
**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**

*Stérilisation des produits de santé — Exigences générales pour la
caractérisation d'un agent stérilisant et pour la mise au point, la
validation et la vérification de routine d'un processus de stérilisation
pour dispositifs médicaux*



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

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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 14937 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This second edition cancels and replaces the first edition (ISO 14937:2000) and ISO 14937:2000/Cor.1:2003 which have been technically revised.

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) could, 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 generally can best be described by an exponential relationship between the number of microorganisms surviving and the extent of treatment with the sterilizing agent; inevitably this means that there is always a finite probability that a microorganism might survive regardless of the extent of treatment applied. For a given treatment, the probability of survival is determined by the number and resistance of microorganisms and by the environment in which the organisms exist during treatment. It follows that the sterility of any one medical device in a population subjected to sterilization processing cannot be guaranteed and the sterility of a processed population is defined in terms of the probability of there being a viable microorganism present on a medical device.

This International Standard describes requirements that, if met, will provide a sterilization process with appropriate microbicidal activity intended to sterilize medical devices. Furthermore, compliance with the requirements ensures that the sterilization process is both reliable and reproducible so that predictions can be made, with reasonable confidence, that there is a low level of probability of there being a viable microorganism present on a medical device after sterilization. Specification of this probability is a matter for regulatory authorities and can vary from country to country (see, for example, EN 556-1 and ANSI/AAMI ST67).

Generic requirements of the quality management system 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, 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 is monitored routinely and the equipment is maintained.

Exposure to a properly validated, accurately controlled sterilization process is not the only factor associated with the provision of reliable assurance that a processed medical device is sterile and, in this regard, suitable for its intended use. Attention is also given to a number of factors including:

- a) the microbiological status of incoming raw materials and/or components;
- b) the validation and routine control of any cleaning and disinfection procedures used on the medical device;
- c) the control of the environment in which the medical device is manufactured, assembled and packaged;
- d) the control of equipment and processes;
- e) the control of personnel and their hygiene;
- f) the manner and materials in which the medical device is packaged;
- g) the conditions under which the medical device is stored.

The type of contamination on a medical device to be sterilized varies, and this influences the effectiveness of a sterilization process. Medical devices that have been used in a health care setting and that are being presented for resterilization in accordance with the manufacturer's instructions (see ISO 17664) should be regarded as special cases. There is the potential for such medical devices to possess a wide range of contaminating microorganisms and residual inorganic and/or organic contamination in spite of the application of a cleaning process. Hence, particular attention has to be given to the validation and control of the cleaning and disinfection processes used during reprocessing.

The requirements are the normative parts of this International Standard with which compliance is claimed. The guidance given in Annex E is not normative and is not provided as a checklist for auditors. The guidance provides explanations and methods that are regarded as being a suitable means for complying with the requirements. Methods other than those given in the guidance can be used if they are effective in achieving compliance with the requirements of this International Standard.

The development, validation and routine control of a sterilization process comprise a number of discrete but interrelated activities, for example, calibration, maintenance, product definition, process definition, installation qualification, operational qualification and performance qualification. While the activities required by this International Standard have been grouped together and are presented in a particular order, this International Standard does not require that the activities be performed in the order that they are presented. The activities required are not necessarily sequential, as the programme of development and validation can be iterative. The responsibility for carrying out the activities required by this International Standard will vary from case to case. This International Standard requires that the responsibilities of the various parties be defined (see 4.2) but does not specify to whom the responsibilities are allocated. Annex E provides guidance on allocation of responsibility.

This International Standard has three distinct applications:

- for manufacturers of health care products who wish to apply to their products a sterilization process for which a specific International Standard does not exist;
- for manufacturers and users of sterilization processes in health care settings for which a specific International Standard does not exist;
- as a framework for the preparation or revision of standards for specific sterilization processes.

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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

1 Scope

1.1 Inclusions

1.1.1 This International Standard specifies general requirements for the characterization of a sterilizing agent and for the development, validation and routine monitoring and control of a sterilization process for medical devices.

NOTE Although the scope of this International Standard is limited to medical devices, the requirements specified herein can also be applied to sterilization processes for other health care products.

1.1.2 This International Standard applies to sterilization processes in which microorganisms are inactivated by physical and/or chemical means.

1.1.3 This International Standard is intended to be applied by process developers, manufacturers of sterilization equipment, manufacturers of medical devices to be sterilized, and organizations responsible for sterilizing medical devices.

1.1.4 This International Standard specifies the elements of a Quality Management System which are necessary to assure the appropriate characterization of the sterilizing agent, development, validation and routine monitoring and control of a sterilization process.

NOTE It is not a requirement of this International Standard to have a full quality management system. The necessary elements are normatively referenced at appropriate places in the text (see, in particular, Clause 4). Attention is drawn to the standards for quality management systems (see ISO 13485) that control all stages of production or reprocessing of medical devices. National and/or regional regulations for the provision of medical devices might require the implementation of a full quality management system and the assessment of that system by a third party.

1.2 Exclusions

1.2.1 This International Standard does not apply to sterilization processes that rely solely on physical removal of microorganisms (for example, filtration).

1.2.2 This International Standard does not describe detailed procedures for assessing microbial inactivation.

1.2.3 This International Standard does not specify requirements for characterization of an agent or for development, validation and routine control of a process for inactivating the causative agents of spongiform encephalopathies such as scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob disease. Specific recommendations have been produced in particular countries for the processing of materials potentially contaminated with these agents.

NOTE See also ISO 22442-1, ISO 22442-2 and ISO 22442-3.

1.2.4 This International Standard does not supersede or modify published International Standards for particular sterilization processes.

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 within a risk management process*

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

ISO 11138-1:2006, *Sterilization of health care products — Biological indicators — Part 1: General requirements*

ISO 11140-1, *Sterilization of health care products — Chemical indicators — Part 1: General requirements*

ISO 11737-1, *Sterilization of medical devices — Microbiological methods — Part 1: Determination of a population of microorganisms on products*

ISO 11737-2, *Sterilization of medical devices — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process*

ISO 13485:2003, *Medical devices — Quality management systems — Requirements for regulatory purposes*

IEC 61010-2-040, *Safety requirements for electrical equipment for measurement, control and laboratory use — Part 2-040: Particular requirements for sterilizers and washer-disinfectors used to treat medical materials*

3 Terms and definitions

For the purposes of this International Standard, the following terms and definitions apply.

