INTERNATIONAL STANDARD

ISO 11135-1

First edition
2007-05-01

Corrected version
2007-11-01

Sterilization of health care products — Ethylene oxide —

Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices

Stérilisation des produits de santé — Oxyde d'éthylène —
Partie 1: Exigences de développement, de validation et de contrôle de routine d'un processus de stérilisation pour des dispositifs médicaux

Reference number
ISO 11135-1:2007(E)

ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

Published in Switzerland

Contents

Page

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 11135-1 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

ISO 11135 consists of the following parts, under the general title *Sterilization of health care products — Ethylene oxide*:

— *Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

— *Part 2: Guidance on the application of ISO 11135-1*

ISO 11135-1, together with ISO 11135-2, cancels and replaces ISO 11135:1994 and ISO 11135-4/Cor. 1:1994, which have been technically revised.

This corrected version of ISO 11135-1:2007 includes the following corrections:

— page iv, Foreword: the sentence “ISO 11135-1, together with ISO 11135-2, cancels and replaces ..... technically revised.” has been added.

Introduction

A sterile medical device is one that is free of viable microorganisms. International Standards that 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 minimized. 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 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; 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.

This part of 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 this activity is both reliable and reproducible so that it can be predicted, with reasonable confidence, that there is a low level of probability of there being a viable microorganism present on product after sterilization. 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 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:

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 or reprocessed, 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;

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, it is important to pay particular attention to the validation and control of the cleaning and disinfection processes used during reprocessing.

The requirements are the normative parts of this part 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 provides explanations and methods that are regarded as being suitable means for complying with the requirements. Methods other than those given in the guidance may be used if they are effective in achieving compliance with the requirements of this part 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 this part of ISO 11135 have been grouped together and are presented in a particular order, this part of 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 part of ISO 11135 does not specify the particular individuals or organizations to carry out the activities.

When determining the suitability of ethylene oxide (EO) for sterilization of medical devices, it is important that patient safety is addressed by minimizing exposure to residual EO, ethylene chlorohydrin (ECH) and ethylene glycol (EG) during normal product use (see ISO 10993-7).

Sterilization of health care products — Ethylene oxide —

Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices

1 Scope

This part of ISO 11135 specifies requirements for the development, validation and routine control of an ethylene oxide sterilization process for medical devices.

NOTE 1 Although the scope of this part of ISO 11135 is limited to medical devices, it specifies requirements and provides guidance that may be applicable to other health care products.

Sterilization processes validated and controlled in accordance with the requirements of this part of ISO 11135 are not 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 2 See for example ISO 22442-1, ISO 22442-2 and ISO 22442-3.

This part of ISO 11135 does not detail a specified requirement for designating a medical device as sterile.

NOTE 3 Attention is drawn to national or regional requirements for designating medical devices as “sterile”. See for example EN 556-1 or ANSI/AAMI ST67.

This part of ISO 11135 does not specify a quality management system for the control of all stages of production of medical devices.

NOTE 4 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 part of ISO 11135 to have a complete quality management system during manufacture or reprocessing, but the elements of a quality management system that are the minimum necessary to control the sterilization process are normatively referenced at appropriate places in the text (see in particular Clause 4). National and/or regional regulations for the provision of medical devices might require implementation of a complete quality management system and the assessment of that system by a third party.

This part of ISO 11135 does not specify requirements for occupational safety associated with the design and operation of ethylene oxide sterilization facilities.

NOTE 5 For further information on safety, see examples in the Bibliography. National or regional regulations may also exist.

NOTE 6 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.

This part of ISO 11135 does not cover sterilization by injecting ethylene oxide or mixtures containing ethylene oxide directly into individual product packages, or continuous sterilization processes.

This part of ISO 11135 does not cover analytical methods for determining levels of residual ethylene oxide and/or its reaction products.

NOTE 7 For further information see ISO 10993-7.

