INTERNATIONAL STANDARD

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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.

6.3.2 Clinical trial design

A randomized controlled clinical trial shall be performed. The objective of the study shall be to document the safety of the new viscosurgical device in anterior segment surgery when compared to a control. A risk analysis shall determine the primary hypothesis, and standard biostatistical formulae shall be used to calculate the required number of patients per treatment group.

The control treatment shall be a well-documented OVD, marketed widely for at least the last five years and approved for the same use. No investigator shall contribute less than 20 patients or more than 25 % of the total number of patients in the investigation. The number of patients lost to follow-up in each treatment group shall not be greater than 10 % of the total number enrolled.

NOTE Investigations conducted at a single site may result in additional requirements to satisfy regulations in some countries.

Each investigator shall use the same lens type and the same surgical procedure for all patients.

No "fellow eyes" shall be included in the clinical investigation. If a true masked study comparing the new OVD and the control cannot be achieved, an independent observer, who is unaware of which device has been used, shall perform the required post-operative measurements.

If the manufacturer wishes to make additional claims, e.g. regarding the intra-operative performance of the device, additional endpoints to support these claims shall be included and the appropriate power calculation for determining the patient numbers required.

The following variables shall be evaluated during the course of clinical trials:

a) the size and duration of any postoperative rise in IOP;

b) the corneal endothelial cell count;

c) intra-ocular inflammation or any other adverse intra-operative or post-operative events.

The outline of a method to determine the number of patients in the test and control groups is provided for guidance (see annex D).

6.3.3 Post-operative intra-ocular pressure change

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

— 6 h ± 2 h

— 24 h ± 4 h

— 1 week ± 2 d

— 1 month ± 7 d

— 3 months ± 2 weeks

Whenever the IOP in an individual subject remains elevated for longer than 24 h, additional measurements shall be made until the IOP returns to the pre-operative level.

The administration, at any time, of IOP-reducing drugs shall be documented and the data from those subjects shall be presented separately. If a literature review, animal testing, or clinical experience indicate that the peak IOP occurs at a time outside the 4 h to 8 h postoperative range, the manufacturer shall modify the clinical trial design to include an additional measurement of the IOP at a time closer to the predicted peak value.

The frequency of subjects with an IOP $\geqslant$ 30 mm Hg at one week or later shall be monitored throughout the study. If the frequency is statistically higher than the expected frequency of zero, early termination of the clinical investigation shall be considered. This analysis shall be performed during the study for the entire study population 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 $\geqslant$ 30 mm Hg.

6.3.4 Corneal endothelial cell count

The condition of the corneal endothelium shall be assessed by central corneal endothelial cell counts pre-operatively and 3 months $\pm$ 2 weeks postoperatively.

6.3.5 Postoperative inflammation

Postoperative inflammation shall be evaluated by slit-lamp biomicroscopy and graded clinically at each visit for IOP measurement.

6.3.6 Adverse events

Clinical investigators shall file reports of serious intra-operative and post-operative adverse events with the sponser immediately after learning of their occurrence. All other adverse events shall be documented in the case reports.

7 Sterilization

Wherever possible, the product shall be terminally sterilized. The requirements for sterilization of non-active surgical implants outlined in ISO 14630 shall apply.

For an OVD, or components thereof, sterilized using moist heat, the requirements of ISO 11134 shall apply.

For an OVD, or components thereof, sterilized using ethylene oxide, the requirements of ISO 11135 shall apply.

NOTE 1 It has been found that the requirements determining acceptable limits for ethylene oxide (EO) residuals specified in ISO 10993-7 are inadequate for devices in contact with highly sensitive tissues, such as those of the eye. Reference [3] provides additional guidance to the application of ISO 10993-7. In a special category for intra-ocular devices an EO limit for an intra-ocular lens has been set at 0,5 μg per day, not to exceed 1,25 μg in total. Limits for other intra-ocular devices can be pro-rated on the basis of the mass of the device.

The EO limit for an OVD shall be 60 μg per ml. (See [3] for further information on procedures for measurement.)

