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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

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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 11135-1 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:

$$\mathrm{SLR} = \log N_0 - \log N_u$$

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]

3.39
sterility assurance level
SAL
probability of a single viable microorganism occurring on an item after sterilization

NOTE The term SAL takes a quantitative value, generally 10^{-6} or 10^{-3}. When applying this quantitative value to assurance of sterility, an SAL of 10^{-6} has a lower value but provides a greater assurance of sterility than an SAL of 10^{-3}.

[ISO/TS 11139:2006, definition 2.46]

3.40
sterilization
validated process used to render product free from viable microorganisms

NOTE In a sterilization process, the nature of microbial inactivation is described as exponential and, thus, the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

See 3.39, sterility assurance level.

[ISO/TS 11139:2006, definition 2.47]

3.41
sterilization cycle
treatment in a sealed chamber comprising air removal, conditioning (if used), injection of ethylene oxide, exposure to ethylene oxide, removal of ethylene oxide and flushing (if used), and air/inert gas admission

3.42
sterilization load
product to be, or that has been, sterilized together using a given sterilization process

[ISO/TS 11139:2006, definition 2.48]

3.43
sterilization process
series of actions or operations needed to achieve the specified requirements for sterility

[ISO/TS 11139:2006, definition 2.49]

NOTE This series of actions or operations includes pretreatment (if necessary), exposure to the ethylene oxide under defined conditions and any necessary post-treatment required for the removal of ethylene oxide and its by-products. It does not include any cleaning, disinfection or packaging operations that precede the sterilization process.

3.44
sterilizing agent
physical or chemical entity, or combination of entities, having sufficient microbicidal activity to achieve sterility under defined conditions

[ISO/TS 11139:2006, definition 2.50]

NOTE With respect to this part of ISO 11135, the sterilizing agent is ethylene oxide or a mixture of ethylene oxide and a diluent.

3.45
survivor curve
graphical representation of the inactivation of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions

[ISO/TS 11139:2006, definition 2.51]

3.46
test of sterility
technical operation performed as part of development, validation or requalification to determine the presence or absence of viable microorganisms on product or portions thereof

[ISO/TS 11139:2006, definition 2.53]

3.47
usable chamber volume
defined space within the sterilizer chamber, which is not restricted by fixed or mobile parts and which is available to accept the sterilization load

EXAMPLE The available space on a pallet of defined dimensions.

NOTE The volume allowed for circulation inside the chamber is not included as usable space.

3.48
validation
documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications

[ISO/TS 11139:2006, definition 2.55]

4 Quality management systems

4.1 Documentation

4.1.1 Procedures for development, validation, routine control and product release from sterilization shall be specified.

4.1.2 Documents and records required by this part of ISO 11135 shall be reviewed and approved by designated personnel (see 4.2.1). Documents and records shall be controlled in accordance with the applicable clauses of ISO 13485.

4.2 Management responsibility

4.2.1 The responsibility and authority for implementing and meeting the requirements described in this part of ISO 11135 shall be specified. Responsibility shall be assigned to competent personnel in accordance with the applicable clauses of ISO 13485.

4.2.2 If the requirements of this part of ISO 11135 are undertaken by organizations with separate quality management systems, the responsibilities and authority of each party shall be specified.

4.3 Product realization

4.3.1 Procedures for purchasing shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.

4.3.2 Procedures for identification and traceability of product shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.

4.3.3 A system complying with the applicable clauses of ISO 13485 or ISO 10012 shall be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this part of ISO 11135.

4.4 Measurement, analysis and improvement — Control of nonconforming product

Procedures for control of product designated as nonconforming and for correction, corrective action and preventive action shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.

5 Sterilizing agent characterization

5.1 Sterilizing agent

The composition, storage conditions and shelf life for the sterilizing agent shall be specified.

NOTE With respect to this part of ISO 11135, the sterilizing agent is ethylene oxide or a mixture of ethylene oxide and a diluent.

5.2 Microbicidal effectiveness

Microbicidal effectiveness data shall be developed if it is proposed to use the ethylene oxide outside of the range of compositions that are widely recognized or if a novel diluent is to be used.

NOTE The inactivation of microorganisms by ethylene oxide has been comprehensively documented in the literature. This literature provides a knowledge of the manner in which the process variables affect microbial inactivation. Reference to these general studies on microbial inactivation is not required by this part of ISO 11135.

5.3 Material effects

The effects of ethylene oxide on a wide variety of materials used to manufacture medical devices have been comprehensively documented and such documentation is of value to those designing and developing medical devices that are to be sterilized by ethylene oxide. This part of ISO 11135 does not require the performance of specific studies on material effects, but does require performance of studies of the effects of ethylene oxide on product (see Clause 7). The materials and outcomes of all tests shall be recorded, together with the criteria against which the properties of materials were assessed.

5.4 Environmental considerations

5.4.1 The potential effect on the environment of the operation of the sterilization process shall be assessed and measures to protect the environment shall be identified. This assessment, including potential impact and measures for control, shall be documented.

5.4.2 Users of ethylene oxide shall comply with applicable local, national and international requirements regarding the emission and disposal of ethylene oxide and its diluents.

6 Process and equipment characterization

6.1 Process characterization

6.1.1 The range of process variables and the equipment necessary to deliver the sterilization process safely and reproducibly shall be defined and documented.

6.1.2 Process characterization shall include:

a) preconditioning (if used);

b) the sterilization cycle;

c) aeration (if used).

6.1.3 The characterization of the sterilization cycle shall include:

a) air removal;

b) conditioning (if used);

c) ethylene oxide injection;

d) maintenance of specified conditions for the exposure time;

e) ethylene oxide removal;

f) flushing (if used);

g) air/inert gas admission.

6.1.4 (Pre)treatment of product to achieve specified temperature and humidity within the load shall be accomplished by preconditioning and/or conditioning and shall be performed under controlled conditions. Humidity used for the preconditioning and/or conditioning of product shall be generated by steam.

6.1.5 The tolerances for the process variables, including but not limited to temperature, humidity, ethylene oxide concentration, pressure/vacuum and time, shall be established and specified.

6.1.6 The means of monitoring and controlling the process variables shall be determined and specified.

6.2 Equipment characterization

6.2.1 The specification for the equipment to be used shall be developed and documented. This specification shall include the preconditioning area (if used), the sterilizer and the aeration environment.

NOTE Some aspects of the equipment design may be influenced by national or regional regulatory requirements or standards.

6.2.2 The specification shall include:

a) description of the equipment, together with any necessary ancillary items, including materials of construction;

b) composition of the sterilizing agent and the means by which it is delivered to the chamber;

c) description of any other gas(es) used in the process and the means by which they are delivered to the chamber;

d) purity and quality of steam to ensure that it is suitable for its intended use with equipment and product;

e) description of instrumentation for monitoring, controlling and recording the sterilization process, including sensor characteristics and their locations;

f) fault(s) recognized by the sterilizing equipment;

g) safety features, including those for personnel and environmental protection;

h) installation requirements, including requirements for the control of emissions, if applicable.

6.2.3 Software used to control and/or monitor the process shall be prepared and validated in accordance with the elements of a quality system that provides documented evidence that the software meets its design specification.

NOTE For further information, attention is drawn to ISO/IEC 90003.

6.2.4 Means shall be provided to ensure that failure in a control function does not lead to failure in recording of process parameters such that an ineffective process appears effective.

NOTE This may be achieved either by the use of independent systems for control and monitoring or a by cross-check between control and monitoring which identifies any discrepancies and indicates a fault.

7 Product definition

7.1 General

7.1.1 Product definition shall be performed prior to the introduction of a new or altered product, package or loading pattern.

7.1.2 A demonstration of equivalence (with reference to the challenge to the sterilization process) to a previously validated product, package or loading pattern shall be considered to meet the requirement of 7.1.1. Any demonstration of equivalence shall be documented.

7.1.3 Product shall be designed to allow the penetration of humidity and ethylene oxide to the most difficult-to-sterilize locations.

7.1.4 Packaging shall be designed to allow removal of air and penetration of humidity and ethylene oxide.

7.1.5 It shall be demonstrated that the specified sterilization process is effective at the most difficult-to-sterilize location within the product. This may be achieved by a demonstration of equivalence to a previously validated product or process challenge device (PCD) used to qualify the sterilization process. Equivalence may also be demonstrated by performing process definition and validation of the new product.