**3.1
bioburden**
population of viable microorganisms on or in product and/or sterile barrier system

[ISO/TS 11139:2006, definition 2.2]

**3.2
biological indicator**
test system containing viable microorganisms providing a defined resistance to a specified sterilization process

[ISO/TS 11139:2006, definition 2.3]

**3.3
change control**
assessment and determination of the appropriateness of a proposed alteration to product or procedure

[ISO/TS 11139:2006, definition 2.5]

3.4**chemical indicator****non-biological indicator**

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

[ISO/TS 11139:2006, definition 2.6]

3.5**corrective action**

action to eliminate the cause of a detected non-conformity or other undesirable situation

NOTE 1 There can be more than one cause for a non-conformity.

NOTE 2 Corrective action is taken to prevent recurrence whereas **preventive action** (3.17) is taken to prevent occurrence.

NOTE 3 There is a distinction between **correction** (3.6) and corrective action.

[ISO 9000:2005, definition 3.6.5]

3.6**correction**

action to eliminate a detected non-conformity

NOTE A correction can be made in conjunction with a **corrective action** (3.5).

[ISO 9000:2005, definition 3.6.6]

3.7**development**

act of elaborating a specification

[ISO/TS 11139:2006, definition 2.13]

3.8**establish**

determine by theoretical evaluation and confirm by experimentation

[ISO/TS 11139:2006, definition 2.17]

3.9**fault**

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

[ISO/TS 11139:2006, definition 2.19]

3.10**health care product(s)**

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

[ISO/TS 11139:2006, definition 2.20]

3.11
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]

3.12
material safety data sheet
MSDS

document specifying the properties of a substance, its potential hazardous effects for humans and the environment, and the precautions necessary to handle and dispose of the substance safely

[ISO/TS 11139:2006, definition 2.23]

3.13
medical device

instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other 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, modification or support of the anatomy or of a physiological process,
- supporting or sustaining life,
- 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 primary 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 has been developed by the Global Harmonization Task Force (GHTF 2002).

3.14
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]

3.15
parametric release

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

[ISO/TS 11139:2006, definition 2.29]

3.16**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 specifications

[ISO/TS 11139:2006, definition 2.30]

3.17**preventive action**

action to eliminate the cause of a potential non-conformity or other undesirable potential situation

NOTE 1 There can be more than one cause for a potential non-conformity.

NOTE 2 Preventive action is taken to prevent occurrence, whereas **corrective action** (3.5) is taken to prevent recurrence.

[ISO 9000:2005, definition 3.6.4]

3.18**process challenge device****PCD**

item designed to constitute a defined resistance to a sterilization process and used to assess performance of the process

[ISO/TS 11139:2006, definition 2.33]

3.19**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]

3.20**process variable**

condition within a sterilization process, changes in which alter microbicidal effectiveness

EXAMPLES Time, temperature, pressure, concentration, humidity, wavelength.

[ISO/TS 11139:2006, definition 2.35]

3.21**recognised 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]

3.22**reference microorganism**

microbial strain obtained from a recognised culture collection

[ISO/TS 11139:2006, definition 2.39]

3.23

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]

3.24

services

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

EXAMPLES Electricity, water, compressed air, drainage.

[ISO/TS 11139:2006, definition 2.41]

3.25

specify

stipulate in detail within an approved document

[ISO/TS 11139:2006, definition 2.42]

3.26

sterile

free from viable microorganisms

[ISO/TS 11139:2006, definition 2.43]

3.27

sterility

state of being free from viable microorganisms

NOTE In practice, no such absolute statement regarding the absence of microorganisms can be proven [see **sterilization** (3.28)].

[ISO/TS 11139:2006, definition 2.45]

3.28

sterilization

validated process used to render a product free from viable microorganisms

[ISO/TS 11139:2006, definition 2.47]

NOTE In a sterilization process, the nature of microbial inactivation is exponential, and the survival of a microorganism on an individual item can thus 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 sterility assurance level in ISO/TS 11139.)

3.29

sterilization load

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

[ISO/TS 11139:2006, definition 2.48]

3.30

sterilization process

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

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

[ISO/TS 11139:2006, definition 2.49]

3.31**sterilizing agent**

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

[ISO/TS 11139:2006, definition 2.50]

3.32**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]

3.33**test for sterility**

technical operation, defined in a Pharmacopoeia, performed on product following exposure to a sterilization process or following an aseptic manufacturing process

3.34**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 2.54]

3.35**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 system elements

4.1 Documentation

4.1.1 Procedures for characterization of a sterilizing agent, development, validation, and routine control of a sterilization process and product release from sterilization shall be specified.

4.1.2 Documents and records required by this International Standard 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 International Standard 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 International Standard 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 clause(s) 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 International Standard.

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

Procedures for control of product designated as non-conforming 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 General

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 protection of the environment. This activity may be undertaken in a test or prototype system. Where this occurs, the final equipment specification (see 6.3) shall be relatable to the results of experimental studies undertaken in the test or prototype equipment.

5.2 Sterilizing agent

The sterilizing agent shall be specified. The specification shall include, if appropriate, conditions of storage of the sterilizing agent to maintain the sterilizing agent within its specification for the duration of the stated shelf life.

5.3 Microbicidal effectiveness

5.3.1 Microbicidal effectiveness studies shall

- a) demonstrate the lethal action of the sterilizing agent against a range of representative microorganisms selected in accordance with Annex A;
- b) establish an empirical mathematical relationship defining the microbial inactivation kinetics of identified resistant microorganisms so that the probability of a microorganism surviving exposure to a defined treatment can be predicted;
- c) identify reference microorganism(s) that has (have) known high resistance to the sterilizing agent;
- d) identify the process variables that affect the lethal action of the sterilizing agent and the interactions of these process variables in relation to this lethal action;
- e) assess those factors that can adversely influence the effectiveness of the sterilizing agent based upon physical and/or chemical interactions;

EXAMPLES Interactions with materials and residues from manufacturing, cleaning and/or disinfection.

f) assess those factors that can adversely affect the delivery and/or distribution of the sterilizing agent;

EXAMPLES The environment, materials and residues from manufacturing, cleaning and/or disinfection.

g) identify a means for terminating the activity of the sterilizing agent, if applicable.

5.3.2 The test method(s), acceptance criteria and justification for the choice of test microorganisms shall be documented. Test results shall be recorded (see 4.1.2).

5.4 Effects on materials

5.4.1 The effects of exposure to the sterilizing agent on the physical and/or chemical properties of materials and on their biological safety shall be assessed.

5.4.2 The effects of repeated exposure to the sterilizing agent on the properties of materials shall be studied using the combination of process parameters likely to maximize effects on materials.

5.4.3 The materials tested and the outcomes of tests shall be recorded (see 4.1.2), together with the criteria against which the properties of materials were assessed before and after exposure to the sterilizing agent.

