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Ophthalmic implants — Ophthalmic viscosurgical devices

Implants ophtalmiques — Dispositifs ophtalmiques viscoélastiques

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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).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 170, *Ophthalmic optics,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This fourth edition cancels and replaces the third edition (ISO 15798:2013 and its Amendment, ISO 15798:2013/Amd.1:2017), which has been technically revised.

The main changes compared to the previous edition are as follows:

a) Inclusion of applicable sections from ISO 14630 throughout the document, but removal of any reference to that standard. It was further clarified that ophthalmic viscosurgical devices (OVD) are no implant by their intended use but are likely to share some of the risks related to non-active implants. Therefore, the following clauses and subclauses have been revised: Clauses 4 and 5, 6.1, 6.2.1, Clause 7. A new subclause 5.4 has been added.

b) minor clarifications in Clause 3 (3.3, 3.4) and addition of term *surgical invasive medical device*;

c) clarification in Clause 4 that a recommended removal procedure shall enable removal of the OVD as completely as possible;

d) revised wording in 5.2 to align with defined terminology from Clause 3;

e) revised note in 5.3.2: narrowed recommended measuring range;

f) revised note in 5.3.8: more accurate description of the risk;

g) clarification that control OVD for the intraocular implantation test and the clinical investigation shall be the same in both studies; therefore, the following subclauses have been revised: 6.1, 6.2.5, 6.3.2, and Annex A;

h) revised wording in 6.2.2 of this document to include ISO 15798:2013/Amd.1:2017 and guidance on standard LAL-test;

i) revised wording in 6.2.3 to address the potential risk of interaction of the OVD with fluorescence or radioisotope labelling;

j) revised 6.3 to clarify requirement of a clinical evaluation, clarification of the clinical investigation protocol, revision of the clinical investigation design, and additional standardization for evaluation and reporting of result from the clinical investigation;

k) inclusion of reference to ISO 10993-7 for acceptable levels of ethylene oxide and ethylene chlorohydrin in Clause 7;

l) packaging integrity has been specifically included into the scope of product stability Clause 8; in addition, reference to ISO 14971 has been included into this clause;

m) "Do not use if sterile barrier is breached" has been aligned with the recommended wording from ISO 15223-1 "Do not use if package is damaged"; in addition, molecular mass distribution has been removed from the list of information to be supplied by the manufacturer in Table 1;

n) major revision of Annex A;

o) correction of a typo in the formula for calculating the minimum number of evaluable patients per treatment group in Annex B.

p) Addition of new informative Annex C on analyses of OVD clinical data.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Ophthalmic implants — Ophthalmic viscosurgical devices

1 Scope

This document is applicable to ophthalmic viscosurgical devices (OVDs), a class of surgical invasive medical devices 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 intraocular tissues and to manipulate tissues during surgery.

This document 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 documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 10993-6, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation*

ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

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, *Sterilization of health-care products — Ethylene oxide — Requirements for the 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 of development, validation and routine control*

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, *Clinical investigation of medical devices for human subjects — Good clinical practice*

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

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 devices*

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 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.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

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

Note 1 to entry: 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
primary container in which the product is supplied and any additional components provided to introduce the product into the eye

3.4
elasticity
$G' = \sigma_0/\varepsilon_0 \cdot \cos\delta$
tendency of a body to return to its original shape after having been deformed

Note 1 to entry: Elasticity is quantitatively defined as stress (the force generated within the body) divided by strain (the change in dimensions of the body) multiplied by cosine of the phase lag between stress and strain.

Note 2 to entry: Elasticity is expressed in pascal (Pa).

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 1 to entry: 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 intraocular 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 1 to entry: 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 to entry: Quantitatively, shear viscosity is the quotient of shear stress divided by shear rate in steady shear flow.

Note 2 to entry: Shear viscosity is expressed in pascal seconds (Pa·s), traditionally in millipascal seconds (mPa·s).

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

Note 4 to entry: 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* (3.3), 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
surgical invasive medical device
invasive device which penetrates inside the body through the surface of the body with the aid or in the context of a surgical operation

3.13
viscoelasticity
characteristics of a fluid having both viscous and elastic properties

Note 1 to entry: 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).

3.14
zero shear viscosity
plateau viscosity at vanishing shear rate in a log-log plot of viscosity versus shear rate

Note 1 to entry: 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

OVDs are surgically invasive medical devices. They shall be compatible with the internal ocular environment. Intended performance is primarily provided for by their viscous and/or viscoelastic properties, which are designed to create and maintain space, to protect intraocular tissues and to manipulate tissues during surgery in the anterior segment of the human eye. OVDs are used intra-

operatively and intended to be removed at the end of surgery. The manufacturer shall describe any performance characteristic to be provided for by the OVD. In addition, the manufacturer shall particularly describe the intended way of application, the performance in protecting the corneal endothelium, the intended time that the OVD resides in the anterior chamber of the eye, and the method for removal. This method shall enable removal of the OVD as completely as possible.

In addition, the manufacturer shall describe and document the functional characteristics of the OVD in terms of its:

a) chemical composition;

b) rheological properties.

5 Design attributes

5.1 General

The following subclauses are listing specific design attributes to be met for the intended performance. Tests described therein are intended to apply when qualifying materials but not necessarily apply as a routine quality assurance/control programme.

A risk assessment shall be performed in accordance with ISO 14971. OVD design attributes shall be documented. Where any of the design attributes is not considered to be relevant, the reason shall be documented and justified.

5.2 Characterization of the components

The manufacturer shall provide a description of the rheologically active component(s).

The manufacturer shall provide a description of each compound belonging to the rheologically active component(s).

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 or one of its compounds 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 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.

The purity of water used shall be water for injection.

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 are usually determined at frequencies between (0,01 to 100) 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, viruses and other transmissible agents (unclassified pathogenic entities, prions and similar entities, or other biological materials). Contaminants derived from the source materials or from the manufacturing process (including sterilization), e.g. cross-linking agents and antioxidants, shall be identified whenever possible, and their concentrations in the finished product shall be reported. Assessment of contaminants shall consider degradation characteristics of active component, including interactions with laser light, ultrasound energy, or other high energy sources likely to be used along with the OVD during surgery, and leachables/extractables from the primary container.

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.

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 can 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 × $[G'/(G'+G'')]$ 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 and the mass distribution 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 mmol/kg or greater than 400 mmol/kg. Osmolality shall be determined using either a vapour pressure or a cryoscopic osmometer under standard conditions.