INTERNATIONAL STANDARD

ISO 11135

First edition
1994-02-01

Medical devices — Validation and routine control of ethylene oxide sterilization

Dispositifs médicaux — Validation et contrôle de routine de la stérilisation à l'oxyde d'éthylène

Reference number
ISO 11135:1994(E)

Contents

International Organization for Standardization
Case Postale 56 • CH-1211 Genève 20 • Switzerland
Printed in Switzerland

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.

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.

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

Annexes A, B, C and D of this International Standard are for information only.

Introduction

International Standards require, when it is necessary to supply a sterile product item, that adventitious microbiological contamination of medical devices from all sources is minimized by all practical means. Even so, product items produced under standard manufacturing conditions in accordance with ISO Quality Systems Standards may well, prior to sterilization, have microorganisms on them, albeit in low numbers. Such product items are nonsterile. The purpose of sterilization processing is to deactivate the microbiological contaminants and thereby transform the nonsterile items into sterile ones.

The deactivation of microorganisms by physical and chemical agents used to sterilize medical devices follows an exponential law; 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 types of microorganisms and the environment in which the organisms exist before and during treatment. It follows that the sterility of any one item in a population of items subjected to sterilization can only be expressed in terms of the probability of the existence of a nonsterile item in that population.

Requirements for the quality system for the design/development, production, supply, installation and servicing are given in the ISO 9000 series.

The ISO 9000 series of Standards designates certain processes used in manufacture as "special" in that the results cannot be fully verified by subsequent inspection and testing of the product. Sterilization is an example of a special process because process efficacy cannot be verified by inspection and testing of the product. For this reason, sterilization processes need to be validated before use and the performance of the process needs to be monitored routinely. The manufacture of a sterile medical device requires attention to product and package characteristics, and to sterilization methods, facilities and controls.

It is important to be aware that exposure to a properly validated and accurately controlled sterilization process is not the only factor associated with the provision of reliable assurance that the product is sterile and suitable for its intended use. Attention should also be given to a number of factors including the microbiological status (bioburden) of incoming raw materials and their subsequent storage, and to the control of the environment in which the product is manufactured, assembled and packaged.

This International Standard contains requirements and offers guidance (as given in the annexes) for the validation and routine monitoring of sterilization by gaseous ethylene oxide. The validation of sterilization procedures presupposes that the sterilization equipment complies with appropriate specifications.

NOTE 1 The requirements are the obligatory parts of this Standard with which compliance has to be achieved. The guidance given in the informative annexes is not obligatory and it is **not** provided as a check-list for auditors.

The guidance included in the annexes provides explanations as well as methods which are accepted as being suitable for achieving compliance with the requirements. This guidance is provided in order to assist in obtaining a uniform understanding and implementation of this International Standard. Methods other than those given in the guidance may be used. However, these methods need to be demonstrated to be effective in achieving compliance with the requirements of this International Standard.

Medical devices — Validation and routine control of ethylene oxide sterilization

1 Scope

1.1 This International Standard establishes requirements and guidance for validation and routine control of ethylene oxide sterilization processes for medical devices.

Particular attention is drawn to the need for specific testing for safety, quality and efficacy, possibly exceeding the requirements of 4.2, which may be necessary for a specific product.

NOTE 2 Although this International Standard has been written for medical device sterilization, it may also apply to other health care products.

1.2 It does not cover the quality assurance system which is essential to control all stages of manufacture which include the sterilization process.

1.3 It does not cover operator safety (for further information, see IEC 1010-2).

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

Attention is drawn to the existence in some countries of statutory regulations laying down limits for the level of ethylene oxide residues within medical devices and products.

1.4 It does not cover sterilization either by the technology of injecting ethylene oxide or its mixtures directly into individual product packages or continuous sterilization processes.

1.5 It does not cover analytical methods for determining levels of residual ethylene oxide and/or its reaction products (see ISO 10993-7).

1.6 It does not cover products that are affected adversely by ethylene oxide or by other ethylene oxide residuals produced in the processes described.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this International Standard. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this International Standard are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 9001:1987, *Quality systems — Model for quality assurance in design/development, production, installation and servicing.*

ISO 9002:1987, *Quality systems — Model for quality assurance in production and installation.*

ISO 9004:1987, *Quality management and quality system elements — Guidelines.*

ISO 10993-7:—[1], *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals.*

ISO 11138-1:—[1], *Sterilization of health care products — Biological indicators — Part 1: General.*

1) To be published.

