BS EN ISO 16671:2015

BSI Standards Publication

Ophthalmic implants — Irrigating solutions for ophthalmic surgery (ISO 16671:2015)

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National foreword

This British Standard is the UK implementation of EN ISO 16671:2015. It supersedes BS EN ISO 16671:2003 which is withdrawn.

The UK participation in its preparation was entrusted to Technical Committee CH/172/7, Eye implants.

A list of organizations represented on this committee can be obtained on request to its secretary.

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

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This European Standard was approved by CEN on 7 May 2015.

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This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the CEN-CENELEC Management Centre has the same status as the official versions.

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EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

CEN-CENELEC Management Centre: Avenue Marnix 17, B-1000 Brussels

European foreword

This document (EN ISO 16671:2015) has been prepared by Technical Committee ISO/TC 172 “Optics and photonics” in collaboration with Technical Committee CEN/TC 170 “Ophthalmic optics” the secretariat of which is held by DIN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by February 2016, and conflicting national standards shall be withdrawn at the latest by February 2016.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN [and/or CENELEC] shall not be held responsible for identifying any or all such patent rights.

This document supersedes EN ISO 16671:2003.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive(s).

For relationship with EU Directive(s), see informative Annex ZA, which is an integral part of this document.

The following referenced documents are indispensable for the application of this document. For undated references, the latest edition of the referenced document (including any amendments) applies. For dated references, only the edition cited applies. However, for any use of this standard ‘within the meaning of Annex ZA’, the user should always check that any referenced document has not been superseded and that its relevant contents can still be considered the generally acknowledged state-of-art.

When an IEC or ISO standard is referred to in the ISO standard text, this shall be understood as a normative reference to the corresponding EN standard, if available, and otherwise to the dated version of the ISO or IEC standard, as listed below.

NOTE The way in which these referenced documents are cited in normative requirements determines the extent (in whole or in part) to which they apply.

Table — Correlation between normative references and dated EN and ISO standards

Normative references as listed in Clause 2 of the ISO standard	Equivalent dated standard	
	EN	ISO
ISO 10993-1:2009	EN ISO 10993-1:2009 + AC:2010	ISO 10993-1:2009 + Cor 1:2010
ISO 10993-2:2006	EN ISO 10993-2:2006	ISO 10993-2:2006
ISO 11607-1:2006	EN ISO 11607-1:2009 + A1:2014	ISO 11607-1:2006 + Amd 1:2014
ISO 13408-1:2008 + Amd 1:2013	EN ISO 13408-1:2011 + A1:2013	ISO 13408-1:2008 + Amd 1:2013
ISO 14155:2011	EN ISO 14155:2011 + AC:2011	ISO 14155:2011 + Cor 1:2011
ISO 14630:2012	EN ISO 14630:2012	ISO 14630:2012
ISO 14971:2007	EN ISO 14971:2012	ISO 14971:2007
ISO 15223-1:2012	EN ISO 15223-1:2012	ISO 15223-1:2012
ISO 22442-1:2007	EN ISO 22442-1:2007	ISO 22442-1:2007
EN 1041:2008 + A1:2013	EN 1041:2008 + A1:2013	—

According to the CEN-CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Endorsement notice

The text of ISO 16671:2015 has been approved by CEN as EN ISO 16671:2015 without any modification.

Annex ZA
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 93/42/EEC

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to the Essential Requirements of Directive 93/42/EEC on medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the normative clauses of this standard given in Table ZA.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA Regulations.

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with Directive 93/42/EEC, as amended by 2007/47/EC. This means that risks have to be reduced 'as far as possible', 'to a minimum', 'to the lowest possible level', 'minimized' or 'removed', according to the wording of the corresponding essential requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with essential requirements 1, 2, 5, 6, 7, 8, 9, 11 and 12 of the Directive.

NOTE 3 This Annex ZA is based on normative references according to the table of references in the European foreword, replacing the references in the core text.

NOTE 4 When an Essential Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

Table ZA.1 — Correspondence between this European Standard and Directive 93/42/EEC

Clause(s)/subclause(s) of this European Standard	Essential Requirements (ERs) of Directive 93/42/EEC	Qualifying remarks/notes
5.4.3 & 5.4.6, 7 in respect of EO contamination only.	7.2	
6.3	7.3	
7	7.6	
7	8.1	
5.2, 5.4.3, 6.2.1	8.2	
9, 10 in respect of exposure to environmental elements	8.3	
7 in respect of EO sterilization	8.4	
10	13.1	
10	13.2	
10	13.3 a), b), c), d), e), f), i), j), k), m)	

10	13.4	
10	13.6 a), b), e), f), g)	

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this standard.

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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.

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 on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

This second edition cancels and replaces the first edition (ISO 16671:2003), which has been technically revised.

INTERNATIONAL STANDARD ISO 16671:2015(E)

Ophthalmic implants — Irrigating solutions for ophthalmic surgery

1 Scope

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

This International Standard applies to ophthalmic irrigating solutions (OIS), used during ophthalmic surgery. These solutions do not provide any primary immunological, pharmacological, or metabolic function.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-1:2009, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-2:2006, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 11607-1:2006, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 13408-1:2008 + Amd.1:2013, *Aseptic processing of health care products — Part 1: General requirements*

ISO 14155:2011, *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14630:2012, *Non-active surgical implants — General requirements*

ISO 14971:2007, *Medical devices — Application of risk management to medical devices*

ISO 15223-1:2012, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*

ISO 22442-1:2007, *Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management*

EN 1041:2008 + A1:2013, *Information supplied by the manufacturer of medical devices*

3 Terms and definitions

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

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

3.2
ophthalmic irrigating solution
OIS
aqueous solution that is physiologically compatible with the intraocular environment and functions solely by mechanical means

Note 1 to entry: It does not provide any primary immunological, pharmacological, or metabolic function.

