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Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices

Stérilisation des produits de santé — Oxyde d'éthylène — Exigences pour le développement, la validation et la vérification de routine d'un processus de stérilisation pour les appareils médicaux

[Revision of first edition (ISO 11135-1:2007) and ISO/TS 11135-2:2008]

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This draft is hereby submitted to the ISO member bodies and to the CEN member bodies for a parallel five-month enquiry.

Should this draft be accepted, a final draft, established on the basis of comments received, will be submitted to a parallel two-month approval vote in ISO and formal vote in CEN.

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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.

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.

ISO 11135 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

ISO 11135:20xx cancels and replaces ISO 11135-1:2007 *Sterilization of health care products – Ethylene oxide – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices* and ISO/TS 11135-2:2008 *Sterilization of health care products – Ethylene oxide – Part 2: Guidance on the application of ISO 11135-1*, both of which have been technically revised and condensed into a single standard.

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Introduction

A sterile medical device is one that is free of viable microorganisms. Medical devices produced under standard manufacturing conditions in accordance with the requirements for quality management systems (see for example ISO 13485) may, prior to sterilization, have microorganisms on them, albeit in low numbers. Such medical devices are non-sterile. The purpose of sterilization is to inactivate the microbiological contaminants and thereby transform the non-sterile medical devices into sterile ones.

The kinetics of inactivation of a pure culture of microorganisms by physical and/or chemical agents used to sterilize medical devices can generally best be described by an exponential relationship between the numbers of microorganisms surviving and the extent of treatment with the ethylene oxide (EO); inevitably this means that there is always a finite probability that a microorganism may survive regardless of the extent of treatment applied. For a given treatment, the probability of survival is determined by the number and resistance of microorganisms and by the environment in which the organisms exist during treatment. It follows that the sterility of any one medical device in a population subjected to sterilization processing cannot be guaranteed and the sterility of a processed population is defined in terms of the probability of there being a viable microorganism present on a medical device.

ISO 11135 describes requirements that, if met, will provide an ethylene oxide sterilization process intended to sterilize medical devices, which has appropriate microbicidal activity. Furthermore, compliance with the requirements ensures that validations conducted following this standard will provide products that meet the defined requirements for sterile products with a high degree of confidence. The specification for this probability is a matter for regulatory authorities and may vary from country to country (see for example EN 556-1 and ANSI/AAMI ST67).

Generic requirements of the quality management systems for design and development, production, installation and servicing are given in ISO 9001 and particular requirements for quality management systems for medical device production are given in ISO 13485. The standards for quality management systems recognise that, for certain processes used in manufacturing or reprocessing, the effectiveness of the process cannot be fully verified by subsequent inspection and testing of the product. Sterilization is an example of such a process. For this reason, sterilization processes are validated for use, the performance of the sterilization process monitored routinely and the equipment maintained.

Exposure to a properly validated, accurately controlled sterilization process is not the only factor associated with the provision of reliable assurance that the product is sterile and, in this regard, suitable for its intended use. Attention is therefore given to a number of considerations including:

- the microbiological status of incoming raw materials and/or components;
- the validation and routine control of any cleaning and disinfection procedures used on the product;
- the control of the environment in which the product is manufactured or reprocessed, assembled and packaged;
- the control of equipment and processes;
- the control of personnel and their hygiene;
- the manner and materials in which the product is packaged;
- the conditions under which product is stored.

The type of contamination on a product to be sterilized varies and this impacts upon the effectiveness of a sterilization process. Products that have been used in a health care setting and are being presented for resterilization in accordance with the manufacturer's instructions (see ISO 17664) should be regarded as a

special case. There is the potential for such products to possess a wide range of contaminating microorganisms and residual inorganic and/or organic contamination in spite of the application of a cleaning process. Hence, it is important to pay particular attention to the validation and control of the cleaning and disinfection processes used during reprocessing. . Mixed product loads are common in healthcare facilities with throughput volumes dictated by historical and predicted demand for sterile product.

The requirements are the normative parts of ISO 11135 with which compliance is claimed. The guidance given in the informative annexes is not normative and is not provided as a checklist for auditors. The guidance in Annex D provides explanations and methods that are regarded as being suitable means for complying with the requirements for industry and health care facilities.

The guidance, in Annex D, is intended for people who have a basic knowledge of the principles of EO sterilization. Methods other than those given in the guidance may be used if they are effective in achieving compliance with the requirements of ISO 11135.

