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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 de développement, de validation et de contrôle de routine d'un processus de stérilisation pour des dispositifs médicaux

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Foreword

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The committee responsible for this document is ISO/TC 198, *Sterilization of health care products*.

ISO 11135:2014 cancels and replaces ISO 11135-1:2007 and ISO/TS 11135-2:2008, both of which have been technically revised and condensed into a single standard.

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) might, 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 might 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 International 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 can 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 recognize 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) are 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 health care 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 can 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

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 reusable 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 reusable 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 EO gas and its mixtures are effective sterilants that are primarily used for heat- and/or moisture-sensitive medical devices that cannot be moist heat sterilized.

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

1.2 Exclusions

1.2.1 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.

1.2.2 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.

1.2.3 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.

1.2.4 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.

1.2.5 This International Standard does not cover sterilization by injecting EO or mixtures containing EO directly into packages or a flexible chamber.

NOTE See ISO 14937 for these types of EO processes.

1.2.6 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.

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 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 11138-2:2009, *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 definition, validation and maintenance of a sterilization process*

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

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 1 to entry: This can 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 product and/or sterile barrier system

[SOURCE: 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

[SOURCE: 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

[SOURCE: ISO/TS 11139:2006, definition 2.4]

3.6
chemical indicator
test system that reveals a change in one or more pre-defined process variables based on a chemical or physical change resulting from exposure to a process

[SOURCE: 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 1 to entry: This part of the sterilization cycle can be carried out either at atmospheric pressure or under vacuum.

Note 2 to entry: See 3.27, preconditioning.

3.8
***D* value**
D_{10} value
time or dose required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions

[SOURCE: ISO/TS 11139:2006, definition 2.11]

Note 1 to entry: For the purposes of this International Standard, the *D* value is the exposure time required to achieve 90 % inactivation of the population of the test organism.

3.9
development
act of elaborating a specification

[SOURCE: ISO/TS 11139:2006, definition 2.13]

3.10
dew point
The temperature at which the saturation water vapour pressure is equal to the partial pressure of the water vapour in the atmosphere

Note 1 to entry: Any cooling of the atmosphere below the dew point would produce water condensation.

3.11
establish
determine by theoretical evaluation and confirm by experimentation

[SOURCE: ISO/TS 11139:2006, definition 2.17]

3.12
ethylene oxide (EO) injection time
duration of the stage beginning with the first introduction of the EO (mixture) into the chamber to the completion of that injection

3.13
exposure time
period for which the process parameters are maintained within their specified tolerances

[SOURCE: ISO/TS 11139:2006, definition 2.18]

Note 1 to entry: For the purpose of calculation of cycle lethality, it is the period of sterilization between the end of EO injection and the beginning of EO removal.

3.14
fault
one or more of the process parameters lying outside of its/their specified tolerance(s)

[SOURCE: ISO/TS 11139:2006, definition 2.19]

3.15
flushing
procedure by which the ethylene oxide is removed from the load and chamber by either multiple alternate admissions of filtered air, inert gas or steam and evacuations of the chamber or continuous passage of filtered air, inert gas or steam through the load and chamber

3.16
fractional cycle
a cycle in which the exposure time to EO gas is reduced compared to that specified in the sterilization process

3.17
half cycle
a cycle in which the exposure time to EO gas is reduced by 50 % compared to that specified in the sterilization process

3.18
health care facility
HCF
governmental and private organizations and institutions devoted to the promotion and maintenance of health, and the prevention and treatment of diseases and injuries

EXAMPLE A health care facility can be a hospital, nursing home, extended care facility, free-standing surgical centre, clinic, medical office, or dental office.

3.19
health care product
medical device(s), including *in vitro* diagnostic medical device(s), or medicinal product(s), including biopharmaceutical(s)

[SOURCE: ISO/TS 11139:2006, definition 2.20]

3.20
installation qualification
IQ
process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

[SOURCE: ISO/TS 11139:2006, definition 2.22]

3.21
medical device
any 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

[SOURCE: ISO 13485:2003, definition 3.7]

3.22
microorganism
entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

Note 1 to entry: 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.

[SOURCE: ISO/TS 11139:2006, definition 2.26]

3.23
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[SOURCE: ISO/TS 11139:2006, definition 2.27]

3.24
overkill approach
approach using sterilization process that delivers a minimum of 12 Spore Log Reduction (SLR) to a biological indicator having a resistance equal to or greater than the product bioburden

3.25
parametric release
declaration that product is sterile, based on records demonstrating that the process parameters were delivered within specified tolerances

[SOURCE: ISO/TS 11139:2006, definition 2.29]

Note 1 to entry: This method of process release does not include the use of biological indicators.

3.26
performance qualification
PQ
process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification

[SOURCE: ISO/TS 11139:2006, definition 2.30]

3.27
preconditioning
treatment of product, prior to the sterilization cycle, in a room or chamber to attain specified conditions for temperature and relative humidity

3.28
process challenge device
PCD
item designed to constitute a defined resistance to a sterilization process and used to assess performance of the process

[SOURCE: ISO/TS 11139:2006, definition 2.33]

Note 1 to entry: For the purpose of this International Standard, a PCD can be product, simulated product or other device that is inoculated directly or indirectly. See 7.1.6 and D.7.1.6.

Note 2 to entry: In this International Standard, a distinction is made between an internal PCD and an external PCD. An internal PCD is used to demonstrate that the required product SAL is achieved. A PCD located within the confines of the product or product shipper case is an internal PCD, whereas a PCD located between shipper cases or on the exterior surfaces of the load is an external PCD. An external PCD is an item designed to be used for microbiological monitoring of routine production cycles.

3.29
process parameter
specified value for a process variable

Note 1 to entry: The specification for a sterilization process includes the process parameters and their tolerances.

[SOURCE: ISO/TS 11139:2006, definition 2.34]