3 Definitions

For the purposes of this International Standard, the following 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 3 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 biological indicator (BI): Inoculated carrier contained within its primary pack providing a known resistance to the relevant process.

3.4 calibration: Comparison of a measurement system or device of unknown accuracy to a measurement system or device of known accuracy (traceable to national standards) to detect, correlate, report, or eliminate by adjustment, any variation from the required performance limits of the unverified measurement system or device.

3.5 chamber: Enclosed area which only accommodates sufficient product to fill the sterilizer.

3.6 commissioning; installation qualification: Obtaining and documenting evidence that equipment has been provided and installed in accordance with its specifications and that it functions within predetermined limits when operated in accordance with operational instructions. (See also validation.)

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 cycle completion: That point after completion of the sterilization cycle at which the sterilization load is ready to be removed from the chamber.

3.9 exposure time: Time for which the sterilizer chamber is maintained within the specified range for temperature, sterilant concentration, pressure and humidity.

3.10 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.

3.11 inoculated carrier: Carrier on which a defined number of test organisms has been deposited.

3.12 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 purposes 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.

3.13 parametric release: Declaring product as sterile, based on physical and/or chemical process data rather than on the basis of sample testing or biological indicator results.

3.14 performance qualification: Obtaining and documenting evidence that the equipment as commissioned will produce acceptable product when operated in accordance with the process specification. (See also validation.)

3.15 preconditioning: Treatment of product prior to the sterilization cycle in a room or chamber to attain specified limits for temperature and relative humidity. (See also conditioning.)

NOTE 4 This part of the sterilization cycle may be carried out either at atmospheric pressure or under vacuum.

3.16 preconditioning area: Either a chamber or a room in which preconditioning occurs.

3.17 process challenge device: Object which simulates the worst case of conditions as they are given for the sterilizing agent(s) in the items of the goods to be sterilized.

NOTES

5 The device is so constituted that a biological indicator can be arranged in the place most difficult for the sterilant to reach. The design of the process challenge device depends on the kind of goods to be sterilized and the sterilization procedure. The biological indicator should not interfere with the function of the process challenge device.

6 In some process challenge devices an inoculated carrier may be used in place of a biological indicator.

3.18 process development: Documented programme of studies which is performed in order to define the sterilization process based upon the product/packaging/loading pattern and/or equipment limitations.

3.19 product compatibility: Ability of the sterilization process to achieve the intended results without detrimental effect on the product.

3.20 reference load: Specified sterilization load made up to represent the most difficult combination of products to be sterilized.

3.21 revalidation: Set of documented procedures to confirm an established validation.

3.22 room: Enclosed area capable of holding more product than can be accommodated in the sterilizer(s) at any one time.

3.23 sterilant injection stage: Stage beginning with the first introduction of sterilant into the chamber and ending whenever the set operating pressure has been attained.

3.24 sterilant injection time: Duration of the sterilant injection stage.

3.25 sterilant removal time: Portion of the sterilization cycle in which sterilant is removed from the chamber and sterilization load, but not necessarily desorbed from individual products. (See also aeration.)

3.26 sterility: State of being free from viable microorganisms. (See sterilization.)

NOTE 7 In practice no such absolute statement regarding the absence of microorganisms can be proven.

3.27 sterile: Free from viable microorganisms. (See sterilization and note 7.)

3.28 sterilization: Validated process used to render a product free of all forms of viable microorganisms.

NOTE 8 In a sterilization process, the nature of microbial death is described by an exponential function. Therefore, the presence of viable microorganisms on any individual 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. The probability can be expressed as a sterility assurance level (SAL).

3.29 sterility assurance level; SAL: Probability of a viable microorganism being present on a product unit after sterilization.

NOTE 9 SAL is normally expressed as 10^{-n}.

3.30 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).

3.31 sterilization load: Goods that are to be or have been sterilized simultaneously in the same sterilization chamber.

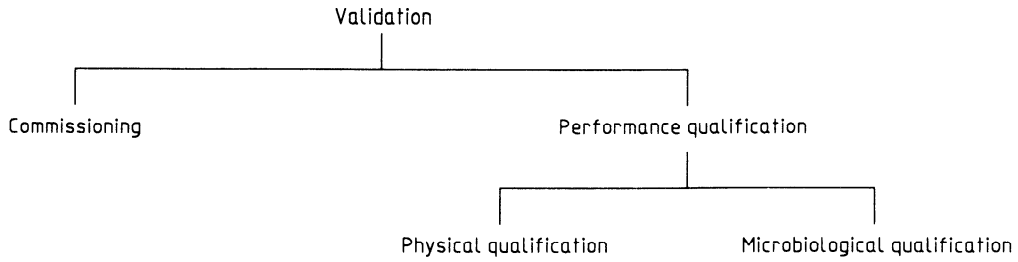
NOTE 10 The sterilization load may include more than one manufacturing batch or lot.

