentration

The concentration of each rheologically active component material 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.

5.3.5 Elasticity

The elasticity of the OVD shall be demonstrated at the same frequencies used to determine the complex viscosity. It shall be demonstrated up to at least 100 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, G'', and log elastic, G', moduli shall be plotted against the log frequency. Data can also be presented as a plot of percent elasticity against log frequency, for example as $100 \times [G'/(G'+G'')]$ versus log frequency.

5.3.6 Molecular mass distribution

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

It is recognized that many OVDs contain high molecular mass polymers that are polydisperse 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. Standard methods shall be used wherever possible.

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 a cryoscopic osmometer under standard conditions.

5.3.8 Particulates

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 OVDs containing synthetic polymers are likely to be at significantly higher risk of formation of microgels, which are difficult to identify and quantify.

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 using a validated method.

A limit for the overall number of particles (e.g., ⩾ 10 µm and ⩾ 25 µm) present, and a limit for each type of particle identified by the risk analysis as a potential ocular hazard at the levels allowed by the overall particle specification, shall be set and an adequate justification for the limits shall be documented.

5.3.9 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.

NOTE The pH meter should be fitted with an electrode suitable for high viscosity solutions. The pH of the product should be close to that of the aqueous humour (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.

5.3.10 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.

5.3.11 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 results, equipment and 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 fluid is stationary, for example 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 fluid is being injected into the eye through a cannula. It is recognised that, for products of low viscosity, it is problematic 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 ($>2 \times 10^3$ Pa·s), shear rates below 0,001 s^{-1} might be required to determine the zero shear viscosity.

The viscosity-shear rate relationship shall be graphically presented on a standard plot of log viscosity versus log shear rate. The zero shear viscosity is determined as the steady shear plateau viscosity at vanishing shear rate. For highly viscous formulations, measurement with a controlled stress rheometer is preferred.

5.3.12 Spectral transmittance

The spectral transmittance shall be recorded over the range 300 nm to 1 100 nm. Results shall be presented graphically, plotting percent transmission against wavelength.

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. 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 ISO 22442-1, ISO 22442-2, and ISO 22442-3 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 device 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 Bacterial endotoxins test

The OVD shall be evaluated for the presence of bacterial endotoxins using the limulus amoebocyte lysate (LAL) test, in accordance with applicable Pharmacopoeia (see Bibliography). Any product that exceeds a bacterial endotoxin limit of 0,5 endotoxin units (EU) per millilitre fails the test.

6.2.3 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.

6.2.4 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.

6.2.5 Evaluation of inflammation and intraocular pressure

A test for inflammatory and intraocular pressure responses shall be performed to compare the test OVD with a control OVD in accordance with the procedure outlined in Annex A. The control OVD shall have been widely used for at least five years and not have been associated with significant material-related adverse events. A rationale for the choice of the control OVD shall be given.

The general requirements for implantation tests outlined in ISO 10993-6 shall apply. The particular requirements for the intraocular implantation test are outlined in Annex A.

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