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Ophthalmic implants — Ocular endotamponades

Implants ophtalmiques — Produits de tamponnement endoculaires

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Foreword

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International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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

ISO 16672 was prepared by Technical Committee ISO/TC 172, *Optics and optical instruments*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

Ophthalmic implants — Ocular endotamponades

1 Scope

This International Standard applies to ocular endotamponades (OEs), 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 OEs, 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 referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-1:1997, *Biological evaluation of medical devices — Part 1: Evaluation and testing*

ISO 10993-2:1992, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 10993-6:1994, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation*

ISO 11607:1997, *Packaging for terminally sterilized medical devices*

ISO 13408-1:1998, *Aseptic processing of health care products — Part 1: General requirements*

ISO 14155-1:—[1)], *Clinical investigation of medical devices for human subjects — Part 1: General requirements*

ISO 14155-2:—[1)], *Clinical investigation of medical devices for human subjects — Part 2: Clinical investigation plans*

ISO 14630:1997, *Non-active surgical implants — General requirements*

ISO 14971:2000, *Medical devices — Application of risk management to medical devices*

ISO/TR 15223:2000, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied*

EN 868-1:1997, *Packaging materials and systems for medical devices which are to be sterilized — Part 1: General requirements and test methods*

EN 1041:1998, *Information supplied by the manufacturer with medical devices*

USP 24 <85> Jan/2000, *United States Pharmacopoeia* <85> *Bacterial endotoxins test*

1) To be published.

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 The dynamic viscosity is expressed in pascal seconds (Pa·s).

3.3
interfacial tension
tension against liquids

NOTE The interfacial tension is expressed in newtons per metre (N/m).

3.4
kinematic viscosity
quotient of the dynamic viscosity with the gravity

NOTE The kinematic viscosity is expressed in metres squared per second (m^2/s).

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

3.6
surface tension
tension against air

NOTE Surface tension is expressed in newtons per metre (N/m).

3.7
vapour pressure
vapour pressure of a liquid OE that defines its volatility

NOTE Vapour pressure is expressed in conventional millimetres of mercury (mmHg) 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, 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 may 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 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 may affect the actual concentration reported, the physical or chemical techniques utilized shall be described.

5.5 Density

The density of liquid forms of OEs shall be specified in kilograms per cubic metre (kg/m³).

5.6 Gaseous expansion

For gaseous forms of OEs 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 shall be expressed in newtons per metre (N/m) at (35 ± 2) °C.

5.8 Kinematic viscosity

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

5.9 Molecular mass distribution

If the OE is a polymer, the average molecular mass 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.

5.10 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.

5.11 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.

5.12 Spectral transmittance

The spectral transmittance of the OE shall be measured by transmission spectrophotometry over the range 300 nm to 1100 nm. Results shall be presented graphically, plotting percentage transmission against wavelength.

5.13 Surface tension

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

5.14 Vapour pressure

Where applicable, the vapour pressure shall be expressed in conventional millimetres of mercury (mmHg) 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 endpoints 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, OEs are categorized as “Implant devices, tissue/bone”. The tests for this and other categories of devices identified in Table 1 of ISO 10993-1:1997 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 Amebocyte Lysate (LAL) test, in accordance with the procedure described in USP 24 <85> 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.

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, the total level of EO in the product shall not exceed 20 µg/g for EO and 100 µg/g for ethylene chlorohydrin (ECH).

If the solubility of EO or ECH in the liquid OE is less than the solubility of EO or ECH in a marketed ophthalmic irrigating solution, EO sterilization shall not be used.

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 14155-1 and ISO 14155-2 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 11134 and EN 554;

— for products, or components thereof, sterilized by dry heat: ANSI/AAMI ST 50:1995;

— for products, or components thereof, sterilized by radiation: ISO 11137 and EN 552;

— for products, or components thereof, sterilized by ethylene oxide: ISO 11135 and EN 550.

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 OEs. 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, may 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 may 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.

10 Packaging

10.1 Protection from damage during storage and transport

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

10.2 Maintenance of sterility in transit

OEs 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 EN 868-1 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 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/TR 15223 shall apply.

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

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, expiration date and sterility data (where applicable) need not be provided on the sterile barrier if it is transparent and the required information can be read directly from the primary container without breaching the seal.

NOTE 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
Address of manufacturer	X	X		
Trade name of product	X	X		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	
Description of how the product and container have been prepared to minimize the risk of microbiological contamination. If sterilized, state the method	X	X		
Statement that the contents are sterile (if applicable)	X	X	X	
Do not use if sterile barrier is breached (if applicable)		X	X	
Batch number preceded by the word LOT	X		X	X
Expiration date	X		X	X

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 Applicability

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

B.2 Clinical investigation design

B.2.1 General

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 endpoint 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.

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 endpoints to support these claims are to be included and the appropriate power calculation 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 endpoints 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 is 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, aphacia, pseudophakia, cataract).

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

a) Intraocular gases ($\leqslant$ 30 days):

   1) IOP;

   2) corneal abnormalities;

   3) subretinal gas.

b) Silicone oil ($>$ 30 days):

   1) IOP;

   2) corneal abnormalities;

   3) emulsification.

c) Perfluorocarbon liquids ($<$ 1 day):

   1) migration into subretinal space;

   2) retained perfluorocarbon liquid.

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 OEs:

1 day $\pm$ 4 h

1 week $\pm$ 2 days

1 month $\pm$ 7 days

3 months $\pm$ 2 weeks

6 months $\pm$ 2 weeks

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

12 months $\pm$ 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 endpoint. 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. An abnormal IOP is the main safety concern with currently used OEs. 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: $\mu_t - \mu_c \leqslant \delta$

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

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

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:

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

B.4 Data management

The safety endpoints are stratified by the presence or absence of the crystalline lens for all types of OEs.

Bibliography

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[5] ISO 11134:1994, *Sterilization of health care products — Requirements for validation and routine control — Industrial moist heat sterilization*

[6] ISO 11135:1994, *Medical devices — Validation and routine control of ethylene oxide sterilization*

[7] ISO 11137:1995, *Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization*

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[9] EN 552, *Sterilization of medical devices — Validation and routine control of sterilization by irradiation*

[10] EN 554, *Sterilization of medical devices — Validation and routine control of sterilization by moist heat*

[11] EN 1441:1997, *Medical devices — Risk analysis*

[12] ANSI/AAMI ST 50:1995, *Dry heat (heated air) sterilizers*

[13] AAMI TIR No.19:1998, *Guidance for ANSI/AAM/ISO 10993-7:1995, Biological evaluation of medical devices — Part 7: Ethylene oxide residuals*

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