The development, validation and routine control of a sterilization process comprises a number of discrete but interrelated activities; e.g. calibration, maintenance, product definition, process definition, installation qualification, operational qualification and performance qualification. While the activities required by ISO 11135 have been grouped together and are presented in a particular order, ISO 11135 does not require that the activities be performed in the order in which they are presented. The activities required are not necessarily sequential, as the programme of development and validation may be iterative. It is possible that performing these different activities will involve a number of separate individuals and/or organizations, each of whom undertakes one or more of these activities. This International Standard does not specify the particular individuals or organizations to carry out the activities.

It is important that patient safety be addressed by minimizing exposure to EO and its by-products during normal product use. ISO 10993-7 specifies limits for EO and ethylene chlorohydrin (ECH); however, no exposure limits are set for ethylene glycol (EG) because risk assessment indicates that when EO residues are controlled, it is unlikely that biologically significant residues of (EG would be present.

Sterilization of health care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices

1 Scope

1.1 Inclusions

1.1.1 This International Standard specifies requirements for the development, validation and routine control of an ethylene oxide sterilization process for medical devices in both the industrial and health care facility settings, and it acknowledges the similarities and differences between the two applications.

NOTE 1 Among the similarities are the common need for quality systems, staff training, and proper safety measures. The major differences relate to the unique physical and organizational conditions in health care facilities, and to the initial condition of re-usable medical devices being presented for sterilization.

NOTE 2 Health care facilities differ from medical device manufacturers in the physical design of processing areas, in the equipment used, and in the availability of personnel with adequate levels of training and experience. The primary function of the health care facility is to provide patient care; medical device reprocessing is just one of a myriad of activities that are performed to support that function.

NOTE 3 In terms of the initial condition of medical devices, medical device manufacturers generally sterilize large numbers of similar medical devices that have been produced from virgin material. Health care facilities, on the other hand, must handle and process both new medical devices and re-usable medical devices of different descriptions and with varying levels of bioburden. They are therefore faced with the additional challenges of cleaning, evaluating, preparing and packaging a medical device prior to sterilization. In this International Standard, alternative approaches and guidance specific to health care facilities are identified as such.

NOTE 4 In general, moist heat sterilization (also known as steam sterilization) is the method of choice for medical devices and supplies that are sterilized in health care facilities. However, EO gas and its mixtures are effective sterilants that are primarily used for heat- and moisture-sensitive medical devices that cannot be steam sterilized.

NOTE 5 Although the scope of this International Standard is limited to medical devices, it specifies requirements and provides guidance that may be applicable to other health care products.

1.2 Exclusions

This International Standard does not specify requirements for the development, validation and routine control of a process for inactivating the causative agents of spongiform encephalopathies such as scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob disease. Specific recommendations have been produced in particular countries for the processing of materials potentially contaminated with these agents.

NOTE See ISO 22442-1, ISO 22442-2 and ISO 22442-3.

1.2.1 This International Standard does not detail a specified requirement for designating a medical device as sterile.

NOTE Attention is drawn to national or regional requirements for designating medical devices as “sterile”. See for example EN 556-1 or ANSI/AAMI ST67.

1.2.2 This International Standard does not specify a quality management system for the control of all stages of production of medical devices.

NOTE The effective implementation of defined and documented procedures is necessary for the development, validation and routine control of a sterilization process for medical devices. Such procedures are commonly considered to be elements of a quality management system. It is not a requirement of this International Standard to have a full quality management system during manufacture or reprocessing. The necessary elements are normatively referenced at appropriate places in the text (see, in particular, Clause 4). Attention is drawn to the standards for quality management systems (see ISO 13485) that control all stages of production or reprocessing of medical devices. National and/or regional regulations for the provision of medical devices might require the implementation of a full quality management system and the assessment of that system by a third party.

1.2.3 This International Standard does not specify requirements for occupational safety associated with the design and operation of EO sterilization facilities.

NOTE 1 For further information on safety, see examples in the Bibliography. National or regional regulations may also exist.

NOTE 2 EO is toxic, flammable and explosive. Attention is drawn to the possible existence in some countries of regulations giving safety requirements for handling EO and for premises in which it is used.

1.2.4 This International Standard does not cover sterilization by injecting EO or mixtures containing EO directly into packages.

NOTE See ISO 14937 for these types of EO processes.

1.2.5 This International Standard does not cover analytical methods for determining levels of residual EO and/or its reaction products.

NOTE 1 For further information see ISO 10993-7.

NOTE 2 Attention is drawn to the possible existence of national or regional regulations specifying limits for the level of EO residues present on or in medical devices and products.

