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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

Stérilisation des produits de santé — Exigences générales pour la caractérisation d'un agent stérilisant et pour le développement, la validation et la vérification de routine d'un processus de stérilisation pour 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 3.

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 International Standard may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

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

Annexes A, B, C and D form a normative part of this International Standard. Annexes E and ZA are for information only.

Introduction

A sterile medical device is one which is free of viable microorganisms. When it is necessary to supply a sterile medical device, International Standards specifying requirements for validation and routine control of sterilization processes require 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 systems (see, for example, ISO 13485 and ISO 13488) or which have been subjected to a cleaning process as part of their reprocessing in a health care establishment may, prior to sterilization, have microorganisms on them, albeit in low numbers. Such products are non-sterile. The purpose of sterilization is to inactivate the microbiological contaminants and thereby transform the non-sterile products into sterile ones.

The kinetics of inactivation of a pure culture of microorganisms by physical and/or chemical agents used to sterilize medical devices can generally best be described by an exponential relationship between the numbers of microorganisms surviving and the extent of treatment with the sterilizing agent. Inevitably this means that there is always a finite probability that a microorganism may survive regardless of the extent of treatment applied. For a given treatment, the probability of survival is determined by the number and resistance of microorganisms and by the environment in which the organisms exist during treatment. It follows that the sterility of any one product in a population subjected to sterilization processing cannot be guaranteed, and the sterility of a processed population has to be defined in terms of the probability of there being a viable microorganism present on a product.

This International Standard describes requirements which will enable sterilizer manufacturers, medical device manufacturers and health care facilities to demonstrate that a process intended to sterilize medical devices has appropriate microbicidal activity, and that this activity is both reliable and reproducible, such that the relationship for the inactivation of microorganisms can be extrapolated with reasonable confidence to low levels of probability of there being a viable microorganism present on a product after sterilization processing. This International Standard does not specify the maximal value to be taken by this probability; specification of this probability is a matter for regulatory authorities and may vary from country to country (see, for example, EN 556 and AAMI ST67).

Generic requirements of the quality system for design/development, production, installation and servicing are given in the ISO 9000 series and particular requirements for quality systems for medical device production in ISO 13485 and ISO 13488. The standards for quality systems recognize 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 respect, suitable for its intended use. Attention is given to a number of factors, including:

a) for a manufacturing process, the microbiological status of incoming raw materials and/or components;

b) the validation and routine control of the cleaning and disinfection procedures used during reprocessing;

c) the control of the environment in which the product is manufactured, assembled and packaged, together with control of personnel and their hygiene; and,

d) the manner in which the items are packaged and the conditions under which the sterilized items are 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, should be regarded as a special case. There is the potential for such products to possess a wide range of contaminating microorganisms and residual inorganic and/or organic contamination, in spite of the application of a cleaning process. Hence, particular attention is given to the validation and control of the cleaning and disinfection processes used during reprocessing.

Sterilization technology is at several levels of development and application. There are processes which are developed and have been in use for appreciable periods, and there are processes which are being developed and introduced either for sterilization of specific products or for general application. Furthermore, there may be processes which have yet to be discovered. Experience has identified the requirements which are appropriate for existing sterilization technologies, and these requirements have been specified in International Standards specific to each established process. The intention in developing this International Standard is to use this experience to provide, for suppliers of sterilization technologies, to their users and to regulatory authorities, a knowledge of the relevant general requirements that will allow development of additional sterilization technologies to continue within a broad framework until sufficient experience, confidence and demand exist to justify the preparation of a specific International Standard.

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; and,

— for manufacturers and users of sterilization systems in health care settings for which a specific International Standard does not exist; and,

— to provide a framework for the preparation or revision of standards for specific sterilization processes.

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 4.1.1) but does not specify to whom the responsibilities are allocated. Annex E provides guidance on allocation of responsibility.

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

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

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

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

1.5 This International Standard is intended to be applied by process developers, manufacturers of sterilization equipment, manufacturers of medical devices to be sterilized and the organization with responsibility for sterilizing the medical device.

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

NOTE 1 Although the scope of this International Standard is limited to medical devices, the principles described may also be applied to other health care products.