3.3
primary container
container providing mechanical and microbiological protection of the content

3.4
sterile barrier system
minimum package that prevents ingress of microorganisms and allows aseptic presentation of the product at the point of use

[SOURCE: ISO/TS 11139:2006, 2.44]

3.5
storage container
part of the packaging intended to protect the device during transport and storage, containing the sterile barrier

4 Intended performance

The general requirements for the intended performance of non-active surgical implants specified in ISO 14630 shall apply.

This International Standard describes non-solid medical devices which are compatible with the ocular environment, used to rinse the ocular surface or intraocular spaces and structures.

The manufacturer shall describe and document the functional characteristics of the OIS in terms of its chemical composition and physical properties, the intended surgical applications, the conditions of use and effects upon ocular tissues, with particular regard to safety.

The intended performance shall be determined taking into account published standards, published clinical and scientific literature, validated test results, pre-clinical and clinical evaluation, and clinical investigations.

5 Design attributes

5.1 General

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

All testing requirements specified below shall be performed with finished, sterilized product, ready for release. Any analytical methods utilized shall be validated.

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

5.2 Concentration of the components

The identification of potentially hazardous chemical or biological contaminants shall be determined by a risk analysis. For raw materials of biological origin, these impurities can include proteins, nucleic acids, or other biological materials. Contaminants of the finished product derived from the source materials or from the manufacturing process, such as cross-linking agents and antioxidants, that are

potentially hazardous to the tissues of the eye, or systemically, shall be identified, whenever possible, and their concentration in the finished products be reported.

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

The concentration of each component material in the finished product shall be determined and documented, and the concentration of each component shall be expressed 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 and documented. Wherever possible, components shall comply with stated compendial standards.

5.3 Water used

The purity of the water used shall be Water for Injections (see Reference [3]).

5.4 Characterization of the finished product

5.4.1 General

The manufacturer shall describe and document the physical characteristics that affect the performance of the OIS efficacy in ophthalmic surgery.

These physical properties should be measured at the conditions expected and relevant at the time of use.

5.4.2 pH and buffering capacity

The pH of the finished product shall be determined and documented with a calibrated pH meter at 25 °C ± 2 °C.

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.

A suitable method shall be used to determine buffering capacity. An example of a suitable method is given in Annex A. The products shall be classified as in Table 1.

Table 1 — Classification according to pH and buffering capacity

Group	Base buffering capacity (mol/l per pH)	Acid buffering capacity (mol/l per pH)	pH range
Essentially unbuffered	<0,000 5	<0,004	6,5 to 8,5
Moderately buffered	0,000 5 to 0,005	0,004 to 0,04	6,7 to 8,2
Buffered	>0,005	>0,04	7,2 to 7,6

5.4.3 Chemical and biological contaminants

Potentially hazardous chemical or biological contaminants and impurities 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 that are potentially hazardous either to the tissues of the eye or systemically, shall be identified, whenever possible, and their concentrations in the finished product reported.

Contaminants shall be determined using standard analytical methods when available, and all methods shall be described. Limits for identified contaminants shall be set and included. Testing for the biological

effects of these contaminants during evaluation of biological safety may be required if the risk analysis determines it necessary.

5.4.4 Osmolality

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

5.4.5 Spectral transmittance

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

5.4.6 Particulates

5.4.6.1 General

There is a potential for adverse events to take place as a result of particles of certain sizes and characteristics in the finished product.

Particulate contamination of OIS consists of extraneous, mobile undissolved particles other than gas bubbles, unintentionally present in the solutions.

A risk assessment shall evaluate the potential for contamination by, or formation of, particulates in the product during manufacture as well as the conditions expected during transport and storage, and during use of the product and the hazards associated with these.

In multi-component products (i.e. where there are two or more separate parts of a product that have to be mixed prior to use) tests shall be applied to the mixed product.

5.4.6.2 Visible particles

The OIS shall be essentially free of visible particles. The method described in Annex B shall be used to determine this.

5.4.6.3 Sub-visible particles

Either the light obscuration test method given in Annex C or the microscopic test method given in Annex D shall be used to determine the sub-visible particulate level for OIS with the corresponding limits of each method as given below.

The following limits shall apply for the light obscuration test method described in Annex C:

— not more than 50 particles equal to or greater than 10 µm per ml of OIS;

— not more than 5 particles equal to or greater than 25 µm per ml of OIS;

— not more than 2 particles equal to or greater than 50 µm per ml of OIS.

The following limits shall apply for the microscopic test method of Annex D:

— not more than 25 particles equal to or greater than 10 µm per ml of OIS;

— not more than 2,5 particles equal to or greater than 25 µm per ml of OIS;

— not more than 1 particle equal to or greater than 50 µm per ml of OIS.