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 10012, *Measurement management systems — Requirements for measurement processes and measuring equipment*

ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

ISO 11138-1:2006, *Sterilization of health care products — Biological indicators — Part 1: General requirements*

ISO 11138-2:2006, *Sterilization of health care products — Biological indicators — Part 2: Biological indicators for ethylene oxide sterilization processes*

ISO 11140-1, *Sterilization of health care products — Chemical indicators — Part 1: General requirements*

ISO 11737-1, *Sterilization of medical devices — Microbiological methods — Part 1: Determination of a population of microorganisms on products*

ISO 11737-2, *Sterilization of medical devices — Microbiological methods — Part 2: Tests of sterility performed in the validation of a sterilization process*

ISO 13485:2003/Cor 1:2009, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 14161:2009, *Sterilization of health care products — Biological indicators — Guidance for the selection, use and interpretation of results*

3 Terms and definitions

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

3.1

aeration

part of the sterilization process during which ethylene oxide and/or its reaction products desorb from the medical device until predetermined levels are reached

NOTE This may be performed within the sterilizer and/or in a separate chamber or room.

3.2

aeration area

either a chamber or a room in which aeration occurs

3.3

bioburden

population of viable microorganisms on or in the product and/or sterile barrier system

[ISO/TS 11139:2006, definition 2.2]

3.4

biological indicator

test system containing viable microorganisms providing a defined resistance to a specified sterilization process

[ISO/TS 11139:2006, definition 2.3]

3.5

calibration

set of operations that establish, under specified conditions, the relationship between values of a quantity indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards

[ISO/IEC Guide 99:2007 (VIM)]

3.6

chemical indicator

test system that reveals a change in one or more predefined process variable(s) based on a chemical or physical change resulting from exposure to a process

[ISO/TS 11139:2006, definition 2.6]

3.7

conditioning

treatment of product within the sterilization cycle, but prior to ethylene oxide admission, to attain a predetermined temperature and relative humidity

NOTE This part of the sterilization cycle can be carried out either at atmospheric pressure or under vacuum.

See 3.26, preconditioning.

3.8

***D* value**

***D*₁₀ value**

time or radiation dose required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions

[ISO/TS 11139:2006, definition 2.11]

NOTE For the purposes of this International Standard, the *D* value refers to exposure time.

3.9

development

act of elaborating a specification

[ISO/TS 11139:2006, definition 2.13]

3.10

establish

determine by theoretical evaluation and confirm by experimentation

[ISO/TS 11139:2006, definition 2.17]

3.11

ethylene oxide injection time

duration of the stage beginning with the first introduction of the sterilizing agent into the chamber to the completion of that injection

3.12

exposure time

period for which the process parameters are maintained within their specified tolerances

[ISO/TS 11139:2006, definition 2.18]

3.13

fault

one or more of the process parameters lying outside of its/their specified tolerance(s)

[ISO/TS 11139:2006, definition 2.19]

3.14

flushing

procedure by which the ethylene oxide is removed from the load and chamber by either

- a) multiple alternate admissions of filtered air, inert gas or steam and evacuations of the chamber or
- b) continuous passage of filtered air, inert gas or steam through the load and chamber

3.15

fractional cycle

a cycle in which the exposure time is reduced compared to that specified in the sterilization process

3.16

half cycle

a cycle in which the exposure time is reduced by 50 % compared to that specified in the sterilization process

3.17

health care facility

hospital, nursing home, extended care facility, free-standing surgical centre, clinic, medical office, or dental office

3.18**health care product**

medical device(s) including *in vitro* diagnostic medical device(s), or medicinal product(s), including biopharmaceuticals

[ISO/TS 11139:2006, definition 2.20]

NOTE In many health care facilities, dedicated departments perform cleaning, disinfection and sterilization activities to reprocess used medical devices.

3.19**installation qualification****IQ**

process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

[ISO/TS 11139:2006, definition 2.22]

3.20**medical device**

instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
- investigation, replacement or modification or support of the anatomy or of a physiological process;
- control of conception;
- disinfection of medical devices;
- providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body;

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

[ISO 13485:2003, definition 3.7]

3.21**microorganism**

an entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

NOTE A specific standard might not require demonstration of the effectiveness of the sterilization process in inactivating all types of microorganisms identified in the definition above for validation and/or routine control of the sterilization process.

[ISO/TS 11139:2006, definition 2.26]

3.22**operational qualification****OQ**

process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[ISO/TS 11139:2006, definition 2.27]