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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.

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 have shown in the past a significantly higher risk of formation of microgels, which are difficult to identify and quantify and which resulted in significant intraocular pressure (IOP) spikes.

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.

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 recognized 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 × 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.

5.4 Usability

The design of the OVD shall be suitable for its intended use.

The viscoelastic properties of the OVD shall support the surgical procedure. Possible effects of the viscoelastic properties on the ocular environment shall be assessed in the risk assessment. The OVD shall have the ability to be removed after surgery and a recommended technique for removal shall be provided by the manufacturer in the instruction for use. The risk assessment shall consider potential changes in the physicochemical properties of the OVD when subjected to the shear forces associated with the various steps in the surgical procedure[6][7].

The delivery system shall be suitable for injection of the OVD into the anterior part of the eye. Potential impact of the manufacturing processes (including sterilization) on the performance of the delivery system shall be assessed in the risk assessment.

If no complete delivery system is supplied, the design development shall include assessment of additional relevant devices, such as recommended type of cannula.

Design development shall include assessment of potential effects on the OVD and its function due to interactions with other materials and substances likely to be used along with the OVD during surgery. Interactions with high energy sources likely to be used along with the OVD during surgery, such as laser light or ultrasound energy, at the conditions likely to be used during surgery, shall not compromise functionality of the OVD.

6 Design evaluation

6.1 General

OVDs shall be evaluated to demonstrate that the intended performance (see Clause 4) is achieved. The extent to which the intended performance has been achieved shall be determined and documented. Safety and intended performance shall be demonstrated by pre-clinical evaluation, clinical evaluation and post market surveillance, including appropriate risk management at all stages of the life cycle of the product in accordance with ISO 14971.

Design evaluation shall include use of a control OVD for the intraocular implantation test and the clinical investigation. The control OVD shall be the same in both studies. The control shall be an OVD with physical properties relevant for the surgical procedure and shall be approved for the same indication as the study OVD. If available, the control OVD shall have been widely used for at least five years. The control OVD shall not have been associated with significant material-related adverse events. A rationale for the choice of the control OVD shall be given.

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.

Currently a significant risk associated with OVDs is related to residual material that remains in the eye after surgery. The severity for this risk shall be evaluated.

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 ISO 10993-1:2018, Table 1, are for guidance only; they do not represent maximum or minimum test requirements.

NOTE 2 It can 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 0,2 endotoxin units (EU) per millilitre fails the test.

The standard LAL test is not designed to determine endotoxin levels in liquids with viscosities typical of OVDs. The accuracy and repeatability of the method shall be validated using OVDs produced with defined levels of endotoxins. Additional guidance is provided in References [8] to [11].

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. The test method shall not impact the physicochemical characteristics of the device.

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 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 intraocular pressure (IOP) increase than the OVD used as control, a risk/benefit evaluation shall be performed.

The results of the test shall be used to determine the likely magnitude and duration of the post-surgical inflammatory reaction and pressure rise. This will influence the design of the clinical investigation and may necessitate additional post-surgical time points for the measurement of IOP in addition to those listed in 6.3.5.

In accordance with ISO 10993-2, animal testing should be reduced to the justifiable minimum.

6.3 Clinical evaluation

6.3.1 General

A clinical evaluation shall be performed for the OVD. If the risk assessment indicates a need for, or if regional or national regulations require a clinical investigation, the following applies. The general

requirements concerning clinical investigations of medical devices for human subjects specified in ISO 14155 shall apply, together with the following particular requirements and the recommended removal procedure.

6.3.2 Clinical investigation design

A randomized controlled clinical investigation shall be performed. The objective of the study shall be to document the safety and performance of the new OVD when compared to a well documented control OVD. The surgical procedure shall be described in detail in the clinical investigation plan (CIP) including the type of any implant used. To validate the recommended method of removal of the new OVD, the potential method(s) shall be specified in the CIP. The recommended method of removal for the control OVD consistent with its approved instructions for use shall also be specified in the CIP. Each step of the method shall be fully described in the CIP for each arm. The method of removal shall be recorded on the Case Report Forms (CRF). A rationale for the choice of control OVD shall be given in the CIP.