5.5 Safety and the environment

5.5.1 Either a material safety data sheet or analogous safety information shall be specified for the sterilizing agent, its precursors (if any) and any by-products of the sterilizing agent. This information may be provided by a supplier for a chemical agent or be prepared as a prelude to experimental studies on the sterilizing agent.

5.5.2 The potential effect on the environment of any substance which could be released, either deliberately or accidentally, during or following use of the sterilizing agent, shall be assessed and measured for the control of the substance(s) established. This assessment, including the potential effect (if any) and the measures for control (if identified), shall be recorded (see 4.1.2).

6 Process and equipment characterization

6.1 General

The purpose of this activity is to define the entire sterilization process and the equipment necessary to deliver the sterilization process safely and reproducibly.

6.2 Process characterization

6.2.1 The process parameters, together with their tolerances, shall be specified. These tolerances shall be based upon knowledge of the combination of process parameters yielding minimal acceptable microbicidal effectiveness. Processing at such process parameters shall routinely yield safe and functional product.

NOTE The establishment of the process parameters follows the definition of process variables [see 5.3.1 d)], including those process variables that are excluded or minimized in ensuring the effectiveness of the sterilization process.

6.2.2 Means of monitoring and controlling the process variables shall be determined.

6.2.3 Any treatment of product that is required prior to exposure to the sterilizing agent to ensure effectiveness of the sterilization process shall be specified.

6.2.4 Any treatment of product that is required following exposure to the sterilizing agent to ensure safety of product shall be specified as part of the sterilization processes.

6.3 Equipment characterization

6.3.1 The equipment to deliver the process in a safe manner within the tolerances stipulated for the process parameters shall be specified.

6.3.2 The specification shall include, but is not limited to:

- a) physical description of the equipment and necessary ancillary items, including materials of construction;
- b) specification of the sterilizing agent (see 5.2) and the means by which it is provided, including any additives or precursors necessary for its delivery;
- c) description of instrumentation for monitoring and controlling the sterilization process, including sensor characteristics and locations, and indicating and recording instruments;
- d) faults recognized by the sterilizing equipment;
- e) safety features, including those for personnel and environmental protection;
- f) installation requirements, including those for the control of emissions, if applicable.

6.3.3 Software used to control and/or monitor the process shall be prepared in accordance with a quality management system that provides documented evidence (see 4.1.2) that the software meets its design intention.

NOTE Attention is drawn to ISO 90003.

6.3.4 Means shall be provided to ensure that a failure in a control function does not lead to a failure in recording of process parameters such that an ineffective process appears effective. This may be achieved either by the use of independent systems for control and monitoring, or by a cross-check between control and monitoring that identifies any discrepancies and indicates a fault.

7 Product definition

7.1 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.

7.2 Product to be sterilized, including the packaging materials to be used and the manner in which product is to be presented to the sterilization process, shall be specified.

Meeting this requirement could necessitate that appropriate information be provided to the organization undertaking the sterilization process by the manufacturer of the medical device and the manufacturer of the sterilization equipment.

NOTE See, for example, ISO 17664.

7.3 A system shall be specified and maintained to ensure that the condition of the product presented for sterilization, including microbiological, organic and inorganic contamination levels, is controlled and does not compromise the effectiveness of the sterilization process.

7.4 The effectiveness of the system defined in accordance with 7.3 shall be demonstrated. For medical devices to be supplied for single use, this demonstration shall include estimation of bioburden in accordance with ISO 11737-1. For medical devices to be reprocessed, this demonstration shall include assessment of the effectiveness of the specified cleaning and, if applicable, disinfecting process.

The intention is that bioburden be stable and low, taking account of the nature of the raw materials, product and manufacturing or reprocessing procedures prior to sterilization. This can be achieved by employing a quality management system complying with ISO 13485 throughout the manufacture of the medical device, or by employing a defined and controlled cleaning process of demonstrated effectiveness, together with a disinfection process (if specified) prior to sterilization, and thereafter preventing recontamination of the medical device.

NOTE International Standards for equipment to be used in cleaning and disinfecting medical devices (ISO 15883 series) include methods to demonstrate the effectiveness of a cleaning and disinfecting process.

8 Process definition

8.1 The purpose of this activity is to obtain a detailed specification for the sterilization process to be applied to defined product (see Clause 7), without compromising the safety, quality and performance of that product.

8.2 The sterilization process appropriate for defined product shall be established. This shall be achieved by:

- a) selecting the process parameters and, if practicable, demonstrating their attainment by measurements;
- b) delivering the sterilizing agent under conditions so designed to represent increments of treatment that deliver less lethality than the intended sterilization process using one of the approaches outlined in Annexes B, C or D.

8.3 If biological indicators are used as part of the establishment of the sterilization process, they shall:

- a) comply with ISO 11138-1 and any subsequent parts of ISO 11138 that are applicable to the sterilization process;
- b) be shown to be resistant to the sterilizing agent relative to the bioburden of product to be sterilized;
- c) be placed either at positions in product where it has been determined that sterilizing conditions are most difficult to achieve or within a process challenge device (PCD).

8.4 If chemical indicators are used as part of the establishment of the sterilization process, they shall comply with ISO 11140-1 and any subsequent parts of ISO 11140 that are applicable to the process. Chemical indicators shall be placed either at positions in product where it has been determined that sterilizing conditions are most difficult to achieve or within a PCD (see 8.6).

8.5 If tests of sterility are performed during the establishment of the sterilization process, such tests shall comply with ISO 11737-2.

8.6 If PCDs are used as part of the establishment of the sterilization process, their appropriateness shall be determined. PCDs shall present a challenge equivalent to or greater than that at the position in product where it has been determined that sterilizing conditions are most difficult to achieve.

8.7 The biological safety of product following exposure to the sterilization process shall be established in accordance with ISO 10993-1.

8.8 A health-based risk assessment shall be conducted in accordance with ISO 10993-17 to identify and specify limits for process residuals on/in product.

8.9 If necessary, means shall be established to reduce level(s) of process residual(s) on/in product below that (those) identified in accordance with 8.8.

8.10 It shall be demonstrated that product meets its specified requirements for safety, quality, and performance following application of the specified sterilization process.

8.11 The sterilization process shall be specified.

9 Validation

9.1 General

The purpose of validation is to demonstrate that the sterilization process established in the 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 (IQ), operational qualification (OQ) and performance qualification (PQ).

IQ is undertaken to demonstrate that the sterilization equipment and any ancillary items have been supplied and installed in accordance with their specification.

OQ is carried out either with unloaded equipment or using appropriate test materials to demonstrate the capability of the equipment to deliver the sterilization process that has been defined (see Clause 8).