7.2 Product safety and performance

7.2.1 It shall be confirmed that the product and its packaging meet specified requirements for safety, quality and performance following the application of the defined sterilization process at the most challenging process parameters for the product/package. The influence of the tolerances for the process parameters shall be taken into consideration.

NOTE Design control is one aspect addressed in ISO 14971.

7.2.2 If multiple sterilization cycles are permitted, the effects of such processing on the product and its packaging shall be evaluated.

NOTE See also ISO 17664.

7.2.3 The biological safety of product following exposure to the sterilization process shall be established in accordance with ISO 10993-1 and any subsequent parts of ISO 10993 that apply.

7.2.4 Maximum allowable limits for ethylene oxide residuals in ethylene-oxide-sterilized medical devices are given in ISO 10993-7. Means shall be established to reduce ethylene oxide residual levels such that the processed products comply with the requirements of ISO 10993-7.

7.3 Microbiological quality

7.3.1 A system shall be specified and maintained to ensure that the microbiological quality and cleanliness of the product presented for sterilization is controlled and does not compromise the effectiveness of the sterilization process.

7.3.2 The effectiveness of the system defined in 7.3.1 shall be demonstrated. For medical devices to be supplied for single use, this demonstration shall include an estimation of bioburden at a defined interval in accordance with ISO 11737-1. For re-usable medical devices, this demonstration shall include an assessment

of the effectiveness of the specified cleaning and, if applicable, disinfecting process. This shall also include an assessment of organic and inorganic contamination.

NOTE Requirements for information to be provided for the reprocessing of resterilizable devices are given in ISO 17664.

7.4 Documentation

The results of product definition shall be documented.

8 Process definition

8.1 The sterilization process to be validated shall be specified prior to the introduction of a new or altered product, package or loading pattern.

8.2 Process definition activities shall be performed in a sterilization chamber that has undergone Installation Qualification (IQ) and Operational Qualification (OQ) procedures (see 9.1 and 9.2).

Process definition may be performed in a research sterilizer or in the equipment to be used to sterilize the product.

8.3 The sterilization process applicable for the defined product shall be established.

8.4 Documentation and records shall support the validity of process parameters and their tolerances as defined in the process specification.

8.5 The rate of inactivation of the cycle shall be determined using one of the methods described in Annexes A or B or by an alternative validated method that demonstrates the achievement of the required sterility assurance level (SAL).

8.6 Biological indicators used as part of the establishment of the sterilization process shall:

a) comply with Clauses 5 and 9.5 of ISO 11138-2:2006;

b) be shown to be at least as resistant to ethylene oxide as is the bioburden of product to be sterilized;

c) be placed within the product at location(s) where sterilizing conditions are most difficult to achieve or be placed within a PCD.

   If a PCD is used for process definition, validation or routine monitoring and control, the appropriateness of the PCD shall be determined. The PCD shall be equivalent or more challenging to the process than the most difficult-to-sterilize part of the product.

NOTE For information on the selection, use and interpretation of biological indicators, see ISO 14161.

8.7 Commercially supplied biological indicators used in the definition of the sterilization process should comply with the applicable clauses of ISO 11138-1.

8.8 If chemical indicators are used as part of the definition of the sterilization process, these shall comply with ISO 11140-1.

Chemical indicators shall not be used as the sole means of establishing the sterilization process.

8.9 If tests of sterility are performed during the definition of the sterilization process, they shall comply with ISO 11737-2.

9 Validation

9.1 Installation qualification

9.1.1 Installation qualification (IQ) shall demonstrate that the sterilization equipment and any ancillary items have been supplied and installed in accordance with their specification.

9.1.2 All equipment used to deliver the ethylene oxide, including any ancillary items, shall be established and specified.

9.1.3 The operating procedures for the equipment (see 6.2) shall be specified. These operating procedures shall include but are not limited to:

a) step-by-step operating instructions;

b) fault conditions, the manner in which they are indicated and actions to be taken;

c) instructions for maintenance and calibration;

d) details of contacts for technical support.

9.1.4 The location in which the equipment is to be installed, including any services required, shall be specified. Any special precautions and provisions shall be identified.

EXAMPLE Verify that storage conditions for ethylene oxide meet the requirements given by the supplier as well as any pertinent national, regional or local requirements.

9.1.5 Instructions for installation shall be documented and shall include instructions pertinent to the health and safety of personnel.

9.1.6 Drawings of the equipment installed, plumbing and other ancillary equipment shall be finalized during IQ.

9.2 Operational qualification

9.2.1 Prior to operational qualification (OQ), the calibration of all instrumentation (including any test instruments) used for monitoring, controlling, indicating or recording shall be confirmed (see 4.3.3).

9.2.2 Operational qualification (OQ) shall demonstrate that the installed equipment is capable of delivering the specified process (see Clause 8) within defined tolerances.

OQ is carried out either with unloaded equipment or using appropriate test material.

9.3 Performance qualification

9.3.1 General

9.3.1.1 Performance qualification (PQ) 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.

PQ is performed in the equipment used to sterilize the product.

9.3.1.2 PQ shall use product to demonstrate that equipment consistently operates in accordance with predetermined criteria and that the process produces product that is sterile.

9.3.1.3 The load used for PQ shall be representative of that to be sterilized routinely and shall be defined based upon the most challenging routine load.

The load may consist of product or materials that have characteristics similar to those of a load to be sterilized routinely.

NOTE If saleable product has been used during validation, see 7.2 and 11.3.

If material other than product is used, it shall present at least as great a challenge to the sterilization process as the product.

If loads are reused for the validation cycles, they should be aerated between exposures to ensure that ethylene oxide residues in the load do not affect the biological indicator.

The loads shall be re-evaluated at a predetermined frequency for appropriateness.

9.3.1.4 The manner of presenting product for sterilization, including the loading pattern of the product, shall be specified.

9.3.1.5 If chemical indicators are used as part of PQ, these shall comply with ISO 11140-1.

Chemical indicators shall not be used as the sole means of PQ.

9.3.2 Performance qualification — Microbiological

NOTE See C.13 and C.14.

9.3.2.1 The microbiological PQ shall demonstrate that, on application of the sterilization process, the specified requirements for sterility are met. Studies shall be performed in the production chamber using defined process parameters selected to deliver less lethality than the specified sterilization process.

During microbiological PQ, it is common practice to reduce the set point of one or more process variables (e.g. EO concentration, temperature, humidity) compared to the set points used in routine sterilization. The defined parameters may be at or below the minimum levels specified for routine control.

9.3.2.2 Microbiological PQ shall confirm the effectiveness of the defined process for the product/load combination in a production sterilizer.

9.3.2.3 The lethality of the cycle shall be determined using one of the methods described in Annex A or Annex B or by an alternative validated method that demonstrates achievement of the required SAL.

9.3.2.4 If process definition was determined in a developmental chamber, the microbiological PQ shall include at least three fractional or half-sterilization cycles in the production sterilizer that confirm the data from the developmental chamber. All biological indicators shall be deactivated with one or more of these validation cycles.

9.3.2.5 Sterilization equipment that delivers the same process parameters, having undergone installation IQ and OQ, shall be qualified either

a) in the same manner as the original chamber or

b) using a reduced PQ that demonstrates the delivery of the required level of microbiological lethality; the rationale for this reduced qualification shall be recorded and documented.

The influence of different geographical locations on the load properties should be determined.

9.3.3 Performance qualification — Physical

9.3.3.1 Physical PQ shall demonstrate:

a) reproducibility of the process, and shall include a minimum of three consecutive, planned qualification runs in which all the specified acceptance criteria are met;

b) that the specified acceptance criteria are met throughout the load for the duration of the proposed routine process specification.

Elements of the physical PQ may be conducted during the microbiological PQ. If a) is performed in parallel with the microbiological PQ, then at least one additional qualification run shall be performed to demonstrate compliance with this requirement. If a failure can be attributed to factors not relevant to the effectiveness of the process being validated, this may be documented as unrelated to the performance of the process without requiring three further consecutive successful runs. Examples of this type of failure may include, but are not limited to, power failures, other loss of services, or failure of external monitoring equipment.