NOTE The light obscuration test method of Annex C is based on light blockage. Amorphous, semi-liquid or otherwise morphologically indistinct materials contribute to light obscuration and therefore contribute to the particle count. In the microscopic test method of Annex D, amorphous, semi-liquid or otherwise morphologically indistinct materials appear as stain or discolouration on the surface of the membrane filter, and are not counted as particles. To compensate for this difference, the limits for the microscopic test method are one half those for the light obscuration method.

6 Design evaluation

6.1 General

The OIS shall be evaluated to demonstrate that the intended performance is achieved. The requirements for evaluation of non-active implants outlined in ISO 14630 shall apply.

6.2 Preclinical evaluation of biological safety

6.2.1 General

The procedure for evaluation of biological safety of an OIS 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 OIS.

For OIS containing material of animal origin the risk analysis and management requirements outlined in ISO 22442-1 shall apply.

During the risk assessment the manufacturer should take into account the interaction with other ophthalmic products.

For all OIS the requirements for evaluation of biological safety specified in ISO 10993-1 shall apply.

NOTE 1 Based upon the typical clinical applications, OIS are categorized as “Implant devices, tissue/bone”. The tests for this and other categories of devices identified in ISO 10993-1:2009, Table A.1, are for guidance only. They do not represent maximum or minimum test requirements.

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

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 OIS.

6.2.2 Bacterial endotoxins test

The OIS shall be evaluated for the presence of bacterial endotoxins using the Limulus Amoebocyte Lysate (LAL) test, in accordance with applicable pharmacopoeias or an equivalent validated test procedure. Any product that exceeds a bacterial endotoxin limit of 0,5 Endotoxin Units (EU) per ml fails the test.

6.2.3 Intraocular irritation and inflammation

If the risk assessment indicates that it is necessary to undertake tests for intraocular irritation, inflammation, intraocular pressure and other local events, such tests shall be conducted in a suitable animal model in accordance with Annex E. The choice of animal species shall be justified and documented. The animal welfare requirements as described in ISO 10993-2 shall apply.

The animal testing shall mirror the intended clinical use as closely as possible.

The study design should assess the intraoperative and postoperative ocular irritation and inflammation of the ophthalmic surgery, with comparative use of the OIS under evaluation and a control OIS that has already been proven to be non-irritating and non-inflammatory in clinical use for five years. The

volume of OIS used shall simulate the intended use, accounting for ocular volume differences between the human eye and that of the animal model.

The post-surgical irritation and inflammation shall be monitored and graded in accordance with Annex E. Based upon the risk management plan, appropriate evaluation at appropriate times can include corneal pachymetry and slit lamp bio microscopy. All adverse effects shall be documented.

The OIS shall show ocular irritation and inflammation results less than or equal to the control OIS, or it shall be excluded from clinical use.

6.3 Clinical evaluation

If clinical evaluation and risk assessment identify the need for a clinical investigation, Annex F shall be considered. In addition, the general requirements concerning clinical investigations of medical devices for human subjects specified in ISO 14155 shall apply.

7 Sterilization

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

Ethylene oxide shall not be used to sterilize the OIS solution and, unless justified, not to sterilize the primary container either. In case of justification and use for the latter, ethylene oxide and related contaminants can diffuse into the solution, for which the following limits shall then apply:

— ethylene oxide: less than 20 µg/ml

— ethylene chlorohydrin: less than 100 µg/ml

NOTE 1 It has been found that the requirements determining acceptable limits for ethylene oxide residuals specified in ISO 10993-7 are inadequate for devices in contact with highly sensitive tissues, such as those of the eye. For this case AAMI TIR No. 19 provides additional guidance to the application of ISO 10993-7.

For OIS that are not terminally sterilized, but aseptically processed, ISO 13408-1 shall apply. The process shall be demonstrated to comply with a contamination rate limit of 10^{-3} by a validated media fill study.

NOTE 2 ISO 13408-1 specifies the general requirements for, and offers guidance on, processes, programmes, and procedures for the validation and control of aseptically processed healthcare products. ISO 13408-1 particularly applies, but is not limited to, the processing of aqueous solutions, and is thus relevant to the preparation of OIS. Future parts of that International Standard will address specialized processes, such as filtration and lyophilisation.

8 Product stability

The manufacturer shall define and state the shelf-life of the product. Real time or accelerated shelf-life testing shall be performed to demonstrate that the finished product remains within specifications for a period of the labelled shelf-life under expected conditions of transport and storage. Real time testing shall reflect normal storage temperature and temperature fluctuations and the relative humidity shall be controlled within 60 % ± 20 %. In accelerated testing the temperature shall not exceed 45 °C and the relative humidity shall be at least 40 %. The parameters that shall be followed during shelf-life studies are the pH, osmolality, particulate levels, colour and clarity, plus any other factors identified by risk analysis as crucial to safe use of the product.

The established shelf-life of the OIS shall be re-validated if a risk assessment identifies any change in manufacture that can affect the stability of the product.

NOTE Changes in the composition of the product, source materials, material suppliers, manufacturing conditions, including the sterilization process, package design or package materials, can affect the shelf-life of the product.

9 Packaging

9.1 Protection from damage during storage and transport

The packaging requirements for medical devices outlined in ISO 11607-1 and ISO 14630 shall apply.

9.2 Maintenance of sterility in transit

OIS shall be packaged in such a way that they remain sterile during transport and storage. The sterile packaging requirements outlined in ISO 11607-1 shall apply.