PQ is the stage of validation that uses product to demonstrate that the equipment consistently operates in accordance with predetermined criteria and the process yields product that is sterile and meets the specified requirements.

9.2 Installation qualification

9.2.1 Equipment

9.2.1.1 Equipment to be used in the sterilization process, including any ancillary items, shall be specified.

9.2.1.2 Sterilization equipment shall comply with IEC 61010-2-040.

9.2.1.3 The operating procedures for the equipment 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.

9.2.2 Installation

9.2.2.1 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 (for example, safety equipment).

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

9.2.2.3 If applicable, conditions for the safe storage of the sterilizing agent to ensure that its quality and composition remain within specification shall be specified.

9.2.2.4 Prior to IQ, the calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating or recording shall be confirmed (see 4.3.3).

9.2.2.5 It shall be demonstrated that the equipment, any ancillary items and storage conditions, as installed, operate as intended.

9.3 Operational qualification

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

9.3.2 OQ shall demonstrate that the installed equipment is capable of delivering the specified process (see 8.11) within defined tolerances.

9.4 Performance qualification

9.4.1 Calibration activities (see 4.3.3) shall be completed for instruments used in PQ.

9.4.2 The manner of presenting the product for sterilization, including the orientation of product, shall be specified.

9.4.3 Product used in PQ shall be packaged identically to that to be sterilized routinely.

9.4.4 Data shall be generated to demonstrate the attainment of the defined physical and/or chemical conditions, within specified tolerances, throughout the sterilization load. Relationship(s) between the conditions occurring at positions used routinely to monitor the sterilization process and those conditions occurring throughout the sterilization load shall be established. This is achieved by determining the attainment of the specified condition(s) at predetermined positions throughout the sterilization load.

9.4.5 Microbiological performance qualification studies shall comprise delivery of the sterilizing agent under conditions so designed that the extent of treatment is reduced relative to that in the sterilization process. Extrapolation of the outcomes of such reduced treatment(s) shall be used to predict that, on application of the sterilization process, the specified requirements for sterility are met. The approaches to process definition described in Annexes B, C or D may also be employed in microbiological performance qualification studies.

9.4.6 Biological indicators employed during microbiological performance qualification shall comply with 8.3.

9.4.7 If tests of sterility are performed on product subjected to conditions as specified in 9.4.5, such tests shall be performed in accordance with ISO 11737-2.

9.4.8 If chemical indicators are used in PQ, they shall comply with 8.4.

9.4.9 If PCDs are used in PQ, they shall comply with 8.6.

9.4.10 PQ shall include a series of at least three successful exposures of product to the sterilization process, within defined tolerances, in order to demonstrate the reproducibility of the process. Results from PQ outside of defined tolerances shall be reviewed and corrective actions determined and instituted before initiating a new series of exposures.

The series of three successful exposures shall be performed consecutively, unless finding outside defined tolerances can be attributed to factors not relevant to the effectiveness of the process being validated. Such findings shall be documented as unrelated to performance of the sterilization process.

EXAMPLES The finding might be attributed, but not limited to, power failures, loss of services or failure of external monitoring equipment.

9.4.11 The levels of any process residues following exposure to the upper tolerances of the process parameters shall be demonstrated as being below the specified limits identified in the health-based risk assessment (see 8.8).

9.4.12 It shall be confirmed that the product meets its specified requirements for safety, quality and performance following application of the defined process at the upper tolerances of the process parameters.

NOTE Information gathered in accordance with 8.9 can be used to meet this requirement.

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 of the sterilization process and to approve the process specification.

9.5.2 Information gathered or produced during IQ, OQ and PQ shall be recorded and reviewed for acceptability (see 4.1.2). The results of this review shall be recorded (see 4.1.2).

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

10.2 There shall be evidence through measurements, supplemented as necessary by biological indicators (see 10.5) or chemical indicators (see 10.6), that the sterilization process was delivered within the defined tolerances (see also 9.5.3).

10.3 Data shall be recorded to demonstrate the attainment of process parameters within defined tolerances.

10.4 All records shall be retained in accordance with 4.1.2.

10.5 If biological indicators are used in routine monitoring, they shall comply with 8.3 a) and b).

10.6 If chemical indicators are used in routine monitoring, they shall comply with 8.4.

10.7 If PCDs are used in routine monitoring and control, they shall comply with 8.6.

11 Product release from sterilization

11.1 A procedure for product release from sterilization shall be specified. This procedure shall define the criteria (see 9.5.3) for designating a sterilization process as conforming to its specification.

11.2 Parametric release shall only be used if all process parameters are specified, controlled and directly monitored. Records of process parameters shall be retained (see 4.1.2).

11.3 If biological indicators or chemical indicators are used to monitor the sterilization process (see 10.5 and 10.6), the results from exposure to these indicators shall be included within the criteria for product release from sterilization.

11.4 If the criteria specified in 11.1 are not met, product shall be considered as non-conforming and handled in accordance with documented procedures (see 4.4).

12 Maintaining process effectiveness

12.1 General

The continued effectiveness of the system for ensuring the condition of product presented for sterilization (see 7.3) shall be demonstrated (see 7.4).

12.2 Recalibration

The accuracy and reliability of the instrumentation used to control and monitor the sterilization process shall be verified periodically (see 4.3.3).

12.3 Maintenance of equipment

12.3.1 Preventative maintenance shall be planned and performed in accordance with documented procedures. The procedure for each planned maintenance task and the frequency at which it is to be carried out shall be specified. Records of maintenance shall be retained (see 4.1.2).

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

12.3.3 The maintenance scheme, maintenance procedures and maintenance records shall be reviewed periodically by a designated person. The results of the review shall be recorded (see 4.1.2).

12.4 Requalification

12.4.1 Requalification of a sterilization process, carried out for defined product and specified equipment, shall be performed at defined intervals. The extent to which requalification is carried out shall be justified.

12.4.2 Requalification procedures shall be specified and records of requalification shall be retained (see 4.1.2).

12.4.3 Requalification data shall be reviewed against specified acceptance criteria in accordance with documented procedures. Records shall be retained (see 4.1.2) of reviews of requalification data together with corrections made and corrective actions taken if specified acceptance criteria are not met (see 4.4).

12.5 Assessment of change

12.5.1 Any change in the sterilization equipment that could affect delivery of the sterilization process shall be assessed. If the effectiveness of the sterilization process is judged to be affected, a repeat of part or all of IQ, OQ or PQ shall be carried out (see Clause 9). The outcome of this assessment, including the rationale for decisions reached, shall be recorded (see 4.1.2).