9.3.3.2 Physical PQ shall confirm the process such that:

a) at the end of the defined preconditioning time (if used), the sterilization load is within the defined temperature and humidity ranges;

b) the specified maximum elapsed time between the completion of preconditioning (if used) and the commencement of the sterilization cycle is appropriate;

c) gaseous ethylene oxide has been admitted to the sterilizer chamber;

d) pressure rise and the quantity of ethylene oxide used [see 9.5.4 c)] or the concentration of ethylene oxide in the sterilizer chamber [see 9.5.5 b)] are within the ranges specified;

e) during the sterilization cycle, the temperature and humidity of the chamber and, where applicable, other process parameters are within the ranges documented in the sterilization process specification;

f) the temperature of the product load during exposure is within the defined range;

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

9.4 Varying load configurations

For establishments that have widely varying load configurations, the extent to which the variation affects the sterilization process shall be evaluated. It shall be demonstrated that all product sterilized with a cycle achieves the required level of sterility assurance.

9.5 Review and approval of validation

9.5.1 The purpose of this activity is to undertake and document a review of the validation data to confirm the acceptability against the approved protocol for the sterilization process and to approve the process specification.

9.5.2 Information gathered or produced during product definition, process definition, IQ, OQ and PQ, including results from incubation of biological indicators, shall be recorded and reviewed for acceptability (see also 4.1.2). The results of this review shall be recorded.

9.5.3 A validation report shall be prepared. The report shall be reviewed and approved by the designated responsible person(s).

9.5.4 The validation report shall describe or reference specific validated product, the defined loading patterns and the documented specification for the ethylene oxide sterilization process. The validation report shall also include the value and tolerances for:

a) preconditioning (if used):

   1) time in chamber/area, temperature and humidity of chamber/area;

   2) minimum temperature of product permitted to enter preconditioning;

   3) temperature and humidity of the sterilization load;

   4) maximum elapsed time between removal of the load from preconditioning and commencement of the sterilization cycle;

b) conditioning (if used):

   1) the initial vacuum level (if used) and time taken to achieve it;

   2) holding time under vacuum;

   3) time in chamber, temperature, pressure and humidity within the chamber;

   4) temperature and humidity of the sterilization load;

c) ethylene oxide injection and exposure:

   1) ethylene oxide injection pressure rise, ethylene oxide injection time and final pressure;

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

      i) mass of ethylene oxide used;

      ii) volume of ethylene oxide used;

      iii) direct measurement of ethylene oxide concentration within the chamber;

   3) sterilizer chamber temperature;

   4) exposure time;

   5) temperature of the sterilization load;

   6) an indication of the satisfactory operation of the chamber gas circulation system (if used) during exposure;

d) aeration (if used):

   1) time and temperature;

   2) pressure changes (if any) within the chamber and/or room;

   3) rate of change of air or other gas;

   4) temperature of the sterilization load.

9.5.5 If parametric release is to be used, the validation report shall also specify:

a) the value and tolerances for chamber humidity by direct measurement during conditioning;

b) the value and tolerances for the ethylene oxide concentration, determined from direct analysis of chamber atmosphere at defined intervals sufficient to verify the required conditions throughout the exposure time.

9.5.6 A process specification, including the process parameters and their tolerances, shall be confirmed. This process specification shall also include the criteria for designating an individual sterilization process used for a particular sterilization load as conforming.

10 Routine monitoring and control

10.1 Data shall be recorded and retained for each sterilization cycle to demonstrate that the sterilization process specification has been met. These data shall include at least the following:

a) evidence that the minimum required temperature of product entering preconditioning (if used) has been achieved; this may be achieved by allowing loads to acclimate for a specified minimum time;

b) temperature and humidity within the preconditioning area (if used), monitored and recorded from a specified position;

c) time of commencement and of removal of load from preconditioning (if used) of each sterilization load;

d) indication of the satisfactory operation of the chamber gas circulation system (if used) during gas exposure;

e) elapsed time between removal of the sterilization load from preconditioning (if used) and the commencement of the sterilization cycle;

f) temperature and pressure in the chamber throughout the sterilization cycle;

g) chamber humidity during conditioning by pressure and/or direct monitoring;

h) evidence that the gaseous ethylene oxide has been admitted to the sterilizer chamber;

i) pressure rise and the quantity of ethylene oxide used or the concentration of ethylene oxide in the sterilizer chamber;

j) conditioning time;

k) exposure time;

l) time, temperature, pressure changes (if any) and/or the operation of the air supply (if used) during aeration.

If biological indicators are used in routine monitoring, they shall comply with 8.6.

NOTE 1 See also 8.7.

If chemical indicators are used in routine monitoring, they shall comply with 8.8.

NOTE 2 Chemical indicators are not intended to replace biological indicators for product release.

10.2 If parametric release is performed, the following additional data shall be recorded and retained:

a) temperature in the chamber from a minimum of two locations throughout the sterilization cycle;

b) chamber humidity during conditioning as determined by direct measurement;

c) the ethylene oxide concentration, determined from direct analysis of chamber atmosphere at defined intervals sufficient to verify the required conditions throughout the exposure time.

11 Product release from sterilization

11.1 The criteria for designating conformance of the sterilization process used for a particular sterilization load shall be documented. These criteria shall include:

a) confirmation that the data recorded during routine processing meet sterilization process specification;

b) confirmation of no growth of the test organism from any biological indicator (if used).

11.2 Product shall be considered as non-conforming and handled in accordance with the applicable clauses of ISO 13485 if one or more of the conformance criteria of 11.1 are not fulfilled.

11.3 If saleable product has been used during validation, the requirements for release of this product for distribution shall be generated before the start of the validation activities.

12 Maintaining process effectiveness

12.1 General

12.1.1 The continued effectiveness of the system for ensuring the condition of the product presented for sterilization (see 7.3.1) shall be demonstrated. This may include, for example, routine monitoring of product bioburden and/or monitoring the effectiveness of the cleaning process.

12.1.2 The accuracy and reliability of the instrumentation used to control and monitor the sterilization process shall be verified periodically in accordance with 4.3.3.

12.2 Maintenance of equipment

12.2.1 Preventative maintenance shall be planned and performed in accordance with documented procedures. All procedures shall follow manufacturers' recommendations as well as any pertinent national, regional or local requirements.

12.2.2 Equipment shall not be used to process product until all specified maintenance tasks have been satisfactorily completed and recorded.

12.2.3 Records of maintenance shall be retained (see 4.1.2).

12.2.4 The maintenance scheme, maintenance procedures and maintenance records shall be reviewed at specified intervals by a designated person and the results of the review shall be documented.

12.3 Requalification

12.3.1 Requalification of a sterilization process carried out with specified equipment shall be performed at defined intervals against specified acceptance criteria and in accordance with documented procedures. These intervals shall be justified.

Requalification may include verification that allowable product EO residuals as delineated in ISO 10993-7 are being met.

12.3.2 IQ, OQ, PQ and subsequent requalification(s) shall be reviewed and a decision shall be taken and documented to what extent requalification is required, including the confirmation of the specified SAL through microbiological studies.

12.3.3 The appropriateness of the biological indicator in relation to the bioburden of the product shall be confirmed at specified intervals (see 8.6).

12.3.4 The load and loading pattern shall be re-evaluated at a predetermined frequency for its appropriateness, and the results of this re-evaluation shall be documented in accordance with 4.1.2.

12.3.5 The validated sterilization process shall be reviewed whenever there has been a change to the sterilization equipment and/or product that could alter the efficacy of the process (see 8.1).

12.3.6 If failures during requalification and/or routine monitoring and control indicate that the sterilization process might no longer be capable of achieving the required SAL, the cause of the failure shall be determined. If this determination shows the process to be no longer adequate, the sterilization process shall be modified to achieve the required SAL, and validated.

12.3.7 Records of reviews of requalification data, reports and resulting corrective actions (if required) shall be retained (see 4.1.2).

12.3.8 If parametric release is used, the following additional requirements shall apply:

a) requalification shall be performed at least annually;

b) requalification shall include confirmation of the specified SAL through microbiological studies.

12.4 Assessment of change

12.4.1 A change to equipment, product, packaging, presentation of product for sterilization or loading pattern, or a modification to the sterilizing agent and/or its presentation shall be assessed for its effect on the effectiveness of the sterilization process.