If a double blinded study comparing the new OVD and the control cannot be achieved, an independent observer, who is unaware of which device has been used in each case, shall perform the postoperative measurements.

A risk analysis shall determine the primary hypothesis, and standard biostatistical formula shall be used to calculate the required number of subjects per treatment group. The primary safety and performance hypotheses to be tested shall be included in the CIP. A method to determine the number of subjects is provided in Annex B. If the manufacturer wishes to make claims, e.g. regarding the intra-operative performance of the device, specific endpoints to support those claims shall be included in the CIP together with the appropriate power calculation.

A subject may only submit one eye in the investigation.

No investigator shall contribute less than 20 subjects or more than 25 % of the total number of subjects in the investigation.

Investigations conducted at a single site may result in additional regulations in some countries.

Efforts shall be made to keep the number of patients lost to follow-up below 10 % of the number enrolled.

The following variables shall be evaluated during the clinical investigation:

a) intraocular pressure;

b) corneal endothelial cell density;

c) intraocular inflammation.

The CIP shall include a description of the analyses to be performed. Some suggested analyses are presented in Annex C.

6.3.3 Corneal endothelial cell density

The condition of the corneal endothelium shall be assessed by measuring central corneal endothelial cell density using specular microscopy pre-operatively and 3 months ±2 weeks postoperatively on all subjects in the investigation.

6.3.4 Postoperative inflammation

Postoperative inflammation shall be evaluated by slit-lamp biomicroscopy and graded clinically at each visit using a standard grading system, such as The Standardization of Uveitis Nomenclature (SUN) Working group[12].

6.3.5 Post-operative intraocular pressure change

The intraocular pressure shall be measured using a Goldmann type applanation tonometer pre-operatively and at least at the following times postoperatively:

a) 8 h ± 2 h;

b) 24 h ± 4 h;

c) 7 d ± 2 d;

d) 30 d ± 7 d;

e) 90 d ± 14 d.

At least for the first examination, the time after surgery of the IOP measurement shall be documented.

If a literature review, animal testing, or clinical experience indicates that the peak IOP occurs at a time outside the 6 h to 10 h postoperative range, the manufacturer shall modify the clinical investigational design to measure the IOP at times closer to the predicted appearance of the peak, for both the test and the control group.

When IOP in an individual subject is elevated at 24 h after surgery, additional IOP measurements shall be performed until the IOP normalizes. The magnitude of the IOP elevation and the frequency of the additional IOP measurements shall be described in the CIP.

The criteria and protocol for use of IOP lowering drugs or interventions shall be specified in the CIP. The administration, at any time, of IOP-reducing drugs, or other interventions, shall be documented (including date and time) and the data from those subjects shall be presented separately. Steroid use shall also be documented at each visit, including generic name, strength, route of administration, dose, frequency of administration, and date and time of last administration prior to IOP measurement. It is suggested that known steroidresponders be excluded from enrollment.

If any subject in the investigation has an IOP ≥ 30 mmHg at one week or later, early termination of the investigation shall be considered[13]. This analysis shall be performed during the study for all subjects and at the end of the study for each treatment group. At the completion of the study, analysis of the IOP measurements at the required time points shall include calculations of the means as well as the frequencies of IOP values ≥ 30 mmHg.

6.3.6 Adverse events

Clinical investigators shall file reports of serious intra-operative and post-operative adverse events with the sponsor immediately after learning of their occurrence. These and all other adverse events shall be documented in the case reports. Manufacturers shall take into account adverse events reports when reviewing their risk analysis.

7 Sterilization

Wherever possible, the product shall be terminally sterilized.

For an OVD, or components thereof, sterilized using moist heat, the requirements of ISO 17665-1 shall apply.

For an OVD, or components thereof, sterilized by radiation, the requirements of ISO 11137-1, ISO 11137-2 and ISO 11137-3 shall apply.

NOTE 1 It is recognized that many OVDs contain high molecular mass polymers that are labile and that the rheological properties of the product can be adversely influenced by sterilization with moist heat or radiation. When a product cannot be terminally sterilized by moist heat or radiation, aseptic processing is an accepted alternative.

For OVDs that are aseptically processed, the requirements specified in ISO 13408-1 shall apply.