NOTE 2 The TIR does not contain requirements for ethylene chlorohydrin (ECH) limits. It is anticipated that a future version of this International Standard include an ECH limit for intra-ocular devices containing chloride that is four times greater than the limit for EO. This should be taken into account when evaluating the biological safety of an OVD and for compliance with a future version of a standard.

For products sterilized by radiation, the requirements of ISO 11137 shall apply.

NOTE 3 It is recognized that many OVDs contain high molecular mass polymers that are heat-labile and that the rheological properties of the product can be adversely influenced by moist heat sterilization. When a product cannot be terminally sterilized by moist heat, aseptic processing is an accepted alternative.

For OVDs that are not terminally sterilized, but aseptically processed, the requirements specified in ISO 13408-1 shall apply. Compliance with this International Standard shall be demonstrated by a validated media-fill study with a contamination rate limit of 10^{-3}.

NOTE 4 ISO 13408-1 specifies the general requirements for, and offers guidance on processes, programmes and procedures for the validation and control of aseptically-processed health care products. That International Standard particularly applies, but is not limited to, the processing of aqueous solutions and is thus relevant to the preparation of OVDs. Future parts of this International Standard will address specialized processes, such as filtration and lyophilization.

8 Product stability

The manufacturer shall define and state the shelf life of the OVD and its delivery system. Real time or validated, accelerated shelf-life testing, at temperatures not to exceed 45 °C, shall be performed to demonstrate that the essential characteristics for safe and effective performance of the finished product and delivery system remain within specified limits 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 and sterility, plus any other factors identified by risk analysis as crucial to safe use of the product.

Changes in the composition of the product, source materials, material suppliers manufacturing conditions, including the sterilization process, package design or package materials may affect the shelf life of the product. The established shelf life of the OVD shall be revalidated if a risk assessment identifies any change in manufacture that may affect the stability 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 use as intended.

Chemical and physical compatibility of the OVD and 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 and ISO 14630 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 EN 868-1 shall apply.

11 Information to be supplied by the manufacturer

The general requirements for information provided by the manufacturer with 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, the requirements of ISO 15223 shall 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 be provided on a self-adhesive label.

A package insert shall be included within the storage container, provided in such a way that it can be removed and read without damaging the sterile barrier.

The minimum information required on the storage container, package insert, sterile barrier and primary container is listed in Table 1.

Table 1 — Information to be supplied by the manufacturer

Point of information	Storage container	Package insert	Sterile barrier	Primary container
Name of the manufacturer or authorized representative	X	X	X	
Address of the manufacturer	X	X		
Trade name of product	X	X	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; molecular mass distribution; pH; osmolality		X		
Graphical presentation of the rheological profile, plotting the log viscosity (mPa·s) vs log shear (s^{-1}) over the range defined in 5.3.2		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 if necessary		X		
Warnings and precautions		X		
Statement that the contents are for single use only	X	X	X	
Statement “Sterile” and the method(s) of sterilization of the product and primary container	X	X	X	
Statement “Do not use if sterile barrier is breached”			X	
Expiration date	X		X	X
Batch number preceded by the word "LOT"	X		X	X

NOTE The batch number, expiration date and sterility data need not be provided on the sterile barrier if it is transparent and the required information can be read directly from the primary container without breaching the seal.

Annex A
(normative)

Intra-ocular implantation test

A.1 General

An implantation test assesses the local effects on living tissue, at both the gross and microscopic levels, of a sample of product surgically implanted in a site appropriate to the intended application, route and duration of contact. The general requirements for implantation tests outlined in ISO 10993-6 provide guidance.

Either the anterior chamber or vitreous cavity of a suitable test animal can be used as the implantation site.

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

A.2 Test procedure

An appropriate volume of the OVD is injected into either the anterior chamber or anterior vitreous cavity of the eye. Prior to injection of the test or control OVD, a volume of aqueous or vitreous humour equal to the volume of OVD to be injected may be aspirated from the relevant chamber.

Implantation is achieved with the minimum possible trauma to the eye so that physical damage to ocular tissues does not mask any injury resulting from exposure to the test or control material.

The control treatment utilizes another well-documented OVD, widely marketed for at least the last five years, and approved for the same use. The control material is implanted into the same site in the opposite eye at the same time.

NOTE A bilateral implantation is preferred, but unilateral implantation is permitted, if local regulations so require.