12.4.2 The magnitude of the change shall be considered in determining the extent to which process definition, IQ, OQ or PQ is undertaken.

12.4.3 The extent of qualification that is necessary shall be determined. The outcome of the assessment, including the rationale for decisions reached, shall be documented.

Annex A
(normative)

Determination of lethal rate of the sterilization process — Biological indicator/bioburden approach

A.1 General

This approach combines knowledge of the resistance of a biological indicator to a given cycle with knowledge of the bioburden population and resistance to establish the cycle parameters (exposure time).

Use of this method requires that product bioburden levels be demonstrated to be relatively consistent over time and the resistance of the bioburden be shown to be equal to, or less resistant than, the resistance of the biological indicator.

The resistance of the biological indicator is demonstrated by running the cycle at graded exposure times and determining the lethal rate (rate of inactivation) of the cycle. Knowledge of this rate and the population and relative resistance of the bioburden allows one to establish exposure time so that an SAL can be predicted.

Guidance on this approach can be found in ISO 14161.

A.2 Procedure

A.2.1 Establish the location within the product at which sterility is most difficult to achieve.

A.2.2 Create a challenge to the sterilization process, comprising a known number of microorganisms with known resistance to the ethylene oxide, by placing biological indicators in the product at locations where sterilizing conditions are most difficult to achieve. If the location of the challenge is other than the most difficult-to-sterilize location, its relationship to the most difficult location shall be established.

Use of a PCD that has demonstrated a greater resistance to the sterilization process than the product meets this requirement. Attention must be given to the impact of packaging and the removal of sterilant from the PCD.

A.2.3 Package the challenge, created in accordance with the above, in the same manner as product produced routinely and included within the sterilization load.

A.2.4 Expose the sterilization load to ethylene oxide under conditions selected to deliver less lethality than those conditions to be used routinely (see Clause 8), such that not all reference microorganisms have been inactivated.

A.2.5 After time-graded exposures to ethylene oxide with all other parameters remaining the same, the lethality of the process can be determined by using one of the following methods:

a) direct enumeration (see A.3.1) or

b) the fraction negative method (see A.3.2 or A.3.3) or

c) a combination of a) or b) above.

NOTE The fraction-negative method uses growth/no growth data from the recovery test on the PCDs after exposure to fractional gas exposure times.

From this result, the rate of inactivation of the reference microorganisms can be calculated.

A.2.6 From knowledge of the product bioburden (see ISO 11737-1), bioburden resistance to the sterilization process and the rate of inactivation of the reference microorganisms determine the extent of treatment required to achieve the specified SAL.

A.3 Process lethality determination

A.3.1 Direct enumeration

A.3.1.1 The lethality of the sterilization cycle shall be determined by construction of a survivor curve using direct enumeration of survivors.

A.3.1.2 Further details on this method are given in ISO 14161 and C.3 of ISO 11138-1:2006.

C.3 of ISO 11138-1:2006 requires a minimum of five exposure points covering:

a) one exposure in which the sample is not subjected to the sterilant (e.g. 0 time exposure);

NOTE The sterilant may be absent or replaced by an inert gas or medium.

b) at least one exposure in which the viable population is reduced to 0,01 % of the original inoculum (4 $\log_{10}$ reduction);

c) a minimum of three exposures covering the intervals between exposure a) and exposure b) above.

A.3.2 Fraction-negative method using Holcomb-Spearman Karber procedure (HSKP)

Biological indicators for ethylene oxide sterilization shall be subjected to time-graded exposures to ethylene oxide with all other parameters remaining constant. After exposure, the test samples are assayed by direct immersion into an appropriate culture medium. The samples are scored as to the proportion of the samples showing no growth after incubation. Further details on this method are given in ISO 14161 and D.3.1 of ISO 11138-1:2006.

D.3.1 of ISO 11138-1:2006 requires a minimum of five exposure conditions covering:

a) at least one set of samples in which all tested samples show growth;

b) at least two sets in which a fraction of the samples show growth (quantal region);

c) at least two sets of samples in which no growth is observed.

A modification of the HSKP, the Limited Holcomb-Spearman-Karber Procedure (LHSKP), may be used if the same number of samples is exposed at each time point and the time interval is constant. For further guidance, see D.3.2 of ISO 11138-1:2006.

A.3.3 Fraction-negative method using Stumbo Murphy Cochran procedure (SMCP)

The formula for the Stumbo Murphy Cochran Procedure (SMCP) requires one result in the fraction negative range consisting of time, t, the number of units negative for growth, r, the number of replicates, n, at one exposure time within the fraction-negative range, and the initial number of microorganisms per replicate, N_0.

To obtain valid data using SMCP, D.3.3 of ISO 11138-1:2006 requires that the D value be calculated as the average of at least three runs in the fraction negative range in order to confirm reproducibility.

For further guidance, see ISO 14161.

Annex B
(normative)

Conservative determination of lethal rate of the sterilization process — Overkill approach

B.1 General

B.1.1 This approach to process definition is based on the inactivation of reference microorganisms and has been widely used. Sterilization processes qualified in this manner are often conservative and use a treatment that may exceed that required to achieve the specified requirements for sterility.

Guidance on this approach can be found in ISO 14161.

B.1.2 Conservative process definition shall require using either the approach given in a) or b) below.

a) Half-cycle approach: a total of three consecutive experiments resulting in total inactivation of the biological indicators (with a population of not less than 10^6) shall be performed in order to confirm the minimum exposure time. The specified exposure time shall be at least double this minimum time. A cycle of short duration from which survivors can be recovered shall also be run to demonstrate the adequacy of the recovery technique.

b) Cycle calculation approach*:* the routine processing parameters that deliver minimally a 12 SLR of the biological indicator shall be established using one of the methods described in A.3. The number of cycles is dictated by the method used.

B.1.3 The conditions used for recovery of biological indicators in validation studies, including duration of incubation, shall be established and documented. The incubation period shall take into account the possibility of delayed outgrowth of spores that have been exposed to ethylene oxide.

B.1.4 The resistance of the bioburden shall be shown to be equal to or less than the resistance of the biological indicator.

B.2 Procedure

B.2.1 Identify a worst case product or PCD which is at least as difficult to sterilize as the most difficult item anticipated for the process.

B.2.2 Determine the location(s) within product where it is most difficult to achieve sterilizing conditions.

B.2.3 Create a challenge to the sterilization process containing a known number of microorganisms with defined resistance to the ethylene oxide by one of the following approaches:

a) placing biological indicators within the product at location(s) where sterilizing conditions are most difficult to achieve or placing them within a PCD or

b) inoculating the location(s) within product where sterilizing conditions are most difficult to achieve with suitable reference organisms.

See Table A.1 in ISO 14937:2000.

If the location of the challenge is other than the most difficult-to-sterilize location, its relationship to the most difficult location shall be established.

B.2.4 Package the challenge, created in accordance with the list above, in an equivalent manner to products produced routinely and included within the sterilization load.

B.2.5 Expose the sterilization load to the ethylene oxide under conditions designed to deliver less lethality than the specified sterilization process.

B.2.6 If the inactivation of a known number of microorganisms has been confirmed according to A.3, determine the extent of treatment for the sterilization process by extrapolation to a known predicted probability of a surviving microorganism, taking account of the required SAL.

Annex C
(informative)

General guidance

NOTE 1 The guidance given in this annex is not intended as a checklist for assessing compliance with this part of ISO 11135. This guidance is intended to assist in obtaining a uniform understanding and implementation of this part of ISO 11135 by providing explanations and acceptable methods for achieving compliance with specified requirements. It highlights important aspects and provides examples. Methods other than those given in the guidance may be used. However, the use of alternative methods is to be demonstrated to be effective in achieving compliance with this part of ISO 11135.

NOTE 2 For ease of reference, the numbering in this annex corresponds to that in the normative part of this part of ISO 11135 (Clauses 1 to 12). For example, guidance on Clause 8 is given in C.8 of this annex. Guidance on Annexes A and B is given in C.13 and C.14 respectively.

C.1 Scope

No guidance offered.

C.2 Normative references

No guidance offered.

C.3 Terms and definitions

No guidance offered.