12.5.2 Any change in product, its package, or the presentation of product for sterilization shall be assessed for the effect on the appropriateness of the sterilization process. Based on the nature of the change, parts of process definition (see Clause 8) and/or PQ (see 9.4) shall be undertaken. The outcome of the assessment, including the rationale for the decisions reached, shall be recorded (see 4.1.2).

Annex A (normative)

Factors to be considered in selection of microorganisms for demonstrating microbicidal effectiveness

A.1 General

This annex presents the factors to be considered in selecting microorganisms used in demonstrating the microbicidal effectiveness of a sterilizing agent. Table A.1 gives examples of microorganisms that can be included in such studies. Table A.1 is not exhaustive and, for a new sterilization process, it should not be assumed that the microorganisms listed in Table A.1 will be the most resistant.

A.2 Identification of reference microorganism

The data obtained in the demonstration of microbicidal effectiveness shall identify a suitable reference microorganism to be employed as a representative model of high resistance during sterilizing agent characterization and, if applicable, process definition studies.

NOTE Generally a bacterial spore is selected.

A.3 Selection of microorganisms

In selecting microorganisms to be used in demonstrating the microbicidal effectiveness of a sterilizing agent, the following shall be considered:

- a) microorganisms with known high resistance to the sterilizing agent or an expectation of a high resistance from information in the scientific literature or a knowledge of the mode of action of the sterilizing agent;
- b) microorganisms with known resistance to well-characterized sterilization processes;
- c) types of microorganisms (aerobic and anaerobic Gram positive and Gram negative bacteria, bacterial spores, mycobacteria, fungi including sporing forms, yeasts, parasites and viruses);
- d) microorganisms present on the materials of construction of the product and in the environment in which the product is manufactured;
- e) microorganisms that have been isolated during determinations of bioburden undertaken on typical product to be processed and, if applicable, microorganisms likely to be present on a re-usable medical device as a result of its prior use on a patient.

The microorganisms selected and the rationale for their choice shall be recorded (see 4.1.2). These microorganisms may be designated by a recognised culture collection reference or other identifier that allows the source to be traced.

NOTE 1 The information with respect to microorganisms given in A.3 b) is to provide a comparison with other sterilization processes and to ensure that well-characterized microorganisms are included in the studies.

NOTE 2 Inactivation of viruses and/or parasites [see A.3 c)] is a particular consideration in processes used to sterilize products containing material of animal origin (see also ISO 22442-3), as well as when reprocessing medical devices in health care facilities.

NOTE 3 In considering the information obtained with respect to microorganisms given in A.3 e), it should be noted that the resistance of microorganisms isolated from product can be modified by recultivation.

Table A.1 — Examples of potential test microorganisms

Bacterial spores	<i>Bacillus atropheus</i> <i>Geobacillus stearothermophilus</i> <i>Clostridium sporogenes</i>
Vegetative bacteria	<i>Staphylococcus aureus</i> <i>Salmonella choleraesuis</i> <i>Pseudomonas aeruginosa</i>
Fungi	<i>Trichophyton mentagrophytes</i> (conidia) <i>Candida</i> spp.
Mycobacteria	<i>Mycobacterium terrae</i>
Non-lipid viruses	Hepatitis A Parvovirus Poliovirus type 1 (attenuated)
Lipid viruses	<i>Herpes simplex</i>
Parasites	<i>Cryptosporidium parvum</i>
NOTE 1 This table is not intended to be a comprehensive list of microorganisms that have to be evaluated and should not be assumed to cover all the factors specified above for any particular sterilization process. This table is informative only.	
NOTE 2 Viral culture can use any suitable cell line which is traceable and for which the number of passage(s) is known.	

Annex B (normative)

Approach 1 — Process definition based on inactivation of the microbial population in its natural state

B.1 General

The methods described in ISO 11137-2 are examples of how process definition can be achieved based on inactivation of the microbial population in its natural state.

B.2 Product selection

Product selected for studies on process definition shall be representative of routine production.

B.3 Procedure

B.3.1 Expose product to the sterilizing agent in predetermined increment(s) of the anticipated sterilization process. Establish the required accuracy and precision of increments, and control and monitor the delivery of the sterilizing agent to meet defined limits.

B.3.2 Following exposure to the sterilizing agent, subject products individually to a test of sterility in accordance with ISO 11737-2.

B.3.3 To define the sterilization process, use knowledge of the relationship between the proportion of products exhibiting no growth in tests of sterility and the extent of exposure to the sterilizing agent.

B.4 Maintaining process effectiveness

Confirm the continued appropriateness of the sterilization process at defined intervals using product representative of routine production (see 12.4).

Annex C (normative)

Approach 2 — Process definition based on inactivation of reference microorganisms and knowledge of bioburden

C.1 General

This approach has been referred to as the “combined biological indicator/bioburden method”. Guidance on this approach is contained in ISO 14161.

C.2 Procedure

C.2.1 Establish the location(s) within product at which sterility is most difficult to achieve.

C.2.2 Create a challenge to the sterilization process, comprising a known number of microorganisms with known resistance to the sterilizing agent, by one of the following approaches:

- a) placing biological indicators within product at position(s) where sterility is most difficult to achieve;
- b) inoculating with reference microorganisms the position(s) within product where sterility is most difficult to achieve.

C.2.3 Package the challenge in the same manner as product produced routinely and include it within the sterilization load.

C.2.4 Treat the sterilization load with the sterilizing agent under conditions selected to deliver less lethality than those conditions to be used routinely, such that not all the reference microorganisms have been inactivated.

C.2.5 If the sterilization process involves treatment with a chemical agent, establish that its microbicidal and/or microbiostatic action(s) have been appropriately neutralized prior to the estimation of survivors.

NOTE See ISO 11138-1:2006, Annex B, for information on a method to determine growth inhibition.

C.2.6 Determine the number of microorganisms surviving, either by direct enumeration or estimated by a most probable number technique.

C.2.7 Calculate the rate of inactivation of the reference microorganisms.

C.2.8 From a knowledge of the bioburden (established in accordance with 7.4) and the rate of inactivation of the reference microorganisms, determine the extent of treatment required to achieve the specified requirements for sterility.

Annex D (normative)

Approach 3 — Conservative process definition based on inactivation of reference microorganisms

D.1 General

This approach to process definition has been widely employed, particularly for products to be re-processed in health care establishments. Qualifying a sterilization process for such products employs an approach different from that adopted with virgin product. This is because the challenge to the sterilization process is difficult to define and preprocessing treatments such as cleaning are difficult to validate and control (see 7.3 and 7.4). Therefore, sterilization processes applied in these situations are often conservative and employ a treatment that exceeds that needed to achieve the specified requirements for sterility. This approach has been referred to as the “overkill approach.” Guidance on this approach can be found in ISO 14161.

