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

Stérilisation des produits de santé — Oxyde d'éthylène — Exigences de développement, validation et contrôle de routine d'un processus de stérilisation pour des dispositifs médicaux

[Revision of first edition (ISO 11135:1994)]

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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.

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

ISO 11135 was prepared by Technical Committee ISO/TC 198.

This second edition cancels and replaces the first edition and has been extensively revised.

Introduction

A sterile medical device is one which is free of viable microorganisms. International Standards, which specify requirements for validation and routine control of sterilization processes, require, when it is necessary to supply a sterile medical device, that adventitious microbiological contamination of a medical device prior to sterilization be minimised. Even so, 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 products are non-sterile. The purpose of sterilization is to inactivate the microbiological contaminants and thereby transform the non-sterile products 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 sterilizing agent; 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 product 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 product.

This International Standard describes requirements which will enable the demonstration that an ethylene oxide sterilization process intended to sterilize medical devices has appropriate microbicidal activity. This activity is both reliable and reproducible, such that the relationship for the inactivation of microorganisms can be extrapolated with reasonable confidence to low levels of probability of there being a viable microorganism present on a product after sterilization processing. This international standard does not specify the maximal value to be taken by this probability; specification of 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/development, production, installation and servicing are given in ISO 9001 and particular requirements for quality management systems for medical device production 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 factors including:

a) the microbiological status of incoming raw materials and/or components,

b) the validation and routine control of any cleaning and disinfection procedures used on the product,

c) the control of the environment in which the product is manufactured, assembled and packaged,

d) the control of equipment and processes,

e) the control of personnel and their hygiene,

f) the manner and materials in which the product is packaged, and,

g) 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, particular attention should be given to the validation and control of the cleaning and disinfection processes used during reprocessing.

The requirements are the normative parts of this standard with which compliance is claimed. The guidance given in the informative annexes is not normative and is not provided as a check list for auditors. The guidance provides explanations as well as methods that are accepted as being suitable means for complying with the requirements. Approaches other than those given in the guidance may be used, if they are effective in achieving compliance with the requirements of this International Standard.

The development, validation and routine control of a sterilization process comprise a number of discrete but interrelated activities, for example calibration, maintenance, product definition, process definition, installation qualification, operational qualification, and performance qualification. While the activities required by this standard have been grouped together and are presented in a particular order; this international standard does not require that the activities be performed in the order that they are presented. The activities required are not necessarily sequential, as the programs 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 undertake one or more of these activities. This International Standard does not specify the particular individuals or organizations to carry out the activities.

Sterilization of health care products — Ethylene oxide — Requirments 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.

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

1.2 Exclusions

1.2.1 Sterilization processes validated and controlled in accordance with the requirements of this standard should not be assumed to be effective in inactivating the causative agents of spongiform encephalopathies such as scrapie, bovine spongiform encephalopathy and Creutzfeld-Jacob disease. Specific recommendations have been produced in particular countries for the processing of materials potentially contaminated with these agents.

NOTE (See, for example, EN 12442-1, -2 and -3).

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

1.2.4 This International Standard does not specify requirements for occupational safety associated with the design and operation of ethylene oxide sterilization facilities**.**

NOTE 1 For further information, (see IEC 61010-2-042)

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

1.2.5 This International Standard does not cover sterilization by the technology of injecting ethylene oxide or its mixtures directly into individual product packages, or continuous sterilization processes.

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

NOTE 1 For further information see ISO 10993-7.

NOTE 2 Attention is drawn to the possible existence of statutory regulations laying down limits for the level of ethylene oxide residues within 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 9001 Quality systems – Model for quality assurance in design/development, production, installation and servicing.

ISO 13485 Quality management systems – Medical devices – Requirements for regulatory purposes

ISO 10012-1 Quality assurance requirements for measuring equipment – Part 1: Metrological confirmation system for measuring equipment.

ISO 10993-1 Biological evaluation of medical devices – Part 1. Evaluation and testing

ISO 10993-7 Biological evaluation of medical devices – Part 7. Ethylene oxide sterilization residuals

ISO 10993-17 Biological evaluation of medical devices – Part 17: Establishment of allowable limits for leachable substances

ISO 11138-1 Sterilization of health care products – Biological indicators. Part 1: General requirements

ISO 11138-2 Sterilization of health care products – Biological indicators. Part 2: Biological indicators for ethylene oxide sterilization

ISO 11140-1 Sterilization of health care products – Chemical indicators. – Part 1: General requirements

ISO 11737-1 Sterilization of health care products – Microbiological methods – Part 1: Estimation of the population of microorganisms on product

ISO 11737-2 Sterilization of health care products – Microbiological methods – Part 2: Tests of sterility performed in the validation of a sterilization process.

ISO 14161 Sterilization of health care products – Biological indicators – Guidance for the selection, use and interpretation of results

IEC 61010-1, Safety requirements for electrical equipment for measurement, control and laboratory use – Part 1: General requirements

IEC 61010-2-042, Safety requirements for electrical equipment for measurement, control and laboratory use – Particular requirements for autoclaves and sterilizers using toxic gas for the treatment of medical materials, and for laboratory processes

3 Terms and definitions

For the purposes of this International Standard, 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 a product and/or a package

[ISO TS 11139:2001]

3.4
biological indicator
microbiological test system providing a defined resistance to a specified sterilization process

[ISO TS 11139:2001]

3.5
calibration
set of operations which establish under specified conditions the relationship between values indicated by a measuring system, or values represented by a material measure or a reference material and the corresponding values of a quantity realised by a reference standard

[ISO TS 11139:2001]

3.6
chemical indicator
system that reveals a change in one or more predefined sterilization process variable(s) based on a chemical or physical change resulting from exposure to a process

[ISO TS 11139:2001]

3.7
conditioning
treatment of product within the sterilization cycle, but prior to sterilant admission to attain a predetermined temperature and relative humidity. This part of the sterilization cycle may be carried out either at atmospheric pressure or under vacuum. (See also preconditioning.)