For components of an OVD sterilized using ethylene oxide, the requirements of ISO 11135 shall apply. The potential for EO derived reaction in products in the OVD shall be taken into account in the risk analysis. Acceptable levels of residues from EO and ECH shall be established using ISO 10993-7, subclause "Special situations", considering injection of OVD, typically 0,5 ml. Applicable methods for determination of ethylene oxide and ethylene chlorohydrin are provided in ISO 10993-7.

NOTE 2 The OVD itself, being an aqueous solution, cannot be sterilized by EO, but EO can diffuse into the OVD if the packaging containing it is sterilized with EO. If so, EO will immediately react with water to form derivatives (e.g. ethylene glycol, ethylene chlorohydrin).

8 Product stability

The manufacturer shall define and state the shelf life of the OVD and its delivery system. Real time or validated accelerated (at temperatures not to exceed 45 °C) shelf-life testing shall be performed to demonstrate that the essential characteristics for safe and effective performance of the finished product and delivery system remain within product specifications over the labelled shelf life under expected conditions of transport and storage. The parameters that shall be followed during shelf-life studies are the rheological profile, pH, packaging integrity, and sterility, plus any other factors identified by risk analysis following ISO 14971 as crucial for the use of the product.

9 Integrity and performance of the delivery system

An OVD is typically supplied in a sealed container, and is often accompanied by a cannula for injection of the product into the eye. These two components comprise the delivery system. Appropriate testing shall demonstrate that mechanical failure of the delivery system will not result from intended use.

Chemical and physical compatibility of the OVD and the delivery system and biocompatibility of the components of the delivery system shall be evaluated.

10 Packaging

10.1 Protection from damage during storage and transport

The packaging requirements for medical devices outlined in ISO 11607-1 shall apply.

10.2 Maintenance of sterility in transit

OVDs shall be packaged in such a way that they remain sterile within the limits specified for conditions of transport, storage and handling. The sterile packaging requirements outlined in ISO 11607-1 shall apply.

11 Information to be supplied by the manufacturer

The general requirements for information provided by the manufacturer of medical devices specified in EN 1041 shall apply, together with the following particular requirements for viscosurgical devices. Symbols may be used instead of text, where appropriate. When symbols are used, ISO 15223-1, ISO 15223-2 or EN 980, depending on region, apply.

If the product is vulnerable to damage by exposure to environmental elements, there shall be clear warning signs on the shipping container.

The batch number and expiration date may also be provided on a self-adhesive label for use in records.

Instructions for use shall be included within the storage container, provided in such a way that it can be read without damaging the sterile barrier.

The minimum information required on the storage container, instructions for use, sterile barrier and primary container is listed in Table 1.

Table 1 — Information to be supplied by the manufacturer

Point of information	Storage container	Instructions for use	Sterile barrier	Primary container
Name of the manufacturer and, if applicable, the authorized representative	X	X	X[a]	X
Address of the manufacturer or authorized representative	X	X		
Trade name of the product	X	X	X[a]	X
Description of the delivery system and instructions for its proper use		X		
Brief description of the chemical composition of the product and the volume supplied	X	X		
Description of the relevant design attributes that may affect the safety and performance of the product, including, but not limited to, all of the following: concentration; pH; osmolality		X		
Graphical presentation of the rheological profile, plotting the log viscosity (Pa·s) versus log shear rate (s^{-1}) over the range defined in 5.3.11		X		
Conditions for storage	X	X		
Indications for use		X		
Contra-indications for use		X		
Instructions for use, including recommendations for removal of the product		X		
Warnings and precautions		X		
Statement “For single use”	X	X	X[a]	
Statement “Sterile” and the method(s) of sterilization of the product and primary container	X	X	X[a]	
Statement “Do not use if package is damaged”			X[a]	
Expiration date	X		X[a]	X
Batch number preceded by the word “LOT”	X		X[a]	X
Date of issue or the latest revision of the instructions for use		X		

[a] This information or part of it can be alternatively given on the primary container and need not be provided on the sterile barrier if that is transparent and the required information is given on and can be read directly from the primary container without breaking the seal. Irrespective of choice, expiration date and the batch number shall in all cases be given on the primary container.