A.3 Test evaluation

The post-injection inflammatory response is monitored and graded according to a standardized ocular scoring system for slit-lamp biomicroscopic examination at 4 h to 6 h, 24 h, 48 h, 72 h and one week post-injection. Additional evaluation times may be added depending on the duration of the implantation study. All test results shall be documented.

Annex B
(normative)

Test for intra-ocular pressure

B.1 General

A transient increase in the intra-ocular pressure (IOP) may 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 may cause pain or discomfort and result in permanent damage to the eye.This test monitors the rise in the intra-ocular pressure following replacement of aqeous 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 the OVD as possible prior to closure of the incision. Thus the duration and magnitude of the change in IOP during preclinical testing may 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.

B.2 Test procedure

A volume of aqueous humour equivalent to 25 % of the volume of the anterior chamber of a suitable test animal is removed and replaced by an equal volume of the OVD The control treatment utilizes the same volume of another well-documented OVD, widely marketed for at least the last five years, and approved for the same use. The control material is implanted into the opposite eye, at the same time.

NOTE A bilateral implantation is preferred, since the number of animals required to ensure validity of the test is less than for unilateral injection. However unilateral injection is permitted if local regulations so require.

B.3 Test evaluation

The intra-ocular pressure is measured by applanation tonometry, pre-operatively and at the following times post-operatively:

— 1 h ± 15 min

— 2 h ± 30 min

— 4 h ± 1 h

— 8 h ± 2 h

— 12 h ± 2 h

— 24 h ± 4 h

— 1 week ± 2 d

— 1 month ± 7 d

The speed at which the intra-ocular pressure rises and the duration of its elevation vary considerably with the nature of the OVD and its viscosity. Once a pattern has been established, the times at which the intra-ocular pressure is measured may 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. All test results shall be documented.

Annex C
(informative)

Microscopic assay for particulate matter

C.1 General

This procedure describes the proper sample preparation for quantitation of particulate matter in OVDs based on the USP method <788>[2]. Because of the viscosity of OVDs, samples shall be diluted prior to filtration and microscopic examination.

Alternative methods for blank determination and sample preparation may be used. It is important to thoroughly evaluate any changes which may affect particulate counts.

C.2 Terms and definitions

C.2.1
GFOV
graticule field of view (area within the large circle)

C.2.2
reference circle
10 μm and 25 μm circles used to measure the equivalent diameter of a particle

C.2.3
equivalent area diameter
diameter of a circle with area equal to that of the particle

C.3 Apparatus

C.3.1 Microscope and related accessories

C.3.1.1 Microscope, compound binocular, with the objective and eyepiece combination of lenses giving a magnification of 100 × ± 10 ×. The objective should be of 10 × nominal magnification, a planar achromat or better in quality, with a minimum numerical aperture of 0,25. In addition the object should be compatible with episcopic illumination. One eyepiece shall be designed to accept and focus an eyepiece graticule. The microscope should have a mechanical stage capable of holding and traversing the entire filtration area of a 25 mm or 47 mm membrane filter.

C.3.1.2 Two illuminators (both may be equipped with blue daylight filters to decrease operator fatigue):

— **external illuminator**, adjustable to give incident oblique illumination at an angle of 10° to 20° to the horizontal;

— **episcopic brightfield illuminator**, internal to the microscope.

C.3.1.3 Improved Microscopic Assay (IMA) graticule, matched to microscope model objective and eyepiece such that the sizing circles are with 2 % of 10 μm and 25 μm at the plane of the stage. An alternative graticulate may be used, provided that it can be adequately calibrated.

C.3.1.4 Micrometer, NIST certified stage micrometer, graduated in 10 μm increments (100 divisions/mm).

C.3.2 Filtration apparatus and supplies

C.3.2.1 Filtration funnel, suitable for the volume to be tested, having a minimum diameter of about 21 mm. The funnel should be plastic, glass or stainless steel.

C.3.2.2 Gelman filter funnel, 25 mm/200 ml (part # 4203).

C.3.2.3 Millipore filter funnel, 47 mm/300 ml (part # XX10 047 24).