NOTE 2 Sterilization processes validated and controlled in accordance with the requirements of this International Standard should not be assumed to be effective in inactivating the causative agents of spongiform encephalopathies such as scrapie, bovine spongiform encephalopathy and Creutzfeld-Jakob disease. Specific recommendations have been produced in particular countries for the processing of materials potentially contaminated with these agents.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this International Standard. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this International Standard are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

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

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing.*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances using health-based risk assessment.*

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

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: Estimation of 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, *Quality systems — Medical devices — Particular requirements for the application of ISO 9001.*

ISO 13488, *Quality systems — Medical devices — Particular requirements for the application of ISO 9002.*

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

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 a product and/or a package

3.2
biological indicator
microbiological test system providing a defined resistance to a specified sterilization process

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

3.4
chemical indicator
system that reveals a change in one or more predefined process variables based on a chemical or physical change resulting from exposure to a process

3.5
development
act of elaborating a specification in preparation for validation

3.6
establish
determine by theoretical evaluation and confirm by experimentation

3.7
fault
one or more of the process parameters which lies outside of its/their specified tolerance(s)

3.8
health care product
medical device, medicinal product (pharmaceuticals and biologics) or *in vitro* diagnostic medical device

3.9
installation qualification
IQ
obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

3.10
material safety data sheet
document specifying the properties of a material, its potential hazardous effects for humans and the environment, and the precautions necessary to handle and dispose of the material safely

3.11
medical device
any instrument, apparatus, appliance material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

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

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

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

— control of conception;

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

3.12
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

3.13
parametric release
declaration that a product is sterile, based on the records demonstrating that the process parameters were delivered within specified tolerances

3.14
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

3.15
process challenge device
item designed to simulate product to be sterilized and to constitute a defined challenge to the sterilization process, and used to assess the effective performance of the process

3.16
process parameter
specified value for a process variable

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

3.17
process variable
condition associated with a sterilization process, changes in which alter microbicidal effectiveness

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

3.18
recognized culture collection
international depository authority under the Budapest Treaty on 'The International Recognition of the Deposit of Microorganisms for the Purpose of Patent and Regulation'

3.19
reference microorganism
microbial strain obtained from a recognized culture collection

3.20
requalification
repetition of part of validation for the purpose of confirming the continued acceptability of a specified process

3.21
services
supplies from an external source, necessary for the correct functioning of sterilizing equipment

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

3.22
specify
stipulate in detail within an approved document

3.23
sterile
free from viable microorganisms

3.24
sterility
state of being free from viable microorganisms

3.25
sterilization
validated process used to render a product free from viable microorganisms

3.26
sterilization load
product to be, or that has been, sterilized together using a given sterilization process

3.27
sterilization process
series of actions or operations to achieve the specified requirements for sterility

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

3.28
sterilizing agent
physical or chemical entity, or combination of entities, that have sufficient microbicidal activity to achieve sterility under defined conditions

3.29
survivor curve
graphical representation of the inactivation of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions

3.30
test for sterility
test defined in an official Pharmacopoeia for product release following exposure to a sterilization process

3.31
test of sterility
test performed as part of development, validation or requalification to establish the presence or absence of viable microorganisms on product units, or portions thereof

3.32
validation
documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications

4 Quality system elements

4.1 General

The purpose of the quality system is to define and document procedures, the implementation of which control all stages of development, application and use of the sterilization process. It is not a requirement of this International Standard to have a complete quality system during design/development and production, but certain elements of a quality system are required and these are normatively referenced at appropriate places in the text. Attention is drawn to ISO 9001 and ISO 13485 which describe a quality system. This International Standard does not require third party assessment of the specified quality system elements.

4.2 Assignment of responsibilities

4.2.1 The responsibility for performing each element of the procedures in this International Standard shall be defined and documented. Responsibility for each element may vary from case to case and this International Standard does not allocate responsibility for each element to particular parties.

The elements are: quality system; sterilizing agent characterization; process/equipment characterization; product definition; process definition; validation; routine monitoring and control; product release from sterilization; and maintaining process effectiveness.

NOTE These elements are illustrated in Table E.1.

4.2.2 Responsibilities shall be further assigned to qualified personnel as specified in ISO 13485 or ISO 13488.

NOTE 4.1.1, 4.1.2.2 and 4.18 of ISO 13485:1996 and ISO 13488:1996 detail requirements for management responsibility, personnel and training.

4.3 Documentation and records

4.3.1 Documented procedures for each phase of the development, validation, routine monitoring and control and product release from sterilization shall be prepared and implemented.

4.3.2 Documentation and records required by this International Standard shall be reviewed and approved by designated personnel (see 4.1.2). A system shall be prepared, documented and maintained to control all procedures and records required by this International Standard. This system shall comply with ISO 13485 or ISO 13488.