D.2 Procedure

D.2.1 Determine the position(s) within product where it is most difficult to achieve sterilizing conditions.

D.2.2 Create a challenge to the sterilization process, comprising a known number of microorganisms with known resistance to the sterilizing agent, by one of the following approaches:

- a) placing biological indicators within product at position(s) where sterility is most difficult to achieve;
- b) inoculating with reference microorganisms the position(s) within product where sterility is most difficult to achieve.

D.2.3 Package the challenge in the same manner as product produced routinely and include it within the sterilization load.

D.2.4 Treat the sterilization load with the sterilizing agent under conditions designed to deliver an exposure reduced in relation to that in the anticipated sterilization process.

D.2.5 Identify the extent of treatment that inactivates 10^6 microorganisms at the selected position(s).

NOTE There are several approaches to identify the extent of treatment to inactivate 10^6 microorganisms. For example:

- 1) with an initial challenge equal to or greater than 10^6 viable microorganisms, this extent of treatment can be identified conservatively as the treatment after which no surviving microorganisms are recovered,
- 2) with an initial challenge greater than 10^6 viable microorganisms, this extent of treatment can be identified as the treatment after which a 6-log reduction in viable microorganisms is observed,

or

- 3) with an initial challenge less than 10^6 viable microorganisms, this extent of treatment can be identified by extrapolation from the treatment after which, for example, a 4-log reduction in viable microorganisms is observed.

D.2.6 If the sterilization process involves treatment with a chemical agent, establish that its microbicidal and/or microbiostatic action(s) have been appropriately neutralized prior to the estimation of the number of survivors.

NOTE See ISO 11138-1:2006, Annex B, for information on a method to determine growth inhibition.

D.2.7 Repeat exposure of fresh challenges to the level of treatment identified in D.2.5 on at least two further occasions.

D.2.8 If the inactivation of 10^6 microorganisms has been confirmed following D.2.7, determine the extent of treatment for the sterilization process by extrapolation to a predicted probability of a surviving microorganism of 10^{-6} or better, taking into account the nature of the inactivation kinetics effected by the sterilizing agent and the number and resistance of the microorganisms on the biological indicator/inoculated product.

NOTE 1 This approach is best suited to sterilizing agents that exhibit linear inactivation kinetics. In such cases, the extent of treatment can be defined conservatively as twice that employed in D.2.6. For sterilizing agents that do not exhibit linear inactivation kinetics, the nature of the inactivation kinetics should be investigated in order to derive a relationship from which it can be predicted that the specified probability of a microorganism surviving is not exceeded on applying the sterilization process.

NOTE 2 A knowledge of the inactivation kinetics can be obtained as in 5.3.1 b); the nature of the inactivation kinetics can be influenced by the product.

Annex E (informative)

Guidance on application of this International Standard

NOTE For ease of reference, the numbering of clauses in this Annex corresponds to that in the normative part of this standard.

E.1 Scope

The guidance given in this annex is not intended as a checklist for assessing compliance with this International Standard. This guidance is intended to assist in obtaining a uniform understanding and implementation of this International Standard 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, providing their performance achieves compliance with this International Standard.

E.2 Normative references

The requirements given in documents that are included as normative references are requirements of this International Standard only to the extent that they are cited in normative parts of this International Standard; the citation may be to a whole standard or limited to specific clauses.

E.3 Terms and definitions

No guidance offered.

E.4 Quality management system elements

E.4.1 Documentation

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

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

E.4.2 Management responsibility

E.4.2.1 Requirements for responsibility and authority are specified in 5.5 of ISO 13485:2003 and requirements for human resources in 6.2 of ISO 13485:2003.

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

The level of qualification, training and experience required by personnel will depend upon the activities being performed. General guidance on training as part of the overall quality management system is given in ISO 9004.

Particular qualifications and training are appropriate for personnel with the following responsibilities: microbiological testing; chemical analysis and formulation; installation of equipment; equipment maintenance; physical PQ; routine sterilizer operation; calibration; process design; equipment specification.

E.4.2.2 The development, validation and routine control of a sterilization process are likely to involve a number of separate parties, each of whom is responsible for certain elements. This International Standard does not require particular elements to be carried out by specific parties but does require that the party accepting particular responsibilities is defined and that this definition of responsibilities is documented. This documented definition of responsibilities should be within the quality management system(s) of the identified parties and can form part of a contractual relationship.

Table E.1 lists the elements of this International Standard and, for illustration only, names parties that might be responsible for identified activities. It should be noted that

- the elements listed might not occur sequentially, as the design and testing programme can be iterative in part;
- responsibilities for the elements can vary from case to case.

The organization accepting responsibilities for defined elements is required to assign these elements to appropriately trained and qualified personnel.

In order to illustrate the variety of possible allocations of responsibility, three sample scenarios are presented below. These scenarios are not intended to be all-inclusive.

Scenario 1 — Health care facility: in this scenario, the user of the sterilization process is a health care facility. Three parties are involved in complying with this International Standard: the health care facility, the sterilizer manufacturer and the medical device manufacturer. The assignment of responsibilities and the means used to undertake these responsibilities might be as follows.

- Quality management system elements: each party has its own quality management system. The limits of responsibility of each party are laid down in formal contracts.
- Sterilizing agent characterization: the health care facility has agreed to a contract to purchase a sterilization system from a sterilizer manufacturer; this sterilizer manufacturer accepts responsibility for sterilizing agent characterization and has the resultant data on file. The health care facility has access to these data and, prior to making the decision to purchase, has reviewed the sterilizer manufacturer's data and the data available in the published scientific literature.
- Process/equipment characterization: the sterilizer manufacturer has undertaken the process/equipment characterization, developed the equipment specification and has the necessary regulatory approval to place the product on the market. The health care facility reviews the equipment specification in conjunction with the sterilizer manufacturer to confirm that the services and infrastructure necessary to operate the sterilization equipment are available.
- Product definition: the health care facility has identified the medical devices that it intends to reprocess. The instructions for reprocessing these medical devices provided by the medical device manufacturer include instructions for cleaning and disinfection. Also, these instructions confirm that the proposed method for sterilization is appropriate. The medical device manufacturer has undertaken process definition studies in collaboration with the sterilizer manufacturer in order to substantiate the reprocessing instructions provided. The health care facility reviews the data on the effectiveness of its cleaning processes and confirms they are adequate for the particular device(s) and sterilization process.
- Process definition: the sterilizer manufacturer and the medical device manufacturer have collaborated to define the sterilization process for the particular medical devices and have included the relevant instructions within each of their instructions for use. The necessary regulatory approvals have been obtained. The health care facility reviews the documentation and confirms that it has the capability to follow these instructions.
- Validation: the health care facility contracts with the sterilizer manufacturer to undertake IQ and OQ in accordance with documented procedures. The health care facility undertakes PQ and then reviews and approves the validation exercise.