3.8
D value
time or radiation dose required to achieve inactivation of 90% of a population of the test microorganism under stated exposure conditions

[ISO TS 11139:2001]

NOTE For ethylene oxide sterilization, the D value refers to exposure time only.

3.9
development
act of elaborating a specification in preparation for validation

[ISO TS 11139:2001]

3.10
establish
determine by theoretical evaluation and confirm by experimentation

[ISO TS 11139:2001]

3.11
exposure time
period for which the process parameters are maintained within their specified tolerances

[ISO TS 11139:2001]

3.12
fault
one or more of the process parameters outside of its/their specified tolerance(s)

[ISO TS 11139:2001]

3.13
flushing
procedure by which the sterilant is removed from the load and chamber by either:

a) multiple alternate admissions of filtered air or inert gas and evacuations of the chamber; or

b) continuous passage of filtered air or inert gas through the load and chamber

3.14
health care product
medical devices, medicinal products (pharmaceuticals including biologicals) and *in vitro* diagnostics

[ISO TS 11139:2001]

3.15
inoculated carrier
supporting material on or in which a defined number of test microorganisms have been deposited

[ISO TS 11139:2001]

3.16
installation qualification (IQ)
obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification [ISO TS 11139:2001]

3.17
medical device
any instrument, apparatus, appliance material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;

— investigation, replacement or modification of the anatomy or of a physiological process;

— control of conception;

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 TS 11139:2001]

3.18
microorganism
an entity, encompassing bacteria, fungi, protozoa and viruses

[ISO TS 11139:2001]

3.19
operational qualification (OQ)
obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[ISO TS 11139:2001]

3.20
overkill
sterilisation process which, when validated, delivers minimally a 12 Spore Log Reduction (SLR) to a biological indicator having a resistance equal to or greater than the product bioburden

3.21
parametric release
declaring a product sterile, based on records demonstrating that the process parameters were delivered within specified tolerances

[ISO TS 11139:2001]

NOTE This method of process release does not include the use of biological indicators.

3.22
performance qualification (PQ)
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

[ISO TS 11139:2001]

3.23
preconditioning

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

3.24
process challenge device (PCD)
item designed to simulate product to be sterilized and to constitute a defined challenge to the sterilization process, and used to assess the effective performance of the sterilization process

[ISO TS 11139:2001]

3.25
process parameter
specified value for a process variable

NOTE The specification for a sterilization process includes the process parameters and their tolerances

[ISO TS 11139:2001]

3.26
process variable
condition associated with a sterilization process, changes in which alter microbicidal effectiveness

NOTE Process variables may include, for example, time, temperature, pressure, concentration, humidity, wavelength.

[ISO TS 11139:2001]

3.27
product
raw materials, intermediate products, sub-assemblies and finished health care products [ISO TS 11139:2000]

3.28
product unit
health care product, collection of products or components, contained within a primary package

[ISO TS 11139:2001]

3.29
recognized culture collection
international depository authority under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent and Regulation

3.30
reference microorganism
microbial strain obtained from a recognized culture collection

3.31
requalification
repetition of part of validation for the purpose of confirming the continued acceptability of a specified process

[ISO TS 11139:2001]

3.32
services
supplies from an external source, necessary for the correct functioning of sterilization equipment

NOTE Examples of services are electricity, water, compressed air, and drainage.

[ISO TS 11139:2001]

3.33
specify
stipulate in detail within an approved document

[ISO TS 11139:2001]

3.34
sterilant injection time
duration of the sterilant injection stage (stage beginning with the first introduction of sterilant into the chamber and ending whenever the operating pressure has been attained)

3.35
sterile
free from viable microorganisms

[ISO TS 11139:2001]

3.36
sterility
state of being free from viable microorganisms

[ISO TS 11139:2001]

3.37
sterility assurance level (SAL)
probability of a viable microorganism being present on a product unit after sterilization

NOTE SAL is normally expressed as 10^{-n}

[ISO TS 11139:2001]

3.38
sterilization
validated process used to render a product free from viable microorganisms

NOTE In a sterilization process, the nature of microbial inactivation is described by an exponential function. Therefore the presence of a viable microorganism on any item can be expressed in terms of probability. While this probability may be reduced to a very low number, it can never be reduced to zero. (See "Sterility Assurance Level" [SAL])

[ISO TS 11139:2001]

3.39
sterilization cycle
treatment in a sealed chamber comprising air removal, conditioning (if used), injection of sterilant, exposure to ethylene oxide, removal of ethylene oxide and flushing (if used)

3.40
sterilization load
product to be, or that has been, sterilized together, using a given sterilization process

[ISO TS 11139:2001]

3.41
sterilization process
series of actions or operations to achieve the specified requirements for sterility

[ISO TS 11139:2001]

NOTE This series of actions or operations includes pretreatment (if necessary), exposure to the sterilizing agent under defined conditions and any necessary post-treatment. It does not include any cleaning, disinfection or packaging operations that precede the sterilization process.

3.42
sterilizing agent
physical or chemical entity, or combination of entities, that have sufficient microbicidal activity to achieve sterility under defined conditions

[ISO TS 11139:2001]

NOTE With respect to this standard, the sterilizing agent is ethylene oxide or a mixture of ethylene oxide and a diluent.

3.43
survivor curve
graphical representation of the inactivation of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions

[ISO TS 11139:2001]

3.44
test of sterility
test performed as part of development, validation or requalification to establish the presence or absence of viable microorganisms on product units or portions thereof

[ISO TS 11139:2001]