NOTE 8 Attention is drawn to the possible existence of regulations specifying limits for the level of ethylene oxide 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 10993-1, *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 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, *Medical devices — Quality management systems — Requirements for regulatory purposes*

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

ISO 14937:2000, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

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

[VIM:1993, definition 6.11]

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 3.25, 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 part of ISO 11135, 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 ethylene oxide into the chamber and ending when addition of ethylene oxide gas or the ethylene oxide gas mixture ceases

3.12
exposure time
period for which the process parameters are maintained within their specified tolerances

[ISO/TS 11139:2006, definition 2.18]

NOTE For the purposes of this part of ISO 11135, it is the period of the sterilization cycle between the end of the ethylene oxide injection time and the initiation of ethylene oxide removal.

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 or inert gas and evacuations of the chamber or

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

3.15
fractional cycle
process in which the exposure time is reduced compared to that specified in the sterilization process

3.16
half cycle
sterilization cycle in which the exposure time is reduced by 50 % compared with the sterilization process

3.17
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]

3.18
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]

3.19
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]

NOTE This definition from ISO 13485:2003 was developed by the Global Harmonization Task Force (GHTF 2002).

3.20
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]

3.21
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]

3.22
overkill
sterilization process that is demonstrated as delivering at least a 12 Spore Log Reduction (SLR) to a biological indicator having a resistance equal to or greater than the product bioburden

3.23
parametric release
declaration that product is sterile, based on records demonstrating that the process parameters were delivered within specified tolerances

[ISO/TS 11139:2006, definition 2.29]

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

3.24
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

[ISO/TS 11139:2006, definition 2.30]

3.25
preconditioning
treatment of product, prior to the sterilization cycle, in a room or chamber to attain specified limits for temperature and relative humidity

3.26
process challenge device
PCD
item designed to constitute a defined resistance to the sterilization process and used to assess performance of the process

[ISO/TS 11139:2006, definition 2.33]

3.27
process parameter
specified value for a process variable

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

[ISO/TS 11139:2006, definition 2.34]

3.28
process variable
condition within a sterilization process, whose changes alter microbicidal effectiveness

EXAMPLE Time, temperature, pressure, concentration and humidity.

[ISO/TS 11139:2006, definition 2.35]

3.29
product
result of a process

[ISO 9000:2005, definition 3.4.2]

NOTE For the purposes of sterilization standards, product is tangible and can be raw material(s), intermediate(s), sub-assembly(ies) and health care products.

3.30
product load volume
defined space within the usable chamber volume occupied by product

3.31
recognized culture collection
depository authority under the Budapest Treaty on *The International Recognition of the Deposit of Microorganisms for the Purpose of Patent and Regulation*

[ISO/TS 11139:2006, definition 2.38]

3.32
reference microorganism
microbial strain obtained from a recognized culture collection

[ISO/TS 11139:2006, definition 2.39]

3.33
requalification
repetition of part of validation for the purpose of confirming the continued acceptability of a specified process

[ISO/TS 11139:2006, definition 2.40]

3.34
services
supplies from an external source, needed for the correct function of equipment

EXAMPLE Electricity, water, compressed air, drainage.

[ISO/TS 11139:2006, definition 2.41]

3.35
specify
stipulate in detail within an approved document

[ISO/TS 11139:2006, definition 2.42]

3.36
Spore Log Reduction
SLR
factor, expressed as the logarithm to base 10, describing the reduction in the number of spores on a biological indicator produced by exposure to specified conditions

NOTE SLR can be calculated as the log of the initial population minus the log of the final population of the biological indicator. See below:

$$SLR = \log N_0 - \log N_u$$

where

N_u is the final population of the biological indicator;

N_0 is the initial population of the biological indicator.

If there are no survivors, the true SLR cannot be calculated. If one positive or surviving organism is assumed, the SLR is reported as “greater than” $\log N_0$.

3.37
sterile
free from viable microorganisms

[ISO/TS 11139:2006, definition 2.43]

3.38
sterility
state of being free from viable microorganisms

NOTE In practice, no such absolute statement regarding the absence of microorganisms can be proven

See 3.40, sterilization.

[ISO/TS 11139:2006, definition 2.45]