Annex A
(normative)

Intraocular implantation test

A.1 General

A transient increase in intraocular pressure (IOP) and an inflammatory reaction can follow anterior segment surgery in which OVDs are utilized. It is an accepted consequence of their use, and should not significantly impair ocular function or the repair of ocular tissues. A significant or prolonged increase in the IOP can cause pain or discomfort and result in permanent damage to the eye. This test monitors the rise in the intraocular pressure and any inflammatory reaction, following replacement of aqueous humour by an equal volume of OVD in the anterior chamber of a suitable test animal. The OVD remains in the eye; thus, the test does not mimic clinical use, where the surgeon removes as much of the OVD as possible prior to closure of the incision. Thus, the duration and magnitude of the change in IOP during preclinical testing can be greater than that encountered during clinical use. This test is only for comparison of the OVD with a control material approved for the same use.

A.2 Test material

The sterile finished OVD under investigation is used as test material.

A.3 Control material

Choose a control OVD that has been widely used for at least five years and has not been associated with significant material related adverse events. The same control OVD shall be used in the animal and clinical study. Provide a rationale for the choice of the control OVD. The control OVD is in the same form as supplied to the market.

A.4 Test procedure

Use a minimum of six animals for the test. If rabbits are used, they should preferably be of the New Zealand white strain and weigh approximately 2,5 kg.

Evaluate the eyes pre-operatively using applanation tonometry, slit-lamp biomicroscopy and pachymetry and record the results. The order in which the assessments are performed is recorded and justified. Use of local medication (anaesthetic, mydriatic agent) may interfere with subsequent ocular assessments. Therefore, provide a justification for the medications used during ophthalmic evaluations and ensure that they do not interfere with the assessments. Reject animals with abnormalities in any eye.

Appoint a person with experience in surgery on the ocular anterior segment to perform the implantations.

Exchange approximately 25 % of the liquid volume in the anterior chamber with the test OVD, in one eye of the test animal. The contra lateral eye is treated in the same way with the control OVD. The eyes of each animal are treated one after the other, preferably in a randomized order, before continuing with the next animal. Record intra-operative complications, if any.

A bilateral implantation is preferred, but unilateral implantation is permitted, if local regulations so require. In this case a minimum of 12 animals should be used.

Implantation should be achieved with the minimum possible trauma to the eye to avoid physical damage to ocular tissue, which can mask the intraocular changes resulting from exposure to the test or control material.

A.5 Test evaluation

A.5.1 Intraocular pressure evaluation

Measure the intraocular pressure by applanation tonometry at the following times, post-operatively:

a) 2 h ± 0,5 h;

b) 4 h ± 1 h;

c) 6 h ± 1 h;

d) 8 h ± 1 h;

e) 12 h ± 1 h;

f) 24 h ± 2 h;

g) 7 d ± 1 d;

h) 30 d ± 7 d;

i) 90 d ± 14 d.

The rate of change of the intraocular pressure and duration can vary considerably with the nature of the OVD and in particular its viscosity. Once a pattern has been established, the times at which the intraocular pressure is measured can be altered to more accurately follow its change. Additional evaluation times may be necessary if the IOP remains elevated for more than 24 h post-injection. IOP can vary during the day. Therefore, the time when the IOP is measured shall be carefully considered and documented. In addition, use of anaesthetic agents shall be carefully considered since sedation may lower IOP. Furthermore, the location on the cornea where IOP is measured and the number of measurements taken/eye will be determined. Document all test results and compare the IOP changes from baseline (prior to implantation) between the investigational and control eyes.

The administration, at any time, of IOP-reducing drugs, or other interventions, shall be documented and the data from those eyes/animals shall be presented separately.

A.5.2 Inflammatory response evaluation

The inflammatory response is monitored and graded according to a standardized ocular scoring system for slit-lamp biomicroscopic examination and pachymetry, such as the standardization of uveitis nomenclature (SUN) working group (for flare and anterior chamber cells)[12] and the McDonald-Shadduck scale (for corneal, iris observations)[14], at the following times post-operatively:

a) 6 h ± 1 h;

b) 24 h ± 2 h;

c) 48 h ± 2 h;

d) 72 h ± 2 h;

e) 7 d ± 1 d;

f) 30 d ± 7 d;

g) 90 d ± 14 d.