- Routine monitoring and control: the health care facility undertakes the routine control and monitoring in accordance with its documented procedures.
- Product release from sterilization: the health care facility undertakes product release from sterilization in accordance with its documented procedures.
- Maintaining process effectiveness: the health care facility accepts responsibility for maintaining process effectiveness. It contracts with the sterilizer manufacturer to undertake planned preventative maintenance and calibration. It defines procedures for requalification. The health care facility defines procedures for the periodic reassessment of the effectiveness of the cleaning and disinfection processes.

Scenario 2 — Medical device manufacturer using in-house facilities: in this scenario, the user of the sterilization process is a manufacturer of single-use medical devices who is installing in-house facilities for sterilization. The parties involved are the medical device manufacturer and the sterilizer manufacturer. The allocation of responsibilities and the means used to undertake these responsibilities might be as follows.

- Quality management system elements: each party has its own quality management system. The limits of responsibility of each party are laid down in formal contracts.
- Sterilizing agent characterization: the sterilizer manufacturer has undertaken the sterilizing agent characterization and made the data available to the medical device manufacturer.
- Process/equipment characterization: the sterilizer manufacturer has developed an equipment specification, including a control system for the equipment, which is capable of being programmed to deliver a predefined process.
- Product definition: the medical device manufacturer is responsible for the specification of the product and its manufacture.
- Process definition: the medical device manufacturer defines a process for the particular medical device(s) to be sterilized. The medical device manufacturer undertakes the biological safety assessments and product compatibility studies. In this instance, these studies are conducted using experimental sterilization equipment.
- Validation: the medical device manufacturer undertakes validation using the sterilization equipment to be used routinely, confirming that it is capable of delivering the defined sterilization process.
- Routine control and monitoring: this is carried out by the medical device manufacturer in accordance with documented procedures.
- Product release from sterilization: this is carried out by the medical device manufacturer in accordance with documented procedures.
- Maintaining process effectiveness: this is carried out by the medical device manufacturer in accordance with documented procedures.

Scenario 3 — Medical device manufacturer using a sterilization subcontractor: in this scenario, the user of the sterilization process is a manufacturer of single-use medical devices who is using a sterilization subcontractor to deliver the sterilization process. Additionally, the medical device manufacturer is using a contract laboratory to undertake defined testing as part of the product release procedures. The parties involved are the medical device manufacturer, the sterilization subcontractor, and the contract laboratory. The allocation of responsibilities and the means used to undertake these responsibilities might be as follows:

- Quality management system elements: each party has its own quality management system. The limits of responsibility of each party are laid down in formal contracts.
- Sterilizing agent characterization: the sterilization subcontractor has licensed the sterilization process from a separate organization that characterized and developed the sterilization process. The process developer has undertaken the sterilizing agent characterization and made the resultant data available to the sterilization subcontractor and the medical device manufacturer.

- Process/equipment characterization: the sterilization subcontractor has developed an equipment specification, including a control system for the equipment, which is capable of being programmed to deliver a predefined process. A sterilizer manufacturer has been contracted to manufacture and install the specified equipment.
- Product definition: the medical device manufacturer is responsible for the specification of the product and its manufacture.
- Process definition: the medical device manufacturer defines a process for the particular medical device(s) to be sterilized. The medical device manufacturer undertakes the biological safety assessments and product compatibility studies. In this instance, these studies are conducted using experimental sterilization equipment.
- Validation: the sterilization subcontractor undertakes IQ and OQ in accordance with documented procedures. The medical device manufacturer then undertakes PQ using the installed sterilization equipment, confirming that the equipment is capable of delivering the defined sterilization process. The medical device manufacturer reviews and approves the validation exercise. A contract laboratory might perform microbiological testing in accordance with methods agreed with the medical device manufacturer.
- Routine control and monitoring: this is carried out by the sterilization subcontractor and the contract laboratory in accordance with documented procedures agreed with the medical device manufacturer.
- Product release from sterilization: this is carried out by the medical device manufacturer in accordance with documented procedures, on the basis of records provided by the sterilization subcontractor and the contract laboratory.
- Maintaining process effectiveness: the sterilization subcontractor carries out equipment maintenance and calibration in accordance with documented procedures. The medical device manufacturer maintains the quality of the product prior to sterilization and takes responsibility for requalification; the sterilization subcontractor carries out any necessary repetition of part or all of IQ or OQ.

E.4.3 Product realization

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

E.4.3.1 Requirements for purchasing are specified in 7.7 of ISO 13485:2003. In particular, it should be noted that the requirements in 7.4 of ISO 13485:2003 for the verification of purchased product apply to all product and services received from outside the organization.

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

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

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

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

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

E.5 Sterilizing agent characterization

E.5.1 General

No guidance offered.

E.5.2 Sterilizing agent

No guidance offered.

E.5.3 Microbicidal effectiveness

E.5.3.1 Many chemicals and processes can be shown to have antimicrobial activity. Not all, however, meet the criteria for a sterilizing agent. The intent and approach of the studies on microbicidal effectiveness are to:

- provide a definition of the sterilizing agent and the associated process and equipment sufficient to establish and maintain reproducible conditions for studies on microbicidal effectiveness; this activity should be documented;
- develop and validate methods for the growth of microorganisms and their inoculation on to carriers for exposure to the sterilizing agent; these procedures include recovery and enumeration of microorganisms from the carriers and estimation of the fraction of exposed carriers rendered sterile; the necessity for neutralization of residues of the sterilizing agent should be considered [see the guidance in E.5.3.1 g)];
- define the microbicidal activity of the sterilizing agent against different types of microorganism;
- identify the highly resistant microorganism(s) [reference microorganism(s)] appropriate for detailed microbial inactivation studies;
- characterize the microbicidal activity of the sterilizing agent in regard to concentration/potency, exposure time/dose, and/or other variables that could effect the microbicidal activity using the highly resistant microorganism(s);
- define the kinetics of microbial inactivation; confirm that the lethal action can be extrapolated to predict the probability of a microorganism surviving exposure to a defined treatment using the inactivation data obtained with the highly resistant microorganism(s).