4.3.3 Records of development, validation, routine monitoring and control and product release from sterilization activities shall be retained.

4.3.4 The records required by this International Standard shall be retained in accordance with ISO 13485 or ISO 13488.

NOTE 4.4.6 of ISO 13485:1996 and ISO 13488:1996 detail requirements for retention of records.

4.4 Design control

Characterization of the sterilizing agent and sterilization process shall be undertaken in accordance with a documented plan. At defined stages, design reviews shall be planned, conducted and documented.

NOTE 4.4.6 of ISO 13485:1996 details requirements for design reviews.

4.5 Calibration

A documented system, complying with ISO 13485, ISO 13488 or ISO 10012-1, shall be established and maintained for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this International Standard.

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 which influence microbicidal effectiveness, assess the effects that exposure to the sterilizing agent have 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; the final equipment specification (see 6.3) should be relatable to the experimental studies undertaken using any such test or prototype equipment.

5.2 Sterilizing agent

A specification for the sterilizing agent shall be generated and documented. This shall include, if appropriate, conditions for storage to maintain the sterilizing agent within its specification for the duration of any 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 representative range of microorganisms selected in accordance with annex A,

b) establish an empirical mathematical relationship defining the microbial inactivation kinetics of identified resistant microorganisms, and confirm that the probability of a microorganism surviving exposure to a defined treatment can be validly predicted.

c) select reference microorganism(s), based on the microbial inactivation kinetics, which have known high resistance(s) to the sterilizing agent for use in establishing the sterilization process,

d) identify the process variables which 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 affect the delivery and/or distribution of the sterilizing agent,

NOTE Such factors may include, for example, the environment, packaging configuration(s), geometry, materials and residues from manufacturing, cleaning and/or disinfection.

f) assess those factors that can adversely influence the effectiveness of the sterilizing agent based upon physical and/or chemical interactions.

NOTE Such factors may include, for example, interactions with 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, test results and justification for the choice of test microorganisms shall be documented.

5.4 Material effects

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. The materials should be selected on the basis of the likely usage of the sterilizing agent.

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

5.4.3 The materials tested and the outcomes of all tests shall be documented, 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 prepared and documented for the sterilizing agent, its precursors (if any) and any by-products of the sterilizing agent. This material safety data sheet 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 impact 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 measures for its control determined. This assessment, including the potential impact (if any) and the measures for control (if identified) shall be documented.

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

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 established and documented. These tolerances shall be based upon knowledge of the combination of process parameters yielding the minimum acceptable microbicidal effectiveness, and shall yield acceptable product.

NOTE The establishment of the process parameters comprises the definition of process variables, including those 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 sterilization process to ensure the effectiveness of the process shall be defined and documented.

6.2.4 Any treatment of product that is required following exposure to the sterilizing agent to ensure the safety of the product shall be defined as part of the sterilization process and documented.

6.3 Equipment characterization

6.3.1 The specification for equipment to deliver the process within the tolerances stipulated for the process parameters and in a safe manner shall be established and documented.

6.3.2 The specification shall include but is not limited to

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

b) specification of the sterilizing agent 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, indicating and recording instruments,

d) fault recognized by the sterilizing equipment,

e) safety features, including those for personnel and environmental protection,

f) installation requirements, including 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 system that provides documented evidence that the software meets its design intention.

NOTE Attention is drawn to ISO 9000-3.

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 a cross-check between control and monitoring which 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 sterilizing agent, shall be defined and documented.

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.

7.3 A system shall be defined, documented 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, given the nature of the raw materials, product and manufacturing or reprocessing procedures prior to sterilization. This can be achieved by employing a quality system complying with ISO 13485 or ISO 13488 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 prior to sterilization are in the course of preparation. These International Standards will 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 applicable for defined product shall be established. This shall be achieved by

a) if practical, demonstrating the attainment of the process parameters by measurements, and

b) delivering the sterilizing agent under conditions so designed to represent increments of treatments that deliver less lethality than the intended sterilization process using one of the approaches outlined in annexes B, C or D to this standard.

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

a) comply with ISO 11138-1 and any subsequent parts of ISO 11138 which 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, and

c) be placed at positions in product where it has been determined that sterilizing conditions are most difficult to achieve.

8.4 If chemical indicators are used as part of the establishment of the sterilization process, these shall comply with ISO 11140-1 and any subsequent parts of ISO 11140 which are applicable to the process and shall be placed at positions in product where it has been determined that sterilizing conditions are most difficult to achieve.

