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Ophthalmic implants — Ocular endotamponades

Implants ophtalmiques — Produits de tamponnement endoculaires

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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 of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see www.iso.org/iso/foreword.html.

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

This third edition cancels and replaces the second edition (ISO 16672:2015), which has been technically revised.

The main changes compared to the previous edition are as follows:

a) the following terms and their definitions have been included: "secondary packaging", surgical invasive medical product" and "minimum utilization pressure";

b) the subclause on chemical description and contaminants has been substantially revised;

c) the bacterial endotoxin limit has been revised from 0,5 to 0,2 Endotoxin Units per ml;

d) the total level of EO in the product has been revised: it shall not exceed 1,25 µg/dose for EO and 5,0 µg/dose for ethylene chlorohydrin (ECH);

e) minimum utilization pressure has been included in the list of information supplied by the manufacturer;

f) B.2.2 giving the clinical variables in a clinical investigation has been revised;

g) Annex C "Method for quantifying incompletely fluorinated contaminants in perfluorocarbon liquids" has been added.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Ophthalmic implants — Ocular endotamponades

1 Scope

This document applies to ocular endotamponades (OE), a group of non-solid surgically invasive medical devices introduced into the vitreous cavity of the eye to flatten and position a detached retina onto the retinal pigment epithelium (RPE), or to tamponade the retina.

With regard to the safety and efficacy of OE, this document 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 are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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

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

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

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

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

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

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

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

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

EN 1041+A1, *Information supplied by the manufacturer with medical devices*

OECD Guidelines for the Testing of Chemicals, Section 1: Physical-Chemical properties, Test No. 104: Vapour Pressure

3 Terms and definitions

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

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

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

3.2
dynamic viscosity
quotient of shear stress and shear velocity

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 *dynamic viscosity* (3.2) and gravity

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

3.5
ocular endotamponade
OE
non-solid *surgically invasive medical device* (3.11) introduced into the vitreous cavity of the eye to flatten and position a detached retina onto the retinal pigment epithelium (RPE), or to tamponade the retina

3.6
primary container
container providing mechanical and microbiological protection of the content

3.7
sterile barrier
minimum package that prevents ingress of microorganisms and allows aseptic presentation of the product at the point of use

3.8
storage container
part of the packaging intended to protect the device during transport and storage, containing the *sterile barrier* (3.7)

3.9
secondary packaging
container external to and providing protection and support for the *primary container* (3.6)

3.10
surface tension
tension against air

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

3.11
surgically invasive medical device
invasive device which penetrates inside the body through the surface with the aid or in the context of a surgical operation

3.12
vapour pressure
pressure exerted by the vapour of a liquid OE when in equilibrium with the liquid OE

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

3.13
minimum utilization pressure
limiting value of the pressure below which the gas or gases mixture shall no longer be withdrawn from the container for its intended use

4 Intended performance

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

This document describes surgically invasive medical devices that are compatible with the internal ocular environment and, through a primary mechanical action, are used to reposition and/or tamponade a detached retina. They are used either intra-operatively and removed at the end of surgery, as in the case of perfluorocarbon liquids, or are designed to remain in the vitreous cavity until removal at a later date as in the case of silicone oils, or they are completely absorbed as in the case of gaseous OE.

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.

All available published standards and published scientific and clinical literature, validated test results, clinical investigations, and pre-clinical and clinical evaluations shall be considered in determining the intended device.

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 and 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 description and contaminants

The manufacturer shall provide a description of each of the components in the finished product, and their respective quality specifications and concentrations.

If the component material is derived from biological sources, the organism from which it is obtained shall be stated along with its source.

Whenever possible, for all polymers, the backbone, any side groups and end-groups shall be identified.

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 by-products, residual monomers, cross-linking agents, catalysts, products derived from

auto-oxidation processes or from containers transport and packaging that are potentially hazardous either systemically or to the tissues of the eye, shall be identified and quantified, whenever possible, and their concentration in the finished product reported. Limits for identified contaminants shall be set, justified and documented. Testing of the biological effects of these contaminants during evaluation of biological safety may be required if the risk analysis determines it necessary. Chemical changes during transport and storage shall be considered. Any contaminant being identified to cause, directly or by being the source for other contaminants, considerable harm to the patient, the user or any third party shall be reduced to a level that the health risk associated with the contaminant is considered acceptable.