10 Information supplied by the manufacturer

The general requirements for information provided by the manufacturer of medical devices specified in EN 1041:2008 + A1:2013 shall apply together with the following particular requirements. Symbols may be used instead of text, where appropriate. When symbols are used, the requirements of ISO 15223-1 shall apply.

The labelling shall contain information on whether the OIS is buffered and if so give information on the buffer type and capacity.

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 2.

Whenever possible, symbols according to ISO 15223-1 should be used.

Table 2 — Information supplied by the manufacturer

Information	Storage container	Package insert	Sterile barrier (if present)	Primary container
Name of the manufacturer or authorized representative	×	×	×[a]	×
Address of the manufacturer or authorized representative	×	×		
Trade name of product	×	×	×[a]	×
Brief description of the chemical composition of the product and the volume supplied	×	×		
Conditions for storage	×	×		
Indications for use		×		
Contra-indications for use		×		
Warnings, precautions and known interactions with other ocular products		×		
Statement that the contents are for single use only	×	×	×	×

[a] The name of the manufacturer or authorized representative, trade name of product, batch number, expiration date and sterility statement need to be provided on the sterile barrier only if it is not transparent and the required information cannot be read directly from the primary container without breaching the seal.

Table 2 *(continued)*

Information	Storage container	Package insert	Sterile barrier (if present)	Primary container
Statement “Sterile” and the method(s) of sterilization of the product and primary container	×	×	×[a]	×
Statement “Do not use if sterile barrier is breached”		×	×	×
Expiration date	×		×[a]	×
Information on whether the OIS is buffered and if so information on the buffer type and capacity		×		
Buffering category (see Table 1)		×		
Batch number preceded by the word “LOT”	×		×[a]	×

[a] The name of the manufacturer or authorized representative, trade name of product, batch number, expiration date and sterility statement need to be provided on the sterile barrier only if it is not transparent and the required information cannot be read directly from the primary container without breaching the seal.

Annex A
(informative)

Example of a suitable method for pH measurement and buffer capacity determination

A.1 General

This Annex gives an example of a suitable method for pH measurement and buffer capacity determination.

A.2 Equipment and reagents

A.2.1 **10-ml burette**, capable of accurately delivering titrant in 0,1 ml increments.

A.2.2 **Stirring plate**.

A.2.3 **Stirring bar**.

A.2.4 **Sodium hydroxide**, 0,005 N volumetric standard.

A.2.5 **Hydrochloric acid**, 0,01 N volumetric standard.

A.3 Method

Sodium hydroxide and hydrochloric acid solutions are prepared and standardized using compendia methods and diluted to the desired concentration prior to use.

To a flask add 25 ml (V_s) of sample and with a calibrated glass pH electrode measure the pH (pH_1). Using the 10 ml burette (A.2.1), add sufficient HCl volumetric standard titrant to give a pH change of 1,0 pH unit (pH_2). Record the volume (V_t) of titrant added. Repeat with a second aliquot of sample using the NaOH volumetric standard as the titrant.

Calculate the buffer capacity using Formula (A.1):

$$\frac{V_t \times N}{V_s \times (pH_2 - pH_1)} \quad \text{(A.1)}$$

where N is the normality of the titrant in question.

Report both buffer capacity against acid and buffer capacity against base in units of mol/l per pH.

For solutions with significant buffer capacity, the sample volume may be adjusted to give a suitable volume of titrant.

Annex B
(normative)

Particulate contamination: Visible particulates

B.1 General

The test is intended to provide a simple procedure for the visual assessment of the OIS as regards visible particles.

B.2 Apparatus

The apparatus consists of a viewing station comprising:

B.2.1 **a mat black panel**, of appropriate size, held in a vertical position.

B.2.2 **a non-glare white panel**, of appropriate size, held in a vertical position next to the black panel.

B.2.3 **an adjustable lamp holder**, fitted with a suitable light source and a suitable light diffuser.

Any appropriate visible light source is acceptable, provided that the intensity of the illumination at the viewing point is greater than 2 000 lx. Higher illumination is preferable for containers of coloured glass and plastic.

B.3 Method

Remove any adherent labels from the container and wash and dry the outside. Gently swirl the container ensuring that air bubbles are not introduced, and observe and count visible particulates for 5 s in front of the white panel. Repeat the procedure in front of the black panel. Document the sum of the counts for both the white and the black panels as the particulate contamination level of the OIS.

Annex C
(informative)

Light obscuration test method for particulate contamination: sub-visible particles

C.1 General

This Annex describes a light obscuration test method for particulate contamination in the case of sub-visible particles.

C.2 Apparatus

C.2.1 General

The apparatus is an electronic, liquid-borne particle counting system that uses a light-obscuration sensor with a suitable sample feeding system. A variety of this type of devices is commercially available. The operator needs to ensure that the operating parameters of the instrumentation are appropriate to the required accuracy and precision of the test result. The operator needs to be adequately trained.

C.2.2 Sensor concentration limits

The apparatus used shall have a concentration limit to the maximum number of particles per ml identified, which is greater than the concentration of the particles expected in the test specimen. The vendor-certified concentration limit is specified as that count level at which coincidence counts due to simultaneous presence of two or more particles in the sensor view volume comprise less than 10 % of the counts collected for 10 µm particles.

C.2.3 Sensor dynamic range

The dynamic range of the apparatus used (range of size of particles that can be accurately sized and counted) shall include the smallest particle size to be enumerated in the test article.