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

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

8.8 If necessary, means shall be established to reduce level(s) of process residual(s) in product below that (those) identified in accordance with 8.7.

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

8.10 The specification for the sterilization process shall be documented.

9 Validation

9.1 General

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.

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

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

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

9.2 Installation qualification

9.2.1 Equipment

9.2.1.1 The complete specification of all equipment used to deliver the sterilizing agent, including any ancillary items, shall be established and documented.

9.2.1.2 Sterilization equipment shall comply with IEC 61010-1 and any subsequent parts of IEC 61010 that are applicable to the sterilization equipment.

9.2.1.3 The operating procedures for the equipment shall be established and documented. 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, and

d) details of contacts for technical support.

9.2.2 Installation

9.2.2.1 A specification shall be documented for the location in which the equipment is to be installed, including any services required. Any special precautions and provisions shall be identified (for example, safety equipment).

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

9.2.2.3 Prior to installation qualification, the calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating or recording shall be confirmed (see 4.4).

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

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

9.3 Operational qualification

9.3.1 Prior to operational qualification, the calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating or recording shall be confirmed (see 4.4).

9.3.2 Operational qualification shall demonstrate that the installed equipment is capable of delivering the specified process (see 8.10) within defined tolerances.

9.4 Performance qualification

9.4.1 The manner of presenting the product for sterilization, including the orientation of product, shall be established and documented.

9.4.2 Product used for performance qualification shall be packaged identically to that to be sterilized routinely.

9.4.3 Data shall be generated to demonstrate the attainment of the defined physical and/or chemical conditions, within specified tolerances, throughout the sterilization load. The 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.

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

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

9.4.6 If test(s) of sterility are performed on product subjected to conditions as specified in 9.4.4, such tests shall be performed in accordance with ISO 11737-2.

9.4.7 If chemical indicators are used in performance qualification, they shall comply with 8.4.

9.4.8 Performance qualification shall include a series of at least three consecutive exposures of product to the sterilization process, within defined tolerances, in order to demonstrate the reproducibility of the process. Any exposures outside of defined tolerances during performance qualification shall be reviewed, and corrective measures determined and instituted before initiating a new series of exposures.

If failure can be attributed to factors not relevant to the effectiveness of the process being validated, this test may be documented as unrelated to performance of the process without requiring three further consecutive successful runs.

EXAMPLES This type of failure may include, but is not limited to, power failures, loss of services or failure of external monitoring equipment.

9.4.9 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 8.7).

9.4.10 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.

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 installation qualification, operational qualification and performance qualification shall be documented and reviewed for acceptability (see also 4.1 and 4.2). The results of this review shall be documented.

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 or chemical indicators, that the sterilization process was delivered within the defined tolerances (see also 9.4.3).

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

10.4 All records shall be retained in accordance with 4.2.4.

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 ISO 11140-1 and any subsequent parts of ISO 11140 that are applicable to the process.

11 Product release from sterilization

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

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

11.3 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 4.2).

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) 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 4.4.

12.2 Maintenance of equipment

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

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.

12.2.4 The maintenance scheme, maintenance procedures and maintenance records shall be reviewed periodically by a designated person. 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.

12.3.2 Requalification report(s) shall be documented and retained in accordance with 4.2.3.

12.3.3 Requalification data shall be reviewed against specified acceptance criteria in accordance with documented procedures. Records of reviews of requalification data, and corrective actions taken in the event that the specified acceptance criteria are not met, shall be retained (see 4.2.3 and 4.2.4).

12.4 Assessment of change

A change to equipment, product, packaging or presentation of product for sterilization, or a modification to the sterilizing agent and/or its presentation, shall be assessed for impact on the effectiveness of the sterilization process. The extent of qualification that is necessary shall be determined. The outcome of the assessment, including the rationale for decisions reached, shall be documented.

The magnitude of the change is considered in determining the extent to which installation qualification, operational qualification or performance qualification is undertaken.

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 may 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 Data

The data obtained in the demonstration of microbicidal effectiveness should establish whether a bacterial spore can be employed as a representative model of high resistance during process characterization studies.