C.4 Quality management systems

C.4.1 Documentation

Requirements for control of documents and records are specified in 4.2.3 and 4.2.4, respectively, of ISO 13485:2003.

In ISO 13485:2003, the requirements for documentation relate to the generation and control of documentation (including specifications and procedures) and records.

C.4.2 Management responsibility

Requirements for responsibility and authority are specified in 5.5 of ISO 13485:2003, and requirements for human resources are specified in 6.2 of ISO 13485:2003.

In ISO 13485:2003, the requirements for management responsibility relate to management commitment, customer focus, quality policy, planning, responsibility, authority and communication, and management review.

The development, validation and routine control of a sterilization process can involve a number of separate parties, each of whom is responsible for certain elements. This part of ISO 11135 requires that the party accepting particular responsibilities be defined and that this definition of responsibilities be documented. This definition of authority and responsibility is documented within the quality management system(s) of the identified parties. The party accepting responsibilities for defined elements is required to assign these elements to competent personnel, with competence demonstrated through appropriate training and qualification.

Personnel with the following responsibilities should receive training and have the necessary qualification:

a) microbiological testing;

b) installation of equipment;

c) equipment maintenance;

d) physical PQ;

e) routine sterilizer operation;

f) calibration;

g) process design;

h) equipment specification;

i) other areas as applicable.

C.4.3 Product realization

NOTE In ISO 13485:2003, the requirements for product realization relate to the product life cycle from the determination of customer requirements, design and development, purchasing, control of production and calibration of monitoring and measuring devices.

C.4.3.1 Requirements for purchasing are specified in 7.4 of ISO 13485:2003. In particular, it should be noted that the requirements in 7.4.3 of ISO 13485:2003 for verification of purchased product apply to all product and services received from outside the organization.

C.4.3.2 Requirements for identification and traceability are specified in 7.5.3 of ISO 13485:2003.

C.4.3.3 Requirements for calibration of monitoring and measuring devices are specified in 7.6 of ISO 13485:2003.

C.4.4 Measurement, analysis and improvement — Control of non-conforming product

Procedures for control of non-conforming product and corrective action are specified in 8.3 and 8.5.2, respectively, of ISO 13485:2003.

In ISO 13485:2003, the requirements for measurement, analysis and improvement relate to process monitoring, control of nonconforming product, analysis of data, and improvement (including corrective and preventive actions).

C.5 Sterilizing agent characterization

NOTE The purpose of this activity is to define the sterilizing agent, demonstrate its microbicidal effectiveness, identify the factors that influence microbicidal effectiveness, assess the effects that exposure to the sterilizing agent has on materials, and identify requirements for safety of personnel and the protection of the environment. This activity may be undertaken in a test or prototype system; the final equipment specification (see 6.2) should be relatable to the experimental studies undertaken using any such test or prototype equipment.

C.5.1 Sterilizing agent

No guidance offered.

C.5.2 Microbicidal effectiveness

No guidance offered.

C.5.3 Materials effects

No guidance offered.

C.5.4 Environmental considerations

C.5.4.1 Principles of an environmental management system can be applied to the ethylene oxide sterilization process. ISO 14001 provides a specification for an environmental management system. ISO 14040 provides guidance on designing a life cycle assessment study. For further guidance, see E.3 of ISO 14937:2000.

C.5.4.2 No guidance offered.

C.6 Process and equipment characterization

NOTE The purpose of this activity is to characterize the ranges of sterilization process variables and the equipment necessary to deliver the sterilization process variables safely and reproducibly.

C.6.1 Process characterization

Process characterization consists of:

— identifying the process variables that should be included in the definition of the process;

— defining ranges for each process variable;

— documenting the process variables and their defined ranges based on theoretical knowledge.

Subsequent studies specified in Clauses 8 and 9 will either:

— confirm the validity of the specifications for the process variables or

— demonstrate that the range(s) of the process variables should be reviewed and redefined.

C.6.2 Equipment characterization

C.6.2.1 No guidance offered.

C.6.2.2 The following items should be considered when preparing the equipment specification.

NOTE Attention is drawn to the existence in some countries of regulations concerning ethylene oxide.

— Areas used for storage of cylinders, tanks or cartridges of ethylene oxide or ethylene oxide gas mixtures should be secure and ventilated.

— Where ambient conditions are subject to temperature variation greater than the range recommended by the supplier, storage areas for the containers of ethylene oxide should include provision for temperature control.

— If the ethylene oxide supply to the sterilizer is from a bulk storage tank that is periodically replenished, the tank should be equipped with a means of removing samples for analysis, a means of emptying the tank completely of ethylene oxide and a provision for cleaning in the event of contamination or excessive accumulation of polymers.

— The system for admission of ethylene oxide to the sterilizer should be equipped with a vaporizer to prevent liquid ethylene oxide from being admitted to the sterilizer chamber.

— The temperature of the ethylene oxide gas flowing from the vaporizer to the sterilizer chamber should be measured to demonstrate that gaseous ethylene oxide has been produced.

— A minimum of two probes to measure chamber temperature should be used.

NOTE The purpose of two separate probes is to prevent the failure of one sensor from causing an out-of-specification load from being erroneously accepted. Comparing two separate temperature sensors will detect that one of the sensors has failed. A dual element temperature probe can be used to meet this need.

— The homogeneity of conditions within the sterilizer chamber is preferably achieved by forced circulation. The gas circulation system should be equipped with a monitoring device that indicates when circulation is ineffective. Devices that monitor "power on" to the fan or pump are not sufficient; it is necessary to demonstrate that the required gas flow is being maintained.

C.6.2.3 No further guidance offered.

C.6.2.4 No further guidance offered.

C.7 Product definition

NOTE The purpose of this activity is to define the product to be sterilized, including the microbiological quality of the product prior to sterilization and the manner in which product is packaged and presented for sterilization.

C.7.1 General

The following should be carried out to minimize the risk of introducing a new or modified product (candidate product) that presents a greater challenge to the sterilization cycle than that which was previously validated.

C.7.1.1 Perform a technical review of the candidate product compared to the validated product and/or PCD that was used to validate the existing EO process. This comparison should also involve an examination of factors that could potentially affect the product bioburden, such as manufacturing, production methods, facilities, location and raw material types and sources that could affect the desired SAL.

C.7.1.2 If the technical review finds that the candidate product is similar to previously validated product and that the differences between them are clearly not significant, then the candidate product may be adopted into the validated EO process without further study. If the product configuration, density or load configuration of the candidate product and its packaging could present a greater challenge to the sterilization process than the previously validated product, then temperature and relative humidity penetration studies and cycle lethality studies should also be conducted.

C.7.1.3 The construction and configuration of the candidate product and its packaging should be carefully examined for any areas that could present obstacles to EO/heat/humidity penetration.

C.7.1.4 No guidance offered.

C.7.1.5 No guidance offered.

C.7.2 Product safety and performance

During the design of medical devices intended for sterilization, attention should be given to functionality, design tolerances, product configuration and the composition of product, including packaging materials, to be used to ensure effective delivery of the ethylene oxide to all parts of the device.

Product can be subjected to various environmental stresses during sterilization, such as vacuum and pressure changes, elevated temperature and changes in humidity. Product could also react with the ethylene oxide

and/or any diluent(s). The product design should ensure that functionality and safety are not compromised by exposure to the anticipated range of sterilization conditions.

Materials composition: certain process conditions can adversely affect the integrity of medical devices and packages. Some packaging materials and devices could impede the sterilization process. Therefore, the effects of the sterilization process on materials and design characteristics and on packaging configurations and materials are evaluated. This evaluation is usually conducted during product development and the results should be documented.

It is important to select materials that exhibit adequate resistance to chemical and physical changes caused by the ethylene oxide and/or any diluents over the anticipated range of sterilization conditions. Properties of materials required to satisfy requirements for product performance, such as physical strength, permeability, physical dimensions and resilience, are evaluated after sterilization to ensure that the materials are still acceptable for use. Degradation effects due to exposure to the sterilization process, such as crazing and embrittlement should be determined and resistant materials specified. Materials should also allow sufficient ethylene oxide transmission or permeation to ensure that target surfaces and materials are sterilized. The materials should allow aeration (if applicable) within a reasonable time and should retain biological safety. If applicable, the effects of exposure to multiple sterilization processes are evaluated.