Guidance specific to 5.3.1 a): qualitative studies can be used to test the activity of the candidate sterilizing agent against a range of microorganisms. The purpose of these studies is two-fold:

- 1) to demonstrate that a range of different types of microorganism is sensitive, to some degree, to the action of the sterilizing agent;
- 2) to choose one or more highly resistant microorganisms for more quantitative inactivation studies.

If, during these studies, bacterial spores are found to be essentially insensitive to the action of the candidate sterilizing agent, the use of the candidate sterilizing agent for sterilization applications is not permissible. The candidate sterilizing agent might, however, be suitable for other purposes, e.g. low-level disinfection.

Further information can be found in the references cited in the Bibliography.

Guidance specific to 5.3.1 b): quantitative microbial inactivation studies are undertaken to demonstrate that the sterilizing agent, when applied in a defined manner, can reliably yield calculable numbers of surviving microorganisms. These studies generally involve the use of graded exposure to or contact with the sterilizing agent to generate survival data defining the inactivation of the previously identified highly resistant microorganism(s). To define the upper section of the microbial survival curve, direct enumeration methods are generally used. For the section of the curve where there is a low number of survivors occurring, fraction negative data are employed. In the construction of such survival curves, the practical lower limit of estimation of average numbers of surviving microorganisms is 0,01. The extent of treatment to provide a probability of a surviving microorganism lower than this limit is inferred by extrapolation.

The empirical relationship can, for example, be defined in an equation or represented as a graph relating extent of treatment to the numbers and probability of surviving microorganisms. The relationship may also be presented in a tabulation of values.

In situations where the survival curve is log-linear, i.e. a plot on semi-log paper yields a straight line and extrapolation is readily performed. A curve that is concave in relation to the X-axis can, when fitted with a straight line, yield a somewhat conservative estimate of the extent of treatment needed to attain a defined probability of survival of a microorganism. Caution shall be used if the microbial inactivation studies indicate a result that is best approximated by a survivor curve that is convex in relation to the X-axis.

Demonstration of the lethal action of the sterilizing agent over a range sufficient to define the microbial inactivation kinetics requires an adequate number of viable microorganisms to be initially present on and recoverable from carriers. In studies requiring quantitative enumeration of surviving organisms from carriers exposed to graded treatments of the sterilizing agent, the numbers of microorganisms recovered from exposed carriers are compared to those recovered from the unexposed controls to construct survivor curves relating log proportion of microorganisms surviving to the extent of treatment.

NOTE 1 Microbial inactivation and failure to recover viable test microorganisms from the surface of an inoculated carrier exposed to the sterilizing agent might not be distinguishable. In this context, use of tracer agents (such as radiolabelled microorganisms) could be useful.

Microbial inactivation studies require the use of test methods validated for the specific sterilizing agent. During the design and validation of the test methods, particular attention should be paid to test conditions that result in spurious data arising from, for example, inadequate recovery conditions, the occurrence of microbiostasis, and false positives. Loss of viability of surviving microorganisms should be considered arising from, for example, transport of test materials to a contract laboratory. Development of the test methods and/or their performance can be carried out in-house or in a contract laboratory.

Guidance specific to 5.3.1 c): selection of test microorganisms for microbial inactivation studies should be justified. Methods to be qualified could include:

- 1) growth, maintenance, and enumeration of the selected test organism;
- 2) preparation of consistent inocula of test microorganisms;
- 3) inoculation of microorganisms on to carriers. Inoculation on to carriers should be carried out in a defined and reproducible manner. The effects of drying the inoculum and storage of the carriers (under defined conditions) upon organism viability and resistance to the sterilizing agent should be considered. The carriers should neither inhibit nor potentiate the action of the sterilizing agent upon the inoculated microorganisms.
- 4) quantitative assessment of inactivation of microorganisms on carriers exposed to a sterilizing agent and recovery of microorganisms from carriers following exposure to a sterilizing agent.

NOTE 2 See also Note 1.

Guidance specific to 5.3.1 d): studies on sterilizing agent characterization may be performed with laboratory, prototype or routine production-type equipment. For each situation, sufficient definition of the sterilizing agent and equipment is required in order to ensure reproducible conditions.

Consideration should be given to a reproducible set-up and operation of equipment and the monitoring and control of variables that can affect the outcome of the microbial inactivation studies. Operational aspects of inactivation studies vary according to the complexity of the sterilizing agent and/or equipment. For example, inactivation studies with a liquid chemical sterilizing agent performed in a simple glass vessel will be, by nature, much less complex than those with a gas plasma agent.

Regardless of the complexity, the set-up for each study should be documented; any changes to the set-up and their effect on the outcome of microbial inactivation studies should be assessed and documented. Operation of the equipment and the performance of studies should preferably be conducted in accordance with a previously written procedure. Data defining the conditions of exposure to the sterilizing agent should be recorded together with the microbiological and any other test measurements.

Guidance specific to 5.3.1 e): no guidance offered.

Guidance specific to 5.3.1 f): no guidance offered.

Guidance specific to 5.3.1 g): before commencing any investigation of microbial inactivation, it is necessary to ensure that the results of the investigation are not influenced adversely by microbicidal or microbiostatic effects due to carry-over of the sterilizing agent or its residual derivatives into the recovery system; such effects can be reduced by:

- 1) dilution of the sterilizing agent;
- 2) removal of the sterilizing agent;
- 3) neutralization of the microbicidal or microbiostatic action of the sterilizing agent by reaction with an appropriate agent.

If a secondary host such as cell culture is used as the detection system for the survival of test organisms, the absence of carry-over effects on the cell culture system itself should also be demonstrated. Cytotoxicity controls should also be included to determine the effect of the sterilizing agent on the cell culture system used for detection of test organisms. In addition, a challenge of the defined cell culture system previously exposed to the residual levels of sterilizing agent and its derivatives, if any, with a low level of microorganisms (around ten) can be used to show that the enumeration assay is functional.

The choice of neutralizing system is influenced by the nature of the sterilizing agent. The effectiveness of the chosen neutralizing agent should be demonstrated prior to the commencement of inactivation studies.

E.5.3.2 No guidance offered.

E.5.4 Effects on materials

E.5.4.1 This subclause considers the effects of the sterilizing agent on material likely to be used to manufacture product to be sterilized. Both short-term and long-term effects on materials should be assessed. Consideration of effects of the sterilizing agent on product is given in Clause 7.

E.5.4.2 Consideration should include the short-term and long-term effects of repeated exposures.

E.5.4.3 No guidance offered.

E.5.5 Safety and the environment

E.5.5.1 No guidance offered.

E.5.5.2 ISO 14001 provides a specification for an environmental management system. ISO 14040 provides guidance on designing a life cycle assessment study.