3.32 sterilization process: All treatments which are required to accomplish sterilization to include preconditioning (if used), the sterilization cycle and aeration.

3.33 usable sterilizer chamber volume: Space inside the sterilizer chamber which is not restricted by fixed or mobile parts (loading units, pallets, etc.) and which is consequently available to accept the sterilization load. This is expressed in terms of height, width and depth.

3.34 validation: Documented procedure for obtaining, recording and interpreting the results needed to show that a process will consistently yield a product complying with predetermined specifications.

NOTE 11 Validation is considered as a total process which consists of commissioning and performance qualification. The relationship between these terms is illustrated below.



4 General

Medical devices to be sterilized shall be manufactured under conditions that ensure that their bioburden is consistently low. Employing a quality system complying with ISO 9001 or ISO 9002 meets this requirement.

The documented procedures and instructions required by this International Standard shall be implemented effectively according to the requirements of ISO 9001 or ISO 9002.

4.1 Personnel

Responsibility for the maintenance of equipment (see 4.4.1), for the validation and routine control of ethylene oxide sterilization and for the release of product shall be assigned to qualified personnel as specified in subclauses 4.1.2.2 and 4.18 of ISO 9001:1987 or in subclauses 4.1.2.2 and 4.17 of ISO 9002:1987.

4.2 Process development and product compatibility

4.2.1 Prior to the introduction of a new or altered product, package, loading pattern or sterilization process, the sterilization process to be validated shall be defined and documented.

A demonstration of equivalence to previously validated product, package or loading pattern shall be considered to meet this requirement. Any demonstration of equivalence shall be documented.

4.2.2 Product and packaging shall be designed to allow removal of air and penetration of steam and ethylene oxide. The location within the product at which sterilization is most difficult to achieve shall be identified.

4.2.3 It shall have been demonstrated that the specified sterilization process does not affect the correct functioning of the product and its packaging.

4.2.4 If resterilization is to be permitted, the effects of such processing shall be evaluated.

4.3 Sterilization process

The sterilization process shall include preconditioning and/or conditioning, sterilization cycle and aeration.

4.3.1 Preconditioning and/or conditioning

Preconditioning and/or conditioning treatments shall be performed under controlled conditions for a defined period of time to achieve specified temperature and relative humidity within the load (see A.3.1).

Humidity during conditioning shall be generated by the introduction of steam into the sterilizer.

4.3.2 Sterilization cycle

The sterilization cycle shall include:

a) air removal;

b) conditioning (if used);

c) sterilant injection;

d) maintenance of specified conditions for the exposure time;

e) sterilant removal;

f) flushing (if used); and

g) air admission to atmospheric pressure.

4.3.3 Aeration

Product shall be retained under specified conditions for a defined period for aeration. (See also 5.3.4.)

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

4.4 Equipment

4.4.1 The specification for the equipment to be used for ethylene oxide sterilization, including the preconditioning area, shall be documented.

NOTE 12 Such a specification for a sterilizer design may be established by local or international regulators or by a relevant standards organization.

4.4.2 The conditions used for storage of sterilant prior to and during use shall ensure that its quality and composition remains within specification.

4.5 Calibration

An effective system shall be established, documented and maintained for the calibration of all controlling, indicating and recording instruments used for validation and routine control of the sterilization process. This system shall comply with the requirements of either subclause 4.12 of ISO 9001:1987 or subclause 4.11 of ISO 9002:1987.

4.6 Maintenance

4.6.1 Preventative maintenance shall be planned and performed in accordance with documented procedures. The procedure for each planned maintenance task and the frequency at which it is to be carried out shall be specified and documented.

4.6.2 Equipment (see 4.4.1) shall not be used to process medical devices until all maintenance tasks have been satisfactorily completed and recorded.

4.6.3 Records of maintenance shall be retained as specified in subclause 4.16 of ISO 9001:1987 or in subclause 4.15 of ISO 9002:1987.