Packaging considerations: the major function of a package for a sterilized medical device is to ensure that the product remains sterile until used. During sterilization, the package is intended to withstand the process conditions without a negative effect on overall product quality (e.g. generation of particulates).

When selecting a primary package for a product that is to be sterilized, certain major design and manufacturing factors are considered with respect to the particular sterilization process. To assure ethylene oxide penetration, the permeability of the package to the particular sterilizing environment is of utmost importance. If air removal is part of the sterilization process, the package also permits air evacuation without damage or rupture.

The ability of the secondary and tertiary packaging, if used, to protect the product during customary handling and distribution should be demonstrated. If the secondary packaging is to be exposed to the sterilization process, evidence is generated to show that the secondary packaging can withstand the process without losing its ability to protect the product.

Packaging considerations are addressed in more detail in ISO 11607-1 and ISO 11607-2.

C.7.3 Microbiological quality

No guidance offered.

C.7.4 Documentation

No guidance offered.

C.8 Process definition

NOTE The purpose of this activity is to obtain a detailed specification for the sterilization process to be applied to defined product (see Clause 7) by microbiological testing.

Selection of the sterilization process: the development of a sterilization process for a particular medical device needs to establish a process that is both effective and compatible with the medical device. Therefore, initial investigations into product compatibility, together with experimentation to identify and/or optimize the sterilization process, may be undertaken whilst the product is in the design phase.

The selection of the sterilization process that is to be used for medical devices should include consideration of all factors that can influence the efficacy of the process. The following should be taken into account.

a) Availability of sterilization equipment.

b) Range of conditions that can be achieved within the available sterilizing equipment.

c) Sterilization processes already in use for other products.

d) Requirements for levels of residual ethylene oxide and/or its reaction products.

e) Results of process development experiments.

Process definition: process definition may consist of a number of elements.

f) Determination of time required to achieve specified conditions of temperature and humidity during preconditioning (if preconditioning is to be used).

g) Determination of the limits for the variables of the sterilization process.

NOTE For guidance on cycle lethality studies that may be required as part of process definition, see C.9.3.2.

h) Estimation of the bioburden on product so that the challenge presented to the sterilization cycle by the bioburden can be established and the appropriateness of the biological indicator to be used for PQ and routine monitoring (if used) can be confirmed. The appropriateness of the biological indicator should be determined by exposure to sublethal (partial) cycle(s). In these studies, the relative inactivation rates for biological indicators and product can be compared through testing.

NOTE Requirements for, and guidance on, bioburden estimation are described in ISO 11737-1;

i) A determination of the minimum aeration time at specified conditions to achieve sufficient out-gassing so that the ethylene oxide and/or its reaction products are at or below those levels established by ISO 10993-7. This activity should be conducted using a full load under production conditions.

As a result of the process development activities, a sterilization process can be defined. The appropriateness of this sterilization process is demonstrated in the PQ studies in a production chamber.

Preconditioning and/or conditioning: the resistance of microorganisms to deactivation by ethylene oxide is affected by their water content. For this reason it is common practice to control and monitor the humidity of the atmosphere to which the product is exposed in order to attempt to equilibrate the water content of the microorganisms with the local conditions. Before commencing the sterilization cycle, it is usual to precondition product at a defined temperature and humidity. Such preconditioning can reduce the duration of the sterilization cycle.

A chamber relative humidity in excess of 30 % is commonly used to humidify the load. The specified relative humidity will depend on the product to be sterilized. Consideration should be given to the potential product and package damage that excessive relative humidity can cause.

Where applicable, a maximum time between removal of the load from the preconditioning and the start of the sterilization cycle needs to be established. A transfer time of 60 min or less is common practice.

Product heating and humidification is used to establish reproducible product temperature and moisture content prior to gas exposure. Studies establishing minimum residence time ensure that the required conditions are reached. Precaution should be taken to prevent water condensation on the sterilization load.

The actual temperature and humidity ranges at the end of preconditioning should be demonstrated during PQ.

Sterilization: performance factors within the sterilization process that should be considered include:

j) depth and rate of attainment of vacuum;

k) chamber leak rate (performed either under vacuum for subatmospheric cycles or under vacuum and at pressure for superatmospheric cycles);

l) during the conditioning phase, pressure rise on injection of steam;

m) pressure rise and rate of attainment of specified pressure on admission of ethylene oxide and correlation of methods used to monitor ethylene oxide concentration;

n) depth and rate of attainment of vacuum used to remove ethylene oxide;

o) pressure rise and rate of attainment of pressure on admission of air (or any other gas used during this stage of the sterilization cycle);

p) number of times these last two stages are repeated and any variations in successive repetitions.

When inert gas make-ups are used instead of the sterilant during exposure, it is important that the impact of the gas concentration be taken into consideration during the establishment of the final cycle parameters to ensure that the desired SAL is achieved.

To achieve reproducible ethylene oxide distribution throughout the sterilizer chamber and sterilization load, it may be necessary to control residual chamber air content prior to sterilant introduction, or to provide active chamber atmosphere recirculation**,** because ethylene oxide and air do not mix well in static situations.

Aeration: residues of ethylene oxide and its reaction products may be hazardous. It is essential for the manufacturer to be aware of the possible occurrence of residues in the product.

Temperature, dwell time, forced air circulation, load characteristics, product and packaging materials all affect the efficiency of aeration.

Aeration may be performed within the sterilizer, in a separate area, or in a combination of both.

The manufacturer shall demonstrate the resistance of the PCD using a fractional cycle for the purpose of demonstrating that the product bioburden is not more resistant than that of the biological indicator.

NOTE This relative resistance evaluation can be performed by having all sterile product tests of sterility and some positive PCDs.

C.9 Validation

NOTE The purpose of validation is to demonstrate that the sterilization process established in process definition (see Clause 8) can be delivered effectively and reproducibly to the sterilization load. Validation consists of a number of identified stages: installation qualification, operational qualification and performance qualification.

C.9.1 Installation qualification

Installation qualification (IQ) demonstrates that the sterilization equipment and any auxiliary items have been supplied and installed in accordance with their specification.

C.9.2 Operational qualification

Operational qualification (OQ) demonstrates the capability of the equipment to deliver the sterilization process.

Preconditioning: with regard to preconditioning, the following guidance is provided.

a) IQ and OQ are performed with the preconditioning area empty in order to establish that the design criteria are met.

b) The pattern of air circulation throughout the area to be occupied by the sterilization load(s) should be determined. This may be performed by smoke tests in combination with calculation of air change rates and anemometric determinations.

c) Temperature and humidity should be monitored throughout the preconditioning area over a period long enough to demonstrate that values are within the desired ranges. The temperature and humidity in a number of locations distributed throughout the preconditioning area should be determined.

NOTE See Table C.1 and Table C.2 for recommendations on temperature and humidity sensors.

Sterilization: in IQ/OQ exercises the recorded temperature range, within the usable chamber volume during gas exposure, of $\pm$ 3 °C of the average recorded chamber temperature allowed by the cycle specification, should be obtained. The recorded temperature range should be within the process specification.

With regard to sterilization, the following guidance is provided.

d) If inert gases are used instead of ethylene oxide, account should be taken of the differences in the relative heat capacity when assessing the results.

e) Temperature sensors should be located in those locations that are likely to represent the maximum temperature differential, such as locations near unheated portions of the chamber or door and locations near steam or gas entry ports. The remaining temperature sensors should be distributed evenly throughout the usable chamber volume.

NOTE See Table C.1 for the recommended number of sensors.

The physical performance factors of the sterilization cycle should be determined for the empty chamber to establish the operational limits. These factors include:

— depth and rate of attainment of vacuum;

— chamber leak rate (performed either under vacuum for subatmospheric cycles or under vacuum and at pressure for superatmospheric cycles);

— pressure rise on injection of steam during the conditioning phase;

— the temperature of the injected gas should be above a defined minimum value to assure it is injected as a gas, not as a liquid;

— pressure rise and rate of attainment on admission of ethylene oxide and correlation of factors with which it is intended to monitor ethylene oxide concentration;

— depth and rate of attainment of vacuum used to remove ethylene oxide;

— pressure rise and rate of attainment of pressure on admission of air (or other gases);

— number of times these last two stages are repeated and any variations in successive repetitions.