The following list, although not exhaustive, provides some information on likely contaminants of common endotamponade materials: Materials of biological origin may contain proteins, nucleic acids, or other biological materials as contaminants. Perfluorocarbon liquids may contain oxygen containing compounds and incompletely fluorinated contaminants, including HF. Specifically incompletely fluorinated contaminants, including HF, are likely to occur and they bear a high risk for the patient already at the ppm level. Therefore, the concentration of incompletely fluorinated contaminants, including HF, shall be as low as possible. Different methods can be used for which the specific limits need to be specified based on the risk analysis. In Annex C a method is described for which a level of 10 ppm has been published, to assure material safety in regard of the aforementioned impurities.

Silicone oils may contain catalysts, heavy metals, residual monomers and short chain oligomers and polymers as a result from their synthesis.

For any liquid OE, control over synthesis of the tamponade material according to applicable standards and monographs and analytically controlled purification procedures according to applicable standards or monographs are minimum requirements.

5.3 Density

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

5.4 Gaseous expansion

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

5.5 Interfacial tension

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

5.6 Kinematic viscosity

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

5.7 Dynamic viscosity

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

5.8 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 named and used.

5.9 Particulates

A risk assessment shall evaluate the potential for the formation of and contamination by particulates in the product throughout the life of the product including manufacture, transport and storage under specified conditions, and during use. The potential for associated hazards shall be described.

The manufacturer shall characterize and set limits for the types, range of sizes and levels of particles present in the finished product. Limits according to USP <789> are deemed acceptable. Alternatively, the manufacturer shall investigate the level of particles 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.

5.10 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 or (589 ± 10) nm wavelength.

5.11 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.

5.12 Surface tension

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

5.13 Vapour pressure

If the vapour pressure exceeds 100 Pa, the vapour pressure shall be determined and expressed in pascal (Pa) at (35 ± 2) °C (OECD Test No. 104: Vapour Pressure).

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 location and duration of intraocular contact;

b) potential interactions of the OE with other materials and energy sources, e.g. laser likely to be used in ophthalmic surgery;

c) for intraocular gases, any impurity profile changes as the gas is withdrawn 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

If the OE is of hydrophobic nature, special consideration shall be taken when performing biocompatibility testing.

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

NOTE 2 To evaluate the biological safety of perfluorocarbon liquids (PFCL), their hydrophobic and volatile nature will have to be taken in consideration. Several methods to evaluate the cytotoxicity of these particular OE including direct contact and extractive methods are described in References [8], [9] and ISO 10993-5.

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 with applicable pharmacopoeias or an equivalent validated test procedure[1][2][3]. Any product that exceeds a bacterial endotoxin limit of 0,2 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.

Due to vascularisation differences between the human retina and the rabbit retina an alternate suitable animal should be considered, especially for non-aqueous substances.

The particular requirements of the 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 is a well-documented OE of the same type as the OE under investigation, marketed widely for at least five years for the same use.

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. If the OE induces intraocular irritation, inflammation and local effects in excess of the control OE, these should be justified by risk benefit analysis.

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 1,25 µg/dose for EO and 5,0 µg/dose 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 a clinical investigation is needed, 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.

In accordance with the relevant standards one of the following sterilization methods can be used:

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

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

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

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

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 document shall be demonstrated by a validated media fill study with a contamination rate limit of 10^{-3}.

ISO 13408–1 specifies the general requirements, 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 document 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 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 if the manufacturer intends to perform sterility testing in lieu of microbial barrier testing. 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 document, 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 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.

If the OE contains a gas, reabsorption and expansion rate information based on clinical study results, as well as warnings about altitude change and air travel shall be provided.

A warning that silicone oil could migrate out of the eye and form lesions in the conjunctiva or eyelid shall be provided. The warning shall include a statement that the use of CO_2 laser should be avoided for the silicone oil related skin lesions, due to potential ignition.

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 any other batch relevant individual information shall be provided on a self-adhesive label.

Table 1 — Information supplied by the manufacturer

	Secondary packaging	Package insert	Sterile barrier	Primary packaging
Name of the manufacturer and, if applicable, the 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		
Minimum utilization pressure for multiple use gas containers[b]		X		X
Statement that the contents are for single use only, if applicable	X	X	X[a]	
Statement “Sterile” and the method(s) of sterilization of the product and primary container (if applicable)	X	X	X[a]	X
Statement not to use the product if the 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 packaging without breaching the seal.

[b] Provision of visual aid, such as red zone, on the regulator display to remind user not to withdraw gas which is below the minimum utilization pressure.

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

When intraocular gas is in the eye 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 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

It is recommended that the animals are randomized and the randomization scheme is provided.

An appropriate volume of the OE, relevant to its intended application(s), is injected into the vitreous cavity of an eye with or without vitrectomy, according to its intended application(s). 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.

A bilateral implantation is preferred, but unilateral implantation is permitted, if local regulations so require. Unilateral implantation should be justified.

A.3 Test evaluation

The post-injection response shall be monitored and graded at appropriate intervals, and shall include intraocular pressure measurement, 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 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.

Justification of the design of the study according the risk analysis will be provided. Either a randomized, concurrent control or a historical control is used. A concurrent control is recommended. When appropriate, 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. Although hypothesis testing is performed only for the primary endpoints, the rates of the other assessments or adverse events should also be used to evaluate the device safety and efficacy profile.

No investigator contributes fewer 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.

The duration of OE use and volume used for each patient is documented. Any adverse intra-operative and post-operative events will be documented including interaction with intraoperative and implanted OE and materials and techniques including ophthalmic lasers.

B.2.2 Clinical variables

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

The following primary safety, primary performance and secondary measures are considered, depending on the type of OE.

a) Intraocular gases:

    1) Primary safety: Intraocular pressure (IOP) ≥30 mm Hg;

2) Primary performance:

   i. Macular hole: complete hole closure as measured by optical coherence tomography compared to SF_6 (sulfur hexafluoride);

   ii. Uncomplicated retinal detachment: anatomical success as compared to other products for equivalent indications;

   iii. Complicated retinal detachment: anatomical success as compared to other products for equivalent indications;

   iv. A secondary outcome is complete macular attachment as compared to other products for equivalent indications.

b) Silicone oil:

   1) Primary safety: IOP ≥30 mm Hg;

   2) Primary performance: Complicated retinal detachment: anatomical success as compared to silicone oil control. A secondary outcome is complete macular attachment as compared to silicone oil control.

c) Perfluorocarbon liquids:

   1) Primary safety: Visual acuity

   2) Primary performance:

      i. Uncomplicated retinal detachment: anatomical success intraoperatively as compared to other products for equivalent indications;

      ii. Complicated retinal detachment: complete anatomical success as compared to other products for equivalent indications. A secondary outcome is macular attachment as compared to the control.

Secondary measures:

1) Change in visual acuity from baseline (analysis plan shall account for expected incident cataracts postoperatively);

2) Intraocular inflammation by standardized nomenclature[10];

3) Unplanned reoperation;

4) Additional surgeries or medications (e.g. for IOP);

5) Intraoperative and postoperative adverse events/complications;

6) For silicone oil: Emulsification.

Additional variables identified by risk assessment are also evaluated.

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

B.2.3 Post-operative evaluation

When applicable, the following post-operative follow-up times apply:

— 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 intended to remain in the eye for more than 30 days:

— 12 months ± 1 month.

B.3 Patient numbers for clinical investigations

An example of a sample size calculation for the investigation of silicone oil is based on the frequency of subjects with an intraocular pressure (IOP) ≥30 mm Hg as the safety primary endpoint. 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 IOP spikes above this level. A non-inferiority analysis should be used to assess the safety and performance endpoints. A similar sample size calculation is performed for intraocular gases and perfluorocarbon liquids with different considerations related to the expected control rate and appropriate non-inferiority margin.

The null hypothesis (H_0) is that the test rate (μ_t) of subjects with an IOP ≥30 mm Hg minus the control rate (μ_c) of the subjects with an IOP ≥30 mm Hg 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 IOP ≥30 mm Hg minus the control rate (μ_c) of subjects with IOP ≥30 mm Hg 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).

Assuming that it has been estimated that the rate (μ_c) for the control silicone oil is 0,13, using a minimally detectable difference (δ) of about 80 % of the control rate (i.e., 0,10), a power ($1 - \beta$) of 0,80, and an α of 0,05, the required number of patients to evaluate per treatment group is:

$$N = \frac{(0{,}842 + 1{,}64)^2 \left[(0{,}13)(0{,}87) + (0{,}13)(0{,}87)\right]}{(0{,}10)^2} \cong 140 \quad \text{(B.2)}$$

B.4 Reporting

The safety and performance outcomes of the test OE are compared to the control, overall and then stratified by the type of retinal detachment.

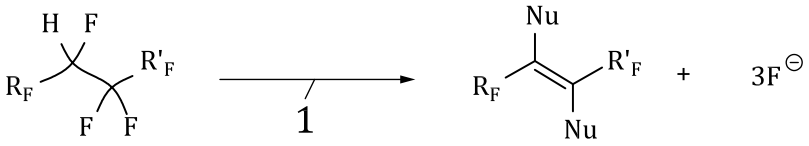
Annex C
(informative)

Method for quantifying incompletely fluorinated contaminants in perfluorocarbon liquids

C.1 General

Principle of the method:

Quantification of fluoride ions by ion-selective potentiometry after digestion of perfluorocarbon liquid. See Figure C.1.



Key

1 1,6-Diaminohexane

Figure C.1 — Reaction scheme of the digestion reaction of incompletely fluorinated contaminants in perfluorocarbon liquids

C.2 Procedure

C.2.1 Digestion

10 ml of the perfluorocarbon liquid are mixed with 3,4 g 1,6-Diaminohexane and 15 ml nonane. This mixture is heated in a 100 ml glass flask equipped with a reflux condenser for 8 h under stirring to a temperature of 120 °C. After cooling down to room temperature, the digestion solution is vigorously mixed with 30 ml of 1,3 molar aqueous hydrochloric acid and the aqueous phase is separated.

C.2.2 Sample preparation

15 ml of the aqueous phase are neutralized with 1,3 molar aqueous hydrochloric acid using phenolphthalein as indicator and diluted to 25 ml with deionized water. 10 ml of this neutralized solution are transferred into a new 25 ml glass beaker and 1 ml TISAB-III is added under stirring.

C.2.3 Quantification of fluoride ions by ion-selective potentiometry

Ion-selective potentiometry is used for quantifying fluoride ions in the sample solution. Prior to sample measurement, a calibration shall be performed, using sodium fluoride solutions with fluoride ion concentrations covering the range of 0,005 mmol/l to 0,05 mmol/l as reference standard. In addition, a blank value is recorded. Subsequently, the sample solution is analysed.

C.2.4 Determination of incompletely fluorinated contaminants from the result of ion-selective potentiometry

The concentration of incompletely fluorinated contaminants is calculated from the fluorine concentration using the following formula:

$$c_{F-C-H} = \frac{1}{3} \times \left[\left(c_{F^-} \times 5 \times \frac{M_{PFCL}}{\rho_{PFCL}} \right) - bv \right] \quad \text{(C.1)}$$

where

c_{F-C-H} is the concentration of incompletely fluorinated contaminants in the sample in ppm;

c_{F^-} is the measured concentration of fluoride ions in the sample in mmol/l;

M_{PFCL} is the molecular weight of the measured perfluorocarbon liquid in g/mol;

ρ_{PFCL} is the density of the measured perfluorocarbon liquid in g/ml;

bv is the recorded blank value in ppm;

5 is the factor to compensate for the dilution steps.

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