C.2.4 Particle-free water

Water to be used is passed through a filter having a porosity of 1,2 µm or finer.

C.2.5 Calibration

Calibrate the apparatus using dispersions of suitable spherical particles of known sizes between 10 µm and 25 µm in mono disperse suspensions. Disperse these standard suspensions in particle-free water to obtain an appropriate concentration of particulates. Take care to avoid aggregation of particles during dispersion.

C.3 Method

C.3.1 General precautions

Carry out the test under conditions of limited particulate contamination, preferably in a laminar-flow cabinet.

Very carefully wash the glassware and filtration equipment to be used, except for the membrane filters, with a warm detergent solution and rinse with abundant amounts of particle-free water to remove all traces of detergent. Immediately before use, rinse the equipment from top to bottom, outside and then inside, with particle-free water.

Take care not to introduce air bubbles into the prepared sample to be examined, especially when fractions of the prepared sample are being transferred to the container in which the determination is to be carried out.

C.3.2 Control test

In order to check that the environment is suitable for the test, that the glassware is properly cleaned and that the water to be used is particle-free, carry out the following test. Determine the particulate contamination of 5 samples of particle-free water each of 5 ml, in accordance with the method described below. If the number of particles of 10 µm or greater exceeds 25 for the combined 25 ml, the precautions taken for the test are not sufficient. Repeat the preparatory steps until the control test is passed.

C.3.3 Procedure

Multipack OIS, which require mixing prior to use, are mixed as directed on the labelling, thus ensuring thorough mixing of the separate components.

Mix the contents of the sample by slowly inverting the container 25 times. If necessary, carefully remove the sealing closure. Clean the outer surfaces of the container opening using a jet of particle-free water and remove the closure, avoiding contamination of the contents. Eliminate gas bubbles by allowing standing for 2 min.

Remove four portions, each of 5 ml ± 0,2 ml and count the number of particles equal to or greater than 10 µm and 25 µm. Disregard the result obtained for the first portion, and calculate and document the average number of particles for the prepared sample under examination.

Annex D
(informative)

Microscopic test method for particulate contamination: sub-visible particles

D.1 General

This test enumerates sub-visible, essentially solid, particulate matter in OIS products on a per-volume basis, after collection on a micro porous membrane filter. In performing the microscopic assay, no attempt is made to enumerate amorphous, semi liquid or otherwise morphologically indistinct materials that have the appearance of a stain or discolouration on the membrane surface. Such materials show little or no surface relief and present a gelatinous or film-like appearance.

D.2 Test apparatus

D.2.1 Microscope

Use a compound binocular microscope that corrects for changes in interpupillary distance by maintaining a constant tube length, and with an objective and eyepiece combination that provides a magnification of 100x ± 10x. The lens has 10x nominal magnification, a planar achromat or better in quality, with a minimum numerical aperture of 0,25. In addition, the lens is compatible with an episcopic illuminator attachment. The eyepieces have 10x magnification. In addition, one eyepiece is designed to accept and focus an eyepiece graticule. The microscope has a mechanical stage capable of holding and traversing the entire circular area of a 25 mm or 47 mm membrane filter.

D.2.2 Illuminators

Two illuminators are required. One is an external, focusable auxiliary illuminator adjustable to give incident oblique illumination at an angle of 10° to 20°. The other is an episcopic bright field illuminator built into the microscope. Both illuminators have sufficient capacity to provide a bright, even source of illumination and can be equipped with blue daylight filters to decrease operator fatigue during use.

D.2.3 Circular diameter graticule

Use a circular diameter graticule (see Figure D.1) matched to the microscope objective and eyepiece such that the sizing circles are within 2 % of the stated size at the plane of the stage.

The large circle divided by crosshairs into quadrants is designated the graticule field of view (GFOV). Transparent and black circles having 10 µm and 25 µm diameters at 100x are provided as comparison scales for particle sizing.

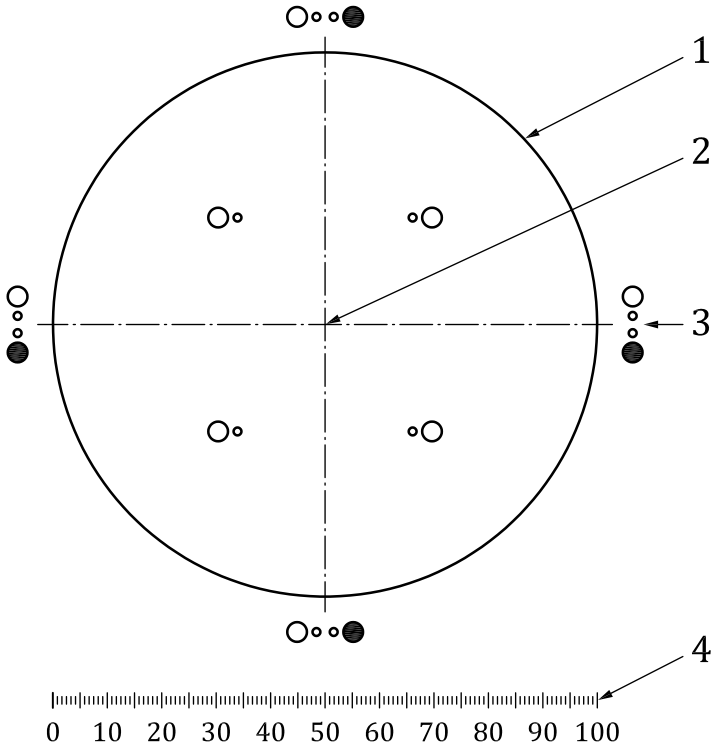
D.2.4 Micrometer

Use a stage micrometer, graduated in 10 µm increments and certified by an appropriate standardizing agency.

D.2.5 Filtration apparatus

Use a filter funnel suitable for the volume to be tested, having a minimum diameter of about 21 mm. The funnel is made of plastic, glass or stainless steel. Use a filter support made out of a stainless steel screen or sintered glass as the filtration diffuser. The filtration apparatus is equipped with a vacuum source, a solvent dispenser capable of delivering solvents filtered at 1,2 µm or finer retention rating at a range

of pressures from 70 kPa to 550 kPa, and membrane filters (25 mm or 47 mm non-gridded or gridded, black or dark grey, of suitable material compatible with the product, with a porosity of 1,0 µm or finer). Use blunt forceps to handle the membrane filters.



Key

1	GFOV circle	3	reference circles
2	cross hairs	4	linear scale

Figure D.1 — Circular diameter graticule

D.3 Method

D.3.1 Preparation details

D.3.1.1 Test environment

A laminar flow hood or other laminar airflow enclosure, having a capacity sufficient to envelope the area in which the analysis is prepared, with HEPA-filtered air having not more than 3 500 particles 0,5 µm or larger per m^3 (100 particles 0,5 µm or larger per ft^3). For the blank determination, supply a 50 ml volume of filtered-distilled or deionised water. Apply vacuum, and draw the entire volume of water through the membrane filter. Remove the membrane from the filter funnel base, and place atop a strip of double-sided tape in a Petri slide or Petri dish. After allowing the membrane to dry, examine it microscopically at a magnification of 100x. If not more than 20 particles 10 µm or larger in size and 5 particles 25 µm or larger are present within the filtration area, the background particle level is sufficiently low for performance of the microscopic assay.

Throughout this procedure, it is preferable to use powder-free gloves and thoroughly cleaned glassware and equipment. Prior to conducting the test, clean the work surfaces of the laminar flow enclosure with an appropriate solvent. Rinse glassware and equipment successively with a warm, residue-free solution of detergent, hot water, filtered-distilled or deionised water, and filtered isopropyl alcohol. Prior to use, filter the distilled or deionised water and the isopropyl alcohol with filters having a porosity of 1,2 µm or finer.

Perform the rinsing under the laminar flow enclosure equipped with HEPA filters. Allow the glassware and filtration apparatus to dry under the hood, upstream of all other operations. Preferably, the hood is located in a separate room that is supplied with filtered air and maintained under positive pressure with respect to the surrounding areas.

D.3.1.2 Microscope preparation

Place the auxiliary illuminator close to the microscope stage, focusing the illuminator to give a concentrated area of illumination on a filter membrane positioned on the microscope stage. Adjust the illuminator height so that the angle of incidence of the light is 10° to 20° to the horizontal. Use the internal episcopic bright field illuminator with fully-opened field and aperture diaphragms. Centre the lamp filament, and focus the microscope on a filter containing particles. Adjust the intensity of reflected illumination until particles are clearly visible and show pronounced shadows. Adjust the intensity of 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.

D.3.1.3 Operation of circular diameter graticule

The relative error of the graticule is initially determined with a certified stage micrometer. To accomplish this, align the graticule micrometer scale with the stage micrometer so that they are parallel. Compare the scales, using as large a number of graduations on each as possible. Read the number of graticule scale divisions, N_{GSD}, compared to stage micrometer divisions, N_{SMD}. Calculate the relative error using Formula (D.1):

$$100\frac{N_{GSD}-N_{SMD}}{N_{SMD}} \tag{D.1}$$

A relative error to within ±2 % is acceptable. The basic technique of measurement applied with the use of the circular diameter graticule is to mentally transform the image of each particle into a circle and then compare it to the 10 µm and 25 µm graticule reference circles. The sizing process is carried out without superimposing the particle on the reference circles; particles are not moved from their locations within the graticule field of view (the large circle) for comparison to the reference circles. Use the inner diameter of the clear graticule reference circles to size white and transparent particles. Use the outer diameter of the black opaque graticule reference circles to size dark particles. Rotate the graticule in the right-hand microscope eyepiece so that the linear scale is located at the bottom of the field of view, bringing the graticule into sharp focus by adjusting the right-hand eyepiece dioptre ring while viewing an out-of-focus specimen. Focus the microscope on a specimen, looking through the right-hand eyepiece only. Then, looking through the left-hand eyepiece, adjust the left-hand eyepiece dioptre to bring the specimen into sharp focus.

D.3.1.4 Preparation of filtration apparatus

Wash the filtration funnel, base, and diffuser in a solution of liquid detergent and hot water. Rinse with hot water. Apply a second rinse with filtered-distilled or deionised water using a pressurized jet of water over the entire exterior and interior surfaces of the filtration apparatus. Repeat the pressurized rinse procedure using filtered isopropyl alcohol. Finally, using the pressurized rinser, rinse the apparatus with filter distilled or deionised water.

Remove a membrane filter from its container, using ultra cleaned blunt forceps. Use a low pressurized stream of filtered purified water to wash both sides of the filter thoroughly by starting at the top and sweeping back and forth to the bottom. Assemble the cleaned filtration apparatus with the diffuser on top of the filtration base, placing the clean membrane filter on top of the diffuser. Place the funnel assembly on top of the filtration base, and lock it into place.

D.3.2 Test procedure

D.3.2.1 Test preparations

Prepare the test specimens in the following sequence. Outside of the laminar enclosure, remove outer closures, sealing bands, and any loose or shedding paper labels. Rinse the exteriors of the containers with filter distilled or deionised water as directed under D.3.1.1. Protect the containers from environmental contamination until analysed. Withdraw the contents of the containers under test in a manner least likely to generate particles that could enter the sample. Contents of containers with removable stoppers can be withdrawn directly by removing the closures. Sampling devices having a needle to penetrate the unit closure can also be used. Products packaged in flexible plastic containers can be sampled by cutting the medication or administration port tube, or a corner, from the unit using a suitably cleaned razor blade or scissors.

The number of test specimens should be adequate to provide a statistically sound assessment of whether a batch or other large group of units represented by the test specimens meets or exceeds the limits. If the volume in the container is less than 25 ml, test a solution pool of 10 or more units. Single small-volume units may be tested if the individual unit volume is 25 ml or more. For large-volume solutions, single units are tested.

For small-volume solutions containing a volume of 25 ml or more and tested singly and for large-volume solutions, the entire solution volume is tested. For large-volume solutions or for small-volume solutions where the individual unit volume is 25 ml or more, fewer than 10 single units may be tested, based on the definition of an appropriate sampling plan.

D.3.2.2 Product determination (liquid preparations)

Thoroughly mix the units to be tested by inverting them 20 times. Open the units in a manner consistent with the generation of the lowest possible numbers of background particles. For products less than 25 ml in volume, open and combine the contents of 10 or more units in a cleaned container. Filter large-volume units individually. Small-volume units having a volume of 25 ml or more may be filtered individually.

Transfer to the filtration funnel the total volume of a solution pool or of a single unit, as applicable, and apply vacuum. If the volume of solution to be filtered exceeds the volume of the filtration funnel, add, stepwise, a portion of the solution until the entire volume is filtered.

After the last addition of solution, begin rinsing the walls of the funnel by directing a low-pressure stream of filter distilled, or deionised water in a circular pattern along the walls of the funnel, and stop rinsing the funnel before the volume falls below about one-fourth of the fill level. Maintain the vacuum until all the liquid in the funnel is gone.

Remove the filtration funnel from the filtration base while maintaining vacuum, then turn the vacuum off and remove the filter membrane using blunt forceps. Place the filter in a Petri dish or similar container, secure it in place with double-sided tape and label with sample identification. Allow the filter to air-dry in the laminar-flow enclosure with the cover ajar.

D.3.3 Enumeration of particles

D.3.3.1 General

The microscopic test described in this section is flexible in that it can count, in particles per ml, specimens containing 1 particle per ml as well as those containing significantly higher numbers of particles per ml.

D.3.3.2 Total count procedure

In performance of a total count, the graticule field of view (GFOV) defined by the large circle of the graticule is ignored, and the vertical cross hair is used. Scan the entire membrane from right to left in

a path that adjoins but does not overlap the first scan path. Repeat this procedure, moving from left to right to left until all particles on the membrane are counted. Record the total number of particles that are 10 µm or larger and the number that are 25 µm or larger, calculate the particle count, in particles per ml, for the units tested using Formula (D.2):

$$\frac{P}{V} \tag{D.2}$$

where

P is the total number of particles counted;

V is the volume, in millilitres, of the solution tested.

Correct for the dilution factor, if applicable, to obtain the number of particles in the OIS as supplied.

Annex E
(normative)

Intraocular irrigation test

E.1 General

An irrigation 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.

The appropriate ocular irrigation site of a suitable test animal will be used as the irrigation site.

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

E.2 Test procedure

An appropriate volume of the OIS, relevant to its intended application(s), is irrigated through the appropriate ocular irrigation site.

Irrigation 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 OIS, widely marketed for at least the last five years, and approved for the same use.

E.3 Test evaluation

The post-injection inflammatory response is monitored and graded according to a standardized ocular scoring system for slit-lamp bio microscopic examination at 4 h to 6 h and bio microscopic examination and pachymetry at 24 h, 48 h, 72 h, and one week post-injection. IOP is measured at the times identified in the risk assessment. Additional evaluation times could be added depending on the duration of the implantation study. All test results are documented.

Annex F
(informative)

Clinical investigation

F.1 General

General requirements concerning clinical investigations of medical devices for human subjects are found in ISO 14155. Additional considerations are given in this Annex.

F.2 Clinical study design

A randomized controlled clinical investigation is performed. The objective of the study is to document the safety and performance of the new OIS when compared to a control. A risk analysis determines the primary hypothesis. Standard bio statistical formulae are used to calculate the required number of patients per treatment group based on the primary end point. The control treatment is a well-documented OIS, marketed widely for at least the last five years and approved for the same use. The number of patients lost to follow-up in each treatment group should be no greater than 10 % of the total number enrolled.

NOTE Investigations conducted at a single site could result, in certain countries, in additional requirements to satisfy regulations.

Each investigator performs the same type of intraocular surgical procedure on all patients using the same OIS. No fellow eyes are included in the clinical investigation. If a true masked study comparing the new OIS and the control cannot be achieved, an independent observer, who is unaware of which device has been used, performs the key efficacy measurements.

The duration of OIS use and volume used for each patient is documented.

Intraoperative and post-operative adverse events and adverse device effects are documented and reported in accordance with ISO 14155.

The patients are examined pre-operatively and at the following intervals post-operatively:

— 6 h ± 2 h (for IOP measurements only);

— 24 h ± 4 h;

— 1 week ± 2 days;

— 1 month ± 7 days;

— 3 months ± 2 weeks.

F.3 End points

F.3.1 Postoperative intraocular pressure change

If the risk assessment shows that monitoring intraocular pressure is required it is measured using a Goldmann-type applanation tonometer. The IOP is measured at all visits.

F.3.2 Corneal thickness

If the risk assessment shows that corneal thickness measurement is required these are performed pre-operatively and at 24 h, 1 week, and 1 month intervals post-operatively.

F.3.3 Postoperative inflammation

Post-operative inflammation is evaluated by slit-lamp bio microscopy and graded clinically at all visits except at 6 h.

F.3.4 Endothelial cell counts

If the risk assessment shows that endothelial cell counts are required these are performed pre-operatively and at 3 months post-operatively.

F.3.5 Visual acuity

Best corrected visual acuity is measured pre-operatively and at 1 week, 1 month and 3 month intervals post operatively.

F.3.6 Additional end points

Additional end points identified by risk assessment are evaluated at the appropriate time points.

F.4 Patient number calculation examples

F.4.1 Patient number calculation based on change in corneal thickness

The following example of a sample size calculation is based on the change in corneal thickness as primary end-point. The null hypothesis, H_0, is that the difference in change in corneal thickness from pre-operatively to 24 h post-operatively between the test article and the control article is greater than or equal to a predetermined equivalence limit, Δ mm. The alternative hypothesis, H_1, is that the difference in change in corneal thickness from pre-operatively to 24 h post-operatively is less than the specified limit. This can be expressed as follows:

$$H_0: \left|\mu_{\text{test}} - \mu_{\text{control}}\right| \ldots \Delta \quad H_1: \left|\mu_{\text{test}} - \mu_{\text{control}}\right| < \Delta \tag{F.1}$$

where μ_{test} and μ_{control} are the population means for the test and control groups, respectively.

To construct a two-sided 95 % confidence interval for the difference in change in corneal thickness that lies within ± Δ mm, when the true difference is null, with a power of 80 % and a standard deviation for the change of σ mm, the required number of patients per group is given by:

$$n = \frac{2\sigma^2\left(z_{\alpha/2} + z_{\beta/2}\right)^2}{\Delta^2} = \frac{2\sigma^2\left(1{,}96 + 1{,}28\right)^2}{\Delta^2} \tag{F.2}$$

where $z_{\alpha/2}$ and $z_{\beta/2}$ are the standard normal deviates corresponding to $\alpha/2$ and $\beta/2$.

The test irrigating solution can be considered equivalent to the control if the two-sided 95 % confidence interval for the difference in change in corneal thickness lies within the clinical relevant equivalence limit ± Δ.

If the standard deviation for the change in corneal thickness from pre-operatively to 24 h post-operatively is 0,05 mm and the equivalence limit is set to ±0,025 mm, 86 patients per treatment group are required. Additional patients (at least 10 %) need to be included to allow for dropouts.

F.4.2 Patient number calculation based on endothelial cell loss

Another example of a sample size calculation is based on the percent change of endothelial cells from pre-operatively to 3 months post-operatively as primary end point. The null hypothesis, H_0, is that the difference in percent change in endothelial cells from pre-operatively to 3 months post-operatively between the test article and the control article is greater than or equal to a predetermined equivalence limit, Δ %. The alternative hypothesis, H_1, is that the difference in percent change in endothelial cells from pre-operatively to 3 months post-operatively is less than the specified limit. This can be expressed as follows:

$$H_0: \left|\mu_{\text{test}} - \mu_{\text{control}}\right| \ldots \Delta \quad H_1: \left|\mu_{\text{test}} - \mu_{\text{control}}\right| < \Delta \tag{F.3}$$

where μ_{test} and μ_{control} are the population means for the test and control groups, respectively.

To construct a two-sided 95 % confidence interval for the difference in percent change in endothelial cells that lies within ± Δ %, when the true difference is null, with a power of 80 % and a standard deviation for the change of σ %, the required number of patients per group is given by:

$$n = \frac{2\sigma^2\left(z_{\alpha/2} + z_{\beta/2}\right)^2}{\Delta^2} = \frac{2\sigma^2\left(1{,}96 + 1{,}28\right)^2}{\Delta^2} \tag{F.4}$$

where $z_{\alpha/2}$ and $z_{\beta/2}$ are the standard normal deviates corresponding to $\alpha/2$ and $\beta/2$.

The test irrigating solution can be considered equivalent to the control if the two-sided 95 % confidence interval for the difference in percent change in endothelial cells lies within the clinical relevant equivalence limit ± Δ.

If the standard deviation for the percent change in endothelial cells from pre-operatively to 3 months post-operatively is 15 percentage points and the equivalence limit is set to ±7,5 percentage points, 86 patients per treatment group are required. Additional patients (at least 10 %) need to be included to allow for dropouts.

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