OQ should also determine the performance of associated ancillary systems. For example, the quality of the steam supplied, the capability of the ethylene oxide vaporizer to achieve a minimum gas input temperature, the reliability of the filtered air and water supplies to the sterilizer and the capability of the steam generator to maintain supplies of the required quality under maximum sterilization load conditions should be demonstrated.

Replicate cycles should be carried out to demonstrate the repeatability of control.

When performing aeration, the temperature profile of the aeration area should be determined in the same manner as recommended for preconditioning areas. The air flow rates and air flow patterns through the area should also be determined. It may not be necessary to measure relative humidity during aeration.

C.9.3 Performance qualification

C.9.3.1 General

Performance qualification (PQ) demonstrates that the equipment consistently operates in accordance with predetermined criteria and the process produces product that meets its specification.

Examples of significant changes that should be qualified include:

— packaging;

— product design;

— sterilization load configuration or density (see C.9.4);

— sterilizing equipment;

— sterilization process.

The effects of such changes on all stages of the sterilization process, including preconditioning and aeration, should be determined.

C.9.3.2 Performance qualification — Microbiological

NOTE The microbial inactivation studies are performed to demonstrate that exposures to ethylene oxide gas under defined conditions will achieve the desired SAL.

Clauses 8 and 9 of this part of ISO 11135 refer to studies to determine cycle lethality. Annexes A and B provide instructions on how to perform the microbial inactivation studies required for process definition or microbiological PQ. Results obtained during process definition and, where applicable, installation and OQ should be used to set the parameters for microbiological PQ.

Biological indicators should be placed in the part of the product that is the most difficult to sterilize. If the design of the product is such that a biological indicator cannot be accommodated in the part most difficult to sterilize, the product should either be inoculated with the spore suspension with a known number of viable spores or have biological indicators placed in locations to which the relationship with the most difficult location to sterilize can be established.

Biological indicators or inoculated product should be evenly distributed in the sterilization load, but distribution should include those locations where sterilization conditions are the most difficult to achieve. Microbiological PQ should demonstrate microbial lethality (inactivation) throughout the sterilization load. The locations used should include those selected for temperature monitoring. Further insight into process efficacy may be gained by placing two biological indicators near each temperature monitor location.

The lethality in gas charge and removal will impact the linearity of the survivor curve.

Biological indicators (see Table C.3) should be removed from the sterilization load and cultured as soon as possible on completion of the cycle. Any effects of delayed recovery, and in particular an effect from exposure to residual ethylene oxide, should be assessed.

NOTE Attention is drawn to the existence of statutory regulations existing in some countries on personnel exposure to ethylene oxide.

For additional guidance on biological indicator sample sizes, see Table C.3.

C.9.3.3 Performance qualification — Physical

C.9.3.3.1 No guidance offered.

C.9.3.3.2

With regard to preconditioning or conditioning, the following apply.

— PQ should be carried out with the loading patterns and pallet separations specified in the documented procedures. Worst case loads should be validated.

— The temperature and humidity profile within the sterilization load should be evaluated over a period of time required for the sterilization load to attain the minimum predetermined temperature and humidity. Guidance on the number of sensors is given in Tables C.1 and C.2.

— Temperature and humidity sensors should be located within the packaging intended to be placed in the sterilizer.

With regard to sterilization, the following apply.

— To ensure that the adequacy of the conditioning process is demonstrated, product used for these PQ studies should be at the temperature specified for product being loaded into the sterilizer. When preconditioning is used, the product should be preconditioned for the specified time.

— The loading pattern or patterns should be documented for each sterilizer. The combination of products permitted within the loading pattern should be documented.

— New products should be compared with original PCDs in the reference load used to validate the process. If judged to present greater difficulty in sterilization, they should be subjected to a full PQ study.

— Temperature profiles of the sterilization load should be determined for each loading pattern or for the reference load. In PQ, throughout gas exposure time, the sterilization load should reach and/or exceed the minimum temperature sufficient to deliver the required lethality and should not exceed the maximum temperature that would negatively impact product and package functionality.

— The temperature within the sterilization load during the aeration process should be measured over the period of time required for the sterilization load temperature to stabilize.

C.9.4 Varying load configurations

When a varying load is to be validated, a worst case reference load should be defined. The defined worst case reference load might consist, for example, of medical devices with lumens of varying size and length, different materials and packaging, and varying physical mass that represents the “worst case” challenge to the sterilization process. Accordingly, evaluation of all relevant factors should be considered. These include, but are not limited to:

a) ethylene oxide absorbency;

b) tortuous pathways;

c) thermodynamic profiles.

C.9.5 Review and approval of validation

NOTE The purpose of this activity is to undertake and document a review of the validation data to confirm the acceptability of the sterilization process and to approve the process specification.

C.9.5.1 No guidance offered.

C.9.5.2 No guidance offered.

C.9.5.3 No guidance offered.

C.9.5.4 On completion of the validation programme, the test results should be compiled into a validation report. The validation report should include or reference the following:

— details of products sterilized (including packaging and load patterns in the sterilizer);

— the specification of the sterilizer;

— the IQ/OQ data;

— the records, physical and biological, of all PQ runs;

— an indication that all gauges, recorders, etc. were within calibration at the time of the PQ;

— provision for future review and requalification;

— the validation protocol(s);

— the documented procedures used;

— documented operating procedures including process control limits;

— maintenance and calibration procedures;

— if a biological or equipment failure occurred, this occurrence and the corrective action taken;

— if a deviation to the protocol occurred, details of this deviation and an assessment of its impact upon the protocol and its results.

C.9.5.5 No guidance offered.

C.9.5.6 No guidance offered.

C.10 Routine monitoring and control

NOTE The purpose of routine monitoring and control is to demonstrate that the validated and specified sterilization process has been delivered to the product.

C.10.1 In order to verify the effectiveness of the validated sterilization process, a number of key process variables should be monitored.

Biological indicators (if used) should be distributed throughout the load, including locations known to be the most difficult to sterilize or for which that relationship is known and understood. Biological indicators (if used) should be placed prior to preconditioning.

If biological indicators are used (see Table C.3), they should be removed from the sterilization load and cultured as soon as possible on completion of the cycle. Any effects of delayed recovery, and in particular an effect from exposure to residual ethylene oxide, should be assessed.

NOTE Attention is drawn to the existence of statutory regulations existing in some countries on personnel exposure to ethylene oxide.

Observations of growth from biological indicators not attributable to failure to meet physical process specifications should be analysed; this can lead to a need for the validation to be repeated.

Pressure rise at ethylene oxide injection provides an indirect measure of the ethylene oxide concentration in the sterilizer chamber. As ethylene oxide concentration is a key variable affecting the efficacy of the sterilization process, it is considered essential that a separate second system be provided for documenting that the pressure rise is due to ethylene oxide admission.

C.10.2 Parametric release is the declaration of adequacy of routine processing for a validated sterilization process based solely on measurement and documentation of physical process parameters rather than biological indicator results.

When parametric release is used, it is necessary to measure the additional process variables specified in 10.2.

C.11 Product release from sterilization

In product release, the physical sterilization process variables and results of biological indicator incubation (if used) are reviewed to assess the conformance of the sterilization process. For parametric release, more data are recorded. All data recorded should be reviewed to assess the conformance of the sterilization process.

Failure to meet the physical specification or growth from a biological indicator (if used) after culture should lead to the sterilization load being placed in quarantine and to an investigation of the cause of failure. The investigation should be documented and the handling of product should be in accordance with documented procedures and the appropriate parts of ISO 13485.

C.12 Maintaining process effectiveness

C.12.1 General

No guidance offered.

C.12.2 Maintenance of equipment

No guidance offered.

C.12.3 Requalification

NOTE Requalification is performed to confirm that inadvertent process changes have not compromised the effectiveness of the sterilization process.

C.12.3.1 The validation, any subsequent revalidation data and routine processing data should be reviewed at least annually, and the extent of revalidation necessary should be determined and documented. Procedures for review should be documented.

