BS EN ISO 16672:2015

BSI Standards Publication

Ophthalmic implants — Ocular endotamponades (ISO 16672:2015)

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National foreword

This British Standard is the UK implementation of EN ISO 16672:2015. It supersedes BS EN ISO 16672:2003 which is withdrawn.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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Ophthalmic implants - Ocular endotamponades (ISO 16672:2015)

Implants ophtalmiques - Produits de tamponnement endoculaires (ISO 16672:2015)

Ophthalmische Implantate - Okulare Endotamponaden (ISO 16672:2015)

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

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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 16672:2015) 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of an identical text or by endorsement, at the latest by February 2016, and conflicting national standards shall be withdrawn at the latest by February 2016.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 16672:2003.

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 16672:2015 has been approved by CEN as EN ISO 16672:2015 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
5.2 & 5.11, 7 in respect of EO contamination only.	7.2	
6.3	7.3	
7	7.6	
7	8.1	
5.2, 6.2.1	8.2	
10, 11 in respect of exposure to environmental elements	8.3	
7 in respect of EO sterilization	8.4	
11	13.1	
11	13.2	
11	13.3 a), b), c), d), e), f), i), j), k), m)	

11	13.4	
11	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.

Contents

Page

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).

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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 16672:2003), which has been technically revised.

INTERNATIONAL STANDARD **ISO 16672:2015(E)**

Ophthalmic implants — Ocular endotamponades

1 Scope

This International Standard applies to ocular endotamponades (OE), a group of non-solid implants used in ophthalmology to flatten and position a detached retina onto the choroid, or to tamponade the retina.

With regard to the safety and efficacy of OE, this International Standard specifies requirements for their intended performance, design attributes, pre-clinical and clinical evaluation, sterilization, product packaging, product labelling and the information supplied by the manufacturer.

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 10993-6:2007, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation*

ISO 11135-1:2007, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-1:2006 + Amd.1:2013, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

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 17665-1:2006, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO 20857:2010, *Sterilization of health care products — Dry heat — Requirements for the development, validation and routine control of a sterilization process for medical devices*

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 component provided to introduce the product into the eye

3.2
dynamic viscosity
quotient of the part of the stress in phase with the rate of strain divided by the rate of strain under sinusoidal conditions

Note 1 to entry: The dynamic viscosity is expressed in pascal seconds (Pa·s).

3.3
interfacial tension
tension against liquids

Note 1 to entry: The interfacial tension is expressed in newton per metre (N/m).

3.4
kinematic viscosity
quotient of the dynamic viscosity with the gravity

Note 1 to entry: The kinematic viscosity is expressed in square metres per second (m^2/s).

3.5
non-solid implants
tamponade media such as gases, liquids, or gels

3.6
ocular endotamponade
OE
non-solid implant used in ophthalmology to flatten and position a detached retina onto the choroid, or to tamponade the retina

3.7
primary container
container providing mechanical and microbiological protection of the content

3.8
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]

3.9
storage container
part of the packaging intended to protect the device during transport and storage, containing the sterile barrier

3.10
surface tension
tension against air

Note 1 to entry: Surface tension is expressed in newton per metre (N/m).

3.11
vapour pressure
vapour pressure of a liquid OE that defines its volatility

Note 1 to entry: Vapour pressure is expressed in Pascal (Pa) at (35 ± 2) °C.

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 reposition and/or tamponade a detached retina, and which function primarily mechanically. They are used either intra-operatively and removed at the end of surgery, as in the case of heavy liquids such as perfluorocarbons, or are designed to remain in the vitreous cavity until a reattachment of the retina is achieved.

The manufacturer shall describe and document the functional characteristics of the OE in terms of its chemical composition and physical properties, the intended surgical applications, the conditions of use and the maximum duration of contact with, 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 specified 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 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 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 and quantified, whenever possible, and their concentration in the finished products 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.

5.3 Chemical description

The manufacturer shall provide a description of each chemical component in the finished product and its quality specifications. If the component material is derived from biological sources, the organism from which it is obtained shall be stated along with its source. For synthetic polymers, the backbone and end-groups shall be identified. Residual monomers and reaction by-products shall be quantified and identified, if possible.

5.4 Concentration of the components

The concentration of each component material in the finished product shall be stated. Since the testing methodology can affect the actual concentration reported, the physical or chemical techniques utilized shall be described and validated.

5.5 Density

The density of liquid forms of OE shall be specified in kilograms per cubic metre (kg/m^3).

5.6 Gaseous expansion

For gaseous forms of OE the intraocular gaseous expansion at (35 ± 2) °C and its dependence on atmospheric pressure shall be expressed.

5.7 Interfacial tension

Where applicable, the interfacial tension against water shall be expressed in newton per metre (N/m) at (35 ± 2) °C.

5.8 Kinematic viscosity

Where applicable, the kinematic viscosity at (35 ± 2) °C shall be expressed in millimetres squared per second (mm^2/s).

5.9 Dynamic viscosity

For viscous or viscoelastic OE, the dynamic viscosity shall be determined at (35 ± 2) °C in the range between 0,01 and 100 s^{-1} and expressed in mPa·s.

5.10 Molecular mass distribution

If the OE is a polymer, the average molecular mass, the range of molecular mass distribution and the polydispersity shall be reported.

The manufacturer shall conduct and report such additional tests as necessary to provide an adequate description of the molecular mass distribution of the components in the finished product. Whenever possible, standard methods shall be used and specified.

5.11 Particulates

An assessment of risk 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 and the associated hazards.

The manufacturer shall characterize and set limits for the types, range of sizes and levels of particles present in the finished product used in the clinical study. For each type of particle present, a limit which has been validated in a clinical study shall be set and an adequate justification for the limit shall be documented.

5.12 Refractive index

Where applicable, the refractive index between OE and air shall be measured with a refractometer at (35 ± 2) °C and (546 ± 10) nm wavelength.

5.13 Spectral transmittance

The spectral transmittance of the OE shall be measured by transmission spectrophotometry over the range 300 nm to 1 100 nm. Results shall be presented graphically, plotting percentage transmission against wavelength.

5.14 Surface tension

Where applicable, the surface tension shall be expressed in newton per metre (N/m) at (35 ± 2) °C.

5.15 Vapour pressure

Where applicable, the vapour pressure shall be expressed in Pascal (Pa) at (35 ± 2) °C.

6 Design evaluation

6.1 General

The OE shall be evaluated for safety by performing a risk assessment in accordance with ISO 14971. The results of the risk assessment shall determine the tests required to evaluate the safety of the OE.

The risk assessment shall take into consideration the following:

a) the type of product and the duration of intraocular contact;

b) potential interactions of the OE with other materials likely to be used in ophthalmic surgery;

c) for intraocular gases, any impurity profile changes as the gas is depleted from the tank.

NOTE Impurity profile changes can occur as the concentration of the chemical species changes due to the differences in vapour pressure as the tank is depleted.

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

6.2 Evaluation of biological safety

6.2.1 General

The relevant biocompatibility end points specified in ISO 10993-1 and identified by the risk analysis shall be taken into account when selecting the tests to evaluate the biological safety of an OE.

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

6.2.2 Bacterial endotoxins test

Where applicable, the OE shall be evaluated for the presence of bacterial endotoxins using the Limulus Amoebocyte Lysate (LAL) test, in accordance 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 implantation test

Tests for intraocular irritation, inflammation, intraocular pressure (IOP) and other local effects of the OE shall be conducted in a suitable animal model, in accordance with animal welfare requirements specified in ISO 10993-2 or following any local legislation.

Due to differences between the vascularised human retina and the avascular rabbit retina especially for non-aqueous substances a suitable animal model has to be validated.

The particular requirements for this intraocular implantation test are specified in Annex A.

The study design shall mirror the intended clinical use as closely as possible.

The study design should assess the intra-operative and postoperative intraocular irritation, inflammation, and local effects of the ophthalmic surgery with comparative use of the OE under evaluation and a control OE which has already been proven in clinical use to be acceptable. The volume of OE used should simulate the intended use, accounting for ocular volume differences between the human and animal models.

The post-surgical irritation, inflammation, and local effects shall be monitored and graded at intervals appropriate to the duration of the intended use. All adverse events shall be documented.

The OE shall show intraocular irritation, inflammation and local effects results comparable to or less than a control OE of the same intended use. Intraocular irritation, inflammation and local effects in excess of the control OE are acceptable if justified by the risk benefit analysis.

NOTE 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 animals are not subjected to undue pain or distress.

6.2.4 Ethylene oxide

If ethylene oxide (EO) is used during the manufacturing of ingredients or in justified sterilization of the packaging, the total level of EO in the product shall not exceed 20 µg/g for EO and 100 µg/g for ethylene chlorohydrin (ECH).

6.3 Clinical investigation

A preclinical evaluation and risk assessment shall be performed to determine if a clinical investigation is needed. If so, Annex B shall be considered. In addition, the general requirements concerning the clinical investigations of medical devices for human subjects specified in ISO 14155 shall apply.

7 Sterilization

Wherever possible, the product shall be terminally sterilized in its final container. The requirements for sterilization of non-active surgical implants specified in ISO 14630 shall apply and an appropriate standard for the method of sterilization shall be applied.

Ethylene oxide shall not be used unless there is documented justification for its use.

NOTE 1 The following standards for sterilization are currently valid:

— for products, or components thereof, sterilized by moist heat: ISO 17665-1;

— for products, or components thereof, sterilized by dry heat: ISO 20857;

— for products, or components thereof, sterilized by radiation: ISO 11137-1;

— for products, or components thereof, sterilized by ethylene oxide: ISO 11135-1.

If a product cannot be terminally sterilized, aseptic processing is an accepted alternative. For such products, 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 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. It particularly applies to, but is not limited to, the processing of aqueous solutions, and is thus relevant to the preparation of OE. 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 product and its delivery system. Real time or validated accelerated shelf-life testing shall be performed to demonstrate that the essential characteristics for safe and effective performance of the finished product and delivery system do not change over the labelled shelf-life under expected conditions of transport and storage. The temperature used in accelerated testing shall not exceed 45 °C. The parameters that shall be followed during shelf-life studies are those factors identified by the risk analysis as being crucial to the 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, can affect the shelf-life of the product.

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

9 Integrity and performance of the delivery system

Chemical and physical compatibility of the OE and the delivery system shall be evaluated and documented.

Appropriate testing should be conducted to demonstrate that mechanical failure of the delivery system will not result from use as intended.

10 Packaging

10.1 Protection from damage during storage and transport

The packaging requirements for medical devices specified in ISO 11607-1 and ISO 14630 shall apply. For the purposes of this International Standard, ISO 11607-1 shall apply also for OE that are not terminally sterilized.

10.2 Maintenance of sterility in transit

OE shall be packaged in such a way that they remain sterile under the normal conditions of transport, storage and handling. The sterile packaging requirements given in ISO 11607-1 shall apply.

11 Information supplied by the manufacturer

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

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

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.

Where applicable, reabsorption and expansion rate information based on clinical study results, as well as warnings about altitude change and air travel shall be provided.

In the case of gases, information about sterile filtering before intraocular injection shall be provided.

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

The batch number and expiration date may be provided on a self-adhesive label.

Table 1 — Information supplied by the manufacturer

	Storage container	Package insert	Sterile barrier	Primary container
Name of the manufacturer or authorized representative	X	X	X[a]	X
Address of manufacturer or authorized representative	X	X		
Trade name of product	X	X	X[a]	X
Brief description of the chemical composition of the product and the volume supplied	X	X		
A description of the relevant design attributes that may affect the safety and performance of the product		X		
Spectral transmittance curve		X		
Refractive index		X		
Conditions for storage	X	X		
Indications for use		X		
Contraindications for use		X		
Instructions for use		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 (if applicable)	X	X	X[a]	X
Do not use if sterile barrier is breached (if applicable)		X	X	
Batch number preceded by the word LOT	X		X[a]	X
Expiration date	X		X[a]	X

[a] The name of the manufacturer or authorized representative, trade name of product, batch number, expiration date and sterility statement (where applicable) 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.

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

A patient medical alert bracelet and a patient information card shall be available to each patient to inform the patient and the healthcare providers, for example surgeons and dentists, regarding the hazards of altitude and air travel, and the use of nitrous oxide for a surgical procedure when intraocular gas is in the eye to prevent serious eye injury and blindness.

The patient medical bracelet shall alert the existence of intraocular gas bubble in the patient under the healthcare provider’s care.

Annex A
(normative)

Intraocular 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 specified in ISO 10993-6 provide guidance.

The vitreous cavity of a suitable test animal shall be used as the implantation site. The choice of animal model shall be justified. The use of appropriate controls shall be included in the test.

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

A.2 Test procedure

An appropriate volume of the OE, relevant to its intended application(s), is injected into the vitreous cavity of a vitrectomized eye. 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 OE.

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

A.3 Test evaluation

The post-injection response shall include intraocular pressure measurement and is monitored and graded at appropriate intervals to include periodic histological evaluation, gross and microscopic assessment and ocular evaluation (such as fundus and slit lamp examinations for irritation, emulsification, cataractogenesis, migration of the material, retinal status, etc.). Additional parameters and/or evaluation times are added depending on the outcome of the risk analysis and duration of the implantation study. All test results shall be documented and reported as specified in ISO 10993-6.

Annex B
(informative)

Clinical investigation

B.1 General

This annex covers the three types of OE currently in use: intraocular gases, silicone oil and perfluorocarbon liquids.

B.2 Clinical investigation design

B.2.1 Procedure

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

A controlled clinical investigation is to be performed. The objective of the investigation is to document the safety and performance of the new OE when compared to the control. The primary hypothesis follows from risk analysis, and standard biostatistical formulae are used to calculate the required number of patients per treatment group.

Either a randomized, concurrent or a historical control is used. In the latter case, the control treatment is a well-documented OE of the same type as the OE under investigation, marketed widely for at least the last five years for the same use. An appropriate safety end point for the claimed indication(s) of the OE is used in the determination of the appropriate sample size for the clinical investigation. An example of the appropriate sample size for an OE based on intraocular pressure is given in B.3. Although hypothesis testing is performed only for the primary end points, the rates of the other assessments or adverse events will also be used to evaluate the device safety and efficacy profile.

No investigator contributes 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 should not be greater than 10 % of the total number enrolled.

If the manufacturer wishes to make additional claims, for instance regarding the intra-operative performance of the device, additional end points to support these claims are to be included and the appropriate power calculations for determining the patient numbers are to be performed.

The duration of OE use and volume used for each patient is documented. Any adverse intra-operative and post-operative events are documented.

B.2.2 Clinical variables

The study end points are assessed in a consistent manner across investigation sites. If a historical control is used, the evaluation methods used to evaluate the OE should be consistent with those used for the historical control.

The following are assessed:

— presence or absence of the crystalline lens and, if present, its status in terms of clarity;

— visual acuity;

— degree of retinal repositioning;

— status of the lens (phakia, aphakia, pseudophakia, cataract).

The following safety end points are assessed, depending on the type of OE:

a) Intraocular gases (≤30 days):

   1) IOP;

   2) corneal abnormalities;

   3) subretinal gas;

b) Silicone oil (>30 days):

   1) Corneal oedema, band keratopathy;

   2) IOP;

   3) emulsification;

c) Perfluorocarbon liquids (<1 day):

   1) retained perfluorocarbon liquid;

   2) migration into subretinal space.

Additional variables identified by risk assessment are also evaluated.

In all cases, the type and status of the lens is documented.

B.2.3 Post-operative evaluation

The following post-operative follow-up times apply to all types of OE:

1 day ± 4 h

1 week ± 2 days

1 month ± 7 days

3 months ± 2 weeks

6 months ± 2 weeks

The following additional post-operative follow-up time applies for products remaining in the eye > 30 days:

12 months ± 1 month

B.3 Patient numbers for clinical investigations

An example of a sample size calculation for the investigation is based on the frequency of subjects with an abnormal intraocular pressure (IOP) as the primary end point. For the purposes of these investigations, an abnormal IOP is defined as an IOP less than 5 mmHg or greater than 25 mmHg occurring at any time during the investigation. The clinical investigation is designed to show that the test product is not significantly inferior to the control in terms of the rate of subjects with abnormal IOP.

The null hypothesis (H_0) is that the test rate (μ_t) of subjects with an abnormal IOP minus the control rate (μ_c) of the subjects with an abnormal IOP is greater than the minimally detectable difference (δ) between the two rates. The alternative hypothesis (H_1) is that the test rate (μ_t) of subjects with

abnormal IOP minus the control rate (μ_c) of subjects with abnormal IOP is less than or equal to the minimally detectable difference (δ) between the two rates.

$$H_0 : \mu_t - \mu_c > \delta$$

$$H_1 : \mu_t - \mu_c \leq \delta$$

The minimum number of patients to evaluate in each treatment group is determined by the formula below:

$$N = \frac{\left(z_{1-\beta} + z_{1-\alpha}\right)^2 \left[\mu_t\left(1-\mu_t\right) + \mu_c\left(1-\mu_c\right)\right]}{\delta^2} \quad \text{(B.1)}$$

where

$z_{1-\alpha}$ is the standard normal quantile for the confidence level;

$z_{1-\beta}$ is the standard normal quantile for power (coverage probability).

With a control rate (μ_c) of 0,2, a minimally detectable difference (δ) of 0,11, a power ($1 - \beta$) of 0,80, and an α of 0,10, the required number of patients to evaluate per treatment group is:

$$N = \frac{(1{,}28+1{,}64)^2\left[(0{,}2)(0{,}8)+(0{,}2)(0{,}8)\right]}{(0{,}11)^2} \cong 296 \quad \text{(B.2)}$$

B.4 Data management

The safety end points are stratified by the presence or absence of the crystalline lens for all types of OE.

Bibliography

[1] European Pharmacopoeia, Appendix XIV C. Test for Bacterial Endotoxins

[2] Japanese Pharmacopoeia, XIV 6. Bacterial Endotoxins Test

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