4.6.4 The maintenance scheme, maintenance procedures and maintenance records shall be reviewed periodically by a designated person (see 4.1).

5 Validation

5.1 General

Procedures for validation shall be documented and records of validation shall be retained as specified in subclause 4.16 of ISO 9001:1987 or in subclause 4.15 of ISO 9002:1987.

5.2 Commissioning

5.2.1 Commissioning shall demonstrate that the equipment specifications for the preconditioning (if used), sterilization and aeration equipment are met.

5.2.2 Commissioning shall commence with the calibration of all instrumentation for controlling, indicating and recording the sterilization process.

5.3 Performance qualification — physical

5.3.1 Physical performance qualification shall be performed on the introduction of new or altered products, packaging, loading patterns, equipment or process parameters, unless equivalence to a previously validated product, packaging or loading pattern combination has been demonstrated.

The demonstration of equivalence shall be documented.

5.3.2 Product used for physical performance qualification shall be packaged as it will be routinely presented for sterilization.

5.3.3 The maximum elapsed time between the completion of preconditioning (if used) and the commencement of the sterilization cycle shall be established and documented.

5.3.4 The physical performance qualification shall demonstrate

a) that at the end of the defined preconditioning time, the sterilization load is within the temperature and humidity ranges documented in the preconditioning specification;

b) the correlation between humidity and the increase in pressure on steam admission;

c) that at the admission of the sterilant to the chamber the sterilization load is within the temperature and humidity ranges documented in the sterilization process specification;

d) that gaseous sterilant has been admitted to the sterilizer chamber;

e) that the temperature and humidity and where applicable other parameters are within the ranges documented in the sterilization process specification;

f) that physical conditions specified for the sterilization load are maintained for the entire exposure time; and

g) that during aeration, the sterilization load is within the specified temperature range.

5.3.5 The levels of residual ethylene oxide and/or its reaction products after aeration in accordance with the documented procedures shall be determined to demonstrate that the levels after aeration are below specified limits.

5.4 Performance qualification — microbiological

5.4.1 Microbiological performance qualification shall be performed on the introduction of new or altered products, packaging, loading pattern, equipment or process parameters, unless equivalence to a previously validated product, package or loading pattern has been demonstrated. The demonstration of equivalence shall be documented.

5.4.2 The appropriateness of the biological indicators shall be established and documented.

5.4.3 Product used for microbiological performance qualification shall be packaged as it will be routinely presented for sterilization.

5.4.4 The microbiological performance qualification shall demonstrate the adequacy of the process for the sterilization of product by the inactivation of biological indicators complying with ISO 11138-1.

These indicators shall be placed at representative positions throughout the sterilization load under the cycle conditions selected to deliver less lethality than those used routinely such that on application of the specified sterilization cycle, assurance of sterility is attained.

5.4.5 If a process challenge device designed to simulate the product is to be used for routine monitoring in combination with indicators for ethylene oxide sterilization, the appropriateness of this process challenge device shall be demonstrated.

5.4.6 Indicators for ethylene oxide sterilization shall be positioned within the sterilization load prior to preconditioning (if used), and remain in position during the sterilization cycle.

5.4.7 The bioburden of the product shall be established and documented. A future International Standard will cover microbiological methods of validation and routine control.

5.5 Certification of validation

5.5.1 A validation report shall be documented. The report shall be signed by persons designated as responsible for preparing, reviewing and accepting this report. The validation report shall be retained as specified in subclause 4.16 of ISO 9001:1987 or in subclause 4.15 of ISO 9002:1987.

5.5.2 The validation report shall contain or reference specific validated product and the documented specification for the ethylene oxide sterilization process. The validation report shall also include the value and tolerances for the following.

5.5.2.1 Preconditioning (if used):

a) time, temperature, humidity;

b) minimum temperature of product permitted to enter preconditioning;

c) loading pattern and separation of product within the preconditioning area;

d) sterilization load temperature and humidity; and

e) maximum elapsed time between removal of the load from preconditioning and commencement of the sterilization cycle.

5.5.2.2 Conditioning, if used (see 4.3.1):

a) if used, the initial vacuum level and time taken to achieve it;

b) holding time under vacuum;

c) time, temperature, pressure and humidity; and

d) temperature and humidity of the sterilization load.

5.5.2.3 Sterilization:

a) sterilant injection pressure rise, sterilant injection time and final pressure;

b) ethylene oxide concentration determined independently from the increase in pressure, using at least one of the following:

1) mass of sterilant used,