A.3 Selection of microorganisms

The selection of species of microorganisms to be used in demonstrating the microbicidal effectiveness of a sterilizing agent shall take account of all of the following factors:

a) known high resistance to the sterilizing agent or an expectation of a high resistance from information in scientific literature or a knowledge of the mode of action of the sterilizing agent;

b) known resistance to well-characterized sterilization processes;

c) representative species of aerobic and anaerobic Gram positive and Gram negative bacteria, bacterial spores, mycobacteria, fungi including spore forms and yeasts, parasites and viruses;

d) species that might be present as a result of the materials of construction of the product or the environment in which it is manufactured;

e) species that have been isolated during estimations of bioburden undertaken on typical product to be processed.

NOTE 1 The information obtained 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 parasites [see A.3 c)] is a particular consideration in processes used to sterilize products containing material of animal origin (see also EN 1244-3), as well as in resterilizing medical devices in health care facilities.

NOTE 3 In considering the information from 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	*Bacillus subtilis* var. *niger* *Bacillus stearothermophilus* *Clostridium sporogenes*
Vegetative bacteria	*Staphylococcus aureus* *Salmonella choleraesuis* *Pseudomonas aeruginosa*
Fungi	*Trichophyton mentagrophytes* (with conidia) *Candida* spp.
Mycobacteria	*Mycobacterium terrae*
Nonlipid viruses	Hepatitis A Parvovirus Poliovirus type 1 (attenuated)
Lipid viruses	*Herpes simplex*
Parasites	*Cryptosporidium parvum*

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 may 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

Methods 1 and 2 in annex B of ISO 11137:1995 + Corrigendum 1:1997 are examples of process definition based on inactivation of the microbial population in its natural state.

This approach has been described as a “bioburden-based method”.

B.2 Sampling

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

B.3 Procedure

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.

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

To define the sterilizing 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 Follow-up

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

Annex C
(normative)

Approach 2 — Process definition based on inactivation of reference microorganisms and knowledge of bioburden on product items to be sterilized

C.1 General

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

C.2 Procedure

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

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 the product at position(s) where sterilizing conditions are most difficult to achieve;

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

If the product is inoculated in this manner, it can be considered to be a biological indicator. Subclause 8.3 requires this packaged, inoculated product to meet the requirements of ISO 11138.

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

Expose the sterilization load to 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.

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

Calculate the rate of inactivation of the reference microorganisms.

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. Therefore, sterilization processes applied in these situations are often conservative and employ a treatment that may exceed that required 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.

Create a challenge to the sterilization process containing a known number of microorganisms with defined resistance to the sterilizing agent by one of the following approaches:

a) placing biological indicators within the product at position(s) where sterilizing conditions are most difficult to achieve;

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

If the product is inoculated in this manner, it can be considered to be a biological indicator. Subclause 8.3 requires this packaged, inoculated product to meet the requirements of ISO 11138.

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

D.2.2 Expose the sterilization load to the sterilizing agent under conditions designed to deliver a reduced level of treatment.

D.2.3 Identify the extent of treatment that inactivates 10^6 microorganisms.

NOTE With an initial challenge of 10^6 viable microorganisms, this extent of treatment can be identified conservatively as the treatment after which no surviving microorganisms are recovered.

D.2.4 Repeat exposure to the level of treatment identified in D.2.3 on at least two further occasions.

D.2.5 If the inactivation of 10^6 microorganisms has been confirmed following D.2.4, 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 of the sterilizing agent and the number and resistance of the microorganisms on the biological indicator.

This approach is best suited to sterilization processes which demonstrate linear inactivation kinetics. In such cases the extent of treatment can be defined conservatively as twice that employed in D.2.4. For sterilization processes that do not demonstrate linear inactivation kinetics, the exact nature of the inactivation kinetics shall be established in order to derive a relationship to use for the extrapolation.

NOTE A knowledge of the inactivation kinetics can be obtained as in 5.3 b), and may be modified by the influence of product.

Annex E
(informative)

Guidance on application of this International Standard

E.1 General

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 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 Quality system elements

E.2.1 Assignment of responsibilities

E.2.1.1 General

The development, validation and routine control of a sterilization process is 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 defined 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 may form part of a contractual relationship.

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

a) the elements listed may not be sequential, as the design and testing programme may be iterative in part, and,

b) responsibilities for the elements may vary from case to case.

The organization accepting responsibilities for defined elements is required to assign these elements to appropriately trained and qualified personnel (see E.2.2).

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

E.2.1.2 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.

a) Quality system

   Each party has its own quality system. The limits of responsibility of each party are laid down in formal contracts.

b) Sterilizing agent characterization

The health care facility has agreed 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 manufacturer's data and the data available in the published scientific literature.

c) 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 onto the market. The health care facility reviews the equipment specification to confