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Ophthalmic implants — Irrigating solutions for ophthalmic surgery

Implants ophtalmiques — Solutions d'irrigation pour la chirurgie ophtalmique

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Foreword

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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).

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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 16671:2003), which has been technically revised.

Ophthalmic implants — Irrigating solutions for ophthalmic surgery

1 Scope

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

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

2 Normative references

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

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

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

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

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

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

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

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

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

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

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

3 Terms and definitions

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

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

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

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

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

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

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

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

4 Intended performance

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

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

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

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

5 Design attributes

5.1 General

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

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

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

5.2 Concentration of the components

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

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

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

The concentration of each component material in the finished product shall be determined and documented, and the concentration of each component shall be expressed as weight of material per unit volume of solution. Since the testing methodology can affect the actual concentration reported, the standard physical or chemical techniques utilized shall be described and documented. Wherever possible, components shall comply with stated compendial standards.

5.3 Water used

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

5.4 Characterization of the finished product

5.4.1 General

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

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

5.4.2 pH and buffering capacity

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

The pH of the product should be close to that of the aqueous humour (pH 7,38) in order to prevent damage to the corneal endothelial cells. *In vitro* studies have shown that the pH range tolerated by the endothelium narrows as exposure time increases.

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

Table 1 — Classification according to pH and buffering capacity

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

5.4.3 Chemical and biological contaminants

Potentially hazardous chemical or biological contaminants and impurities shall be determined by a risk analysis. For raw materials of biological origin, these contaminants can include proteins, nucleic acids or other biological materials. Contaminants of the finished product that are potentially hazardous either to the tissues of the eye or systemically, shall be identified, whenever possible, and their concentrations in the finished product reported.

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

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

5.4.4 Osmolality

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

5.4.5 Spectral transmittance

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

5.4.6 Particulates

5.4.6.1 General

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

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

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

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

5.4.6.2 Visible particles

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

5.4.6.3 Sub-visible particles

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

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

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

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

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

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

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

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

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

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

6 Design evaluation

6.1 General

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

6.2 Preclinical evaluation of biological safety

6.2.1 General

The procedure for evaluation of biological safety of an OIS shall commence with an assessment of risk, carried out and documented in accordance with ISO 14971. The results of the risk analysis shall determine the tests required to evaluate the biological safety of the OIS.

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

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

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

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

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

In addition to the biocompatibility tests identified in ISO 10993-1 and by the risk analysis, all of the following tests shall be considered in the selection of tests to evaluate the biological safety of an OIS.

6.2.2 Bacterial endotoxins test

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

6.2.3 Intraocular irritation and inflammation

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

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

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

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

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

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

6.3 Clinical evaluation

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

7 Sterilization

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

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

— ethylene oxide: less than 20 µg/ml

— ethylene chlorohydrin: less than 100 µg/ml

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

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

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

8 Product stability

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

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

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

9 Packaging

9.1 Protection from damage during storage and transport

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

9.2 Maintenance of sterility in transit

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

10 Information supplied by the manufacturer

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

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

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

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

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

The minimum information required on the storage container, package insert, sterile barrier and primary container is listed in Table 2.

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

Table 2 — Information supplied by the manufacturer

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

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