C.12.3.2 Requalification may include, but is not limited to, verification that:

a) there have been no significant changes to the product design, manufacturing and packaging materials, PCDs, suppliers, manufacturing area or facility, load configuration, or manufacturing process that could affect product sterility;

b) there has not been a significant increase in product bioburden or change in the bioburden characterization which could invalidate the specified SAL;

c) the temperature distribution and chamber operation studies demonstrate no significant changes since the previous (re)qualification;

d) temperature profiles and recirculation checks indicate no significant changes in the preconditioning chamber or room or the aeration areas since the previous (re)qualification;

e) the history of the sterilization process since the last validation demonstrates repeatability;

f) the change control and preventive maintenance programmes indicate that no modifications of, or significant changes to, the sterilizing equipment have been made that could affect the process;

g) there has been no change to the sterilization process that could affect product sterility;

h) if the sterilization process specification is changed, then requalification of the sterilization process should include confirmation that product meets allowable limits for EO residuals as specified in ISO 10993-7.

C.12.3.3 No guidance offered.

C.12.3.4 No guidance offered.

C.12.3.5 If requalification detects a significant change, additional elements of IQ, OQ and PQ may need to be performed again. Records should be retained of any review of requalification, the extent of any additional requalification, any rationale and corrective actions.

C.12.3.6 No guidance offered.

C.12.3.7 No guidance offered.

C.12.3.8 No guidance offered.

C.12.4 Assessment of change

No guidance offered.

Table C.1 — Examples of minimum recommended number of temperature sensors

Examples of volume (m^3)	Number for IQ/OQ (usable chamber/room volume)			Number for PQ (product load volume)		
	Preconditioning	Conditioning/ sterilization	Aeration	Preconditioning	Conditioning/ sterilization	Aeration
1	3	3	3	3		
10	4	10	4	10		
15	6	15	6	15		
20	8	20	8	20		
25	10	25	10	25		
30	12	30	12	30		
35	14	35	14	35		
40	16	40	16	40		
50	20	50	20	50		
100	40	100	40	100		

NOTE For volumes other than the ones given in Table C.1, the equations below should be used.

The recommendation is to use one sensor per 2,5 m^3 for preconditioning and aeration during IQ/OQ to establish a thermal map of the room or chamber that captures potential hot or cold locations. Therefore, monitoring should include more than one plane and locations near doors.

For PQ and IQ/OQ sterilization/conditioning the sensor formula is based on one temperature sensor per cubic meter of product volume with a minimum of three sensors.

EXAMPLES:

For a usable chamber volume of 2 m^3: 2/2,5 = 0,8. The number of sensors to use is at least three (minimum number of sensors).

For a usable chamber volume of 9 m^3: 9/2,5 = 3,6. The number of sensors to use is at least four.

For a usable chamber volume of 70 m^3: 70/2,5 = 28. The number of sensors to use is at least twenty-eight.

Table C.2 — Examples of minimum recommended number of humidity sensors

Volume (m^3)	**IQ/OQ** (usable chamber/room volume)			**PQ** (product load volume)		
	Preconditioning	**Conditioning/ sterilization**	**Aeration**	**Preconditioning**	**Conditioning/ sterilization**	**Aeration**
1	2		N/A	2		N/A
10	4			4		
15	6			6		
20	8			8		
25	10			10		
30	12			12		
35	14			14		
40	16			16		
50	20			20		
100	40			40		

NOTE For volumes other than the ones given in Table C.2, the equations below should be used.

The recommendation is to use one sensor per 2,5 m^3 to establish a humidity map of the product that captures potential variability in the humidity levels. Therefore, monitoring should include pallet centres, edges and surfaces. The minimum number of sensors is two.

EXAMPLES:

For a usable chamber volume of 6 m^3: 6/2,5 = 2,4. The number of sensors to use is at least three (minimum number of sensors).

For a usable chamber volume of 60 m^3: 60/2,5 = 24. The number of sensors to use is at least twenty-four.

Table C.3 — Examples of minimum recommended number of BI/PCDs

Product load volume (m^3)	**Microbiological PQ**	**Routine control** (if used)
1	5	3
10	30	15
15	35	18
20	40	20
25	45	23
30	50	25
35	55	28
40	60	30
50	70	35
100	120	60

NOTE For volumes other than the ones given in Table C.3, the user should use the equations below.

For MPQ:

Up to 10 m^3, the number of BIs is 3 per m^3, with a minimum of 5.

From 10 m^3 up to 100 m^3, the number of additional BIs is one per additional cubic metre.

For routine control, the number of BIs is half the number of BIs during MPQ.

EXAMPLES:

For a usable chamber volume of 3 m^3: $3 \times 3 = 9$. The number of BIs to use is at least 9 for MPQ. For routine control: 9/2 = 4,5. The number of BIs is at least five.

For a usable chamber volume of 18 m^3: $10 \times 3 + (18 - 10) \times 1 = 38$. The number of BIs to use is at least thirty-eight for MPQ. For routine control: 38/2 = 19. The number of BIs is at least nineteen.

C.13 Guidance on Annex A — Determination of lethal rate of the sterilization process — Biological indicator/bioburden approach

If the product bioburden is tested at frequent intervals and is consistent, then a combined biological indicator/bioburden method may be used for cycle development.

This method is based on the assumption that the relationship of biological indicator resistance to bioburden resistance is known. If this is the case, the SLR data developed in a lethality study for the BI can be used to demonstrate the effectiveness of the process for the product. If the data has been generated by using an enumeration data collection process, this can also be predicted from the survivor curve data that has been generated.

Process lethality determinations: process lethality is often expressed as D-value. Because organisms generally die at a rate that is approximately logarithmic for a given process, a time unit of exposure to ethylene oxide gas may be found to result in the destruction of 90 % of the organism's population regardless of the population size. Each of these time units is referred to as the D-value for the process.

Process lethality, or D-value, may be calculated using the results from one of two commonly used methods. The first method (enumeration) consists of an enumeration or physical count of the survivors and the second (fraction negative) uses growth/no growth during fractional cycles. Either of these methods may be used for Annexes A or B. D-values can be calculated by using the results from the fractional cycles or through the use of equations described in ISO 11138-1 and ISO 14161.

Regardless of the method used, it is assumed that:

a) the organism population is homogeneous;

b) the process parameters are constant from run to run;

c) a semi-logarithmic survivor relationship exists;

d) organisms that have survived the process and unexposed organisms respond similarly in the recovery medium.

All microbiological test methods (tests of sterility, enumeration, etc.) should be validated in accordance with ISO 11737-1 and 11737-2.

Enumeration: enumeration consists of exposing BIs or PCDs to the fractional cycle, removing the challenge and performing counts on the samples or biological indicators. The survivor count may be used in developing a survivor curve and D value. The D-value is then calculated using a linear regression model.

See A.3.1 and ISO 14161.

Fraction negative: fraction negative analysis involves running sterilization cycles in which some, but not all, of the biological indicators are inactivated. This includes:

e) Holcomb-Spearman-Karber (HSK) procedure;

f) Limited Holcomb-Spearman-Karber (LHSK) procedure;

g) Stumbo-Murphy-Cochran (SMC) procedure.

See Annex A and ISO 14161.

Sample size: the number of samples depends on the method used and whether the samples are distributed throughout the load or concentrated in one location. Use of a single location may improve consistency of results between samples; however, it may not represent the worst case location in a chamber unless extensive mapping has been performed in each chamber with each possible load configuration.

When evaluating results, consideration needs to be given to ensure that the differences in the number of surviving microorganisms between replicate challenges are due to random variation within a population rather than a variation in exposure conditions.

See ISO 11138-1 and ISO 14161 for guidance on the minimum number of samples.

For further guidance on the number of biological indicators, see Table C.3.

In order to achieve the desired results, it may be necessary to shorten the post-exposure phases of the cycle.

C.14 Guidance on Annex B — Conservative determination of lethal rate of the sterilization process — Overkill approach

General: two methods are commonly used in this approach.

The first method is the half-cycle approach. Due to its relative ease of use and the conservative SAL obtained, medical device manufacturers and health care facilities commonly use this method which is to demonstrate total inactivation of a 10^6 BI at a half-cycle exposure time. When exposure time is doubled, a minimum 12 SLR is delivered during EO exposure.

The second method, the cycle calculation approach, is to achieve a 12 SLR process by the methods given in Annex A (see C.13).

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