C.3.2.4 Filtration diffuser, in the form of a filter support made of stainless steel screen or sintered glass.

C.3.2.5 Suitable vacuum source.

C.3.2.6 Forceps, blunt-tipped.

C.3.2.7 Solvent dispensers, with filter jet gun, capable of delivering solvents filtered at 1,2 μm or finer retention rating at a range of pressures from 689,5 mbar to 5 561 mbar (10 psi to 80 psi).

C.3.2.8 Membrane filters, 25 mm or 47 mm, gridded or nongridded, black or dark grey, mixed cellulose ester, with a pore size of 0,8 μm.

C.3.2.9 Petri slide.

C.3.2.10 Laminar-flow hood, equipped with high-efficiency particulate air (HEPA), filtered air having not more than 100 particles (0,5 μm or greater) per cubic foot (≅ 3 531 particles/m^3).

C.3.2.11 Particle-free gloves.

C.3.2.12 Non-shedding sleeves.

C.3.2.13 De-ionized water.

C.3.2.14 Isopropanol.

C.3.2.15 600 ml beaker, with Teflon stirbar.

C.4 Samples

C.4.1 Initial test: Test a pool of the entire contents of ten units of the OVD.

C.4.2 Retest: Test a pool of the entire contents of 20 units of the OVD.

C.5 Test procedure

C.5.1 General

Prior to use, the relative error of the IMA graticule shall be measured and certified to conform to USP specifications.

C.5.2 Microscope setup

Turn on both illuminators (C.3.1.2) (external auxiliary incident oblique illuminator and the internal episcopic brightfield illuminator).

Select 10 × objective and adjust interpupillary distance until a single image is obtained.

Focus right eyepiece on graticule (C.3.1.3) (specimen in place) by defocussing the microscope (C.3.1.1) until a bright field is obtained with no specimen detail visible. Then close the left eye and rotate the right eyepiece dioptre ring until the image of the graticule is in sharp focus.

Focus microscope on some fine detail in the specimen.

Focus the left eyepiece to be parfocal by closing the right eye and rotating the left eyepiece dioptre ring until the specimen fine detail is in sharp focus.

Open both eyes; the specimen image should be in sharp focus in both eyes.

Adjust the auxiliary incident oblique illuminator at a height so that the angle of incident light is 10° to 20° to the horizontal; particles on a membrane filter (C.3.2.8) should have distinct dark shadows.

Adjust the internal episcopic brightfield illuminator by fully opening the field and aperture diaphragms. Then centre the lamp filament and focus the microscope on a filter containing particles. Finally adjust the intensity of the reflected illumination until particles are clearly visible and show pronounced shadows.

Adjust the intensity of the episcopic illumination to the lowest setting, then increase the intensity of the episcopic illumination until shadows cast by particles show the least perceptible decrease in contrast.

C.5.3 Preparation of filtration apparatus

Don particle-free gloves (C.3.2.11) and non-shedding sleeves (C.3.2.12), rinse hands with 0,22 μm filtered de-ionized water (C.3.2.13).

Cleanse the 600 ml beaker and stirbar (C.3.2.15), filtration funnel (C.3.2.1), base and diffuser by hand washing in hot, nonionic detergent solution. Rinse in flowing hot tap water followed by a pressure rinse of filtered de-ionized water.

Transfer the washed apparatus and other required equipment to a hood (C.3.2.10) protected by HEPA filtered air.

Rinse the exterior and interior surfaces of the filtration apparatus with a pressurized rinse of 1,2 μm filtered isopropanol.

Rinse the exterior and interior surfaces of the filtration apparatus and other required equipment with a final rinse of 1,2 μm filtered de-ionized water.

Use forceps (C.3.2.6) and a low-pressure stream of filtered de-ionized water to thoroughly wash both sides of the filter by starting at the top and sweeping back and forth to the bottom, then centre the cleaned filter on top of the diffuser base.

Complete the assembly by placing the filtration funnel on top of the prepared funnel base with filter and then securing.

C.5.4 Test environment (blank determination)

Using the solvent dispenser (C.3.2.7), fill the 600 ml beaker, including stir bar with approximately 500 ml of filtered DI water.

Pour entire contents of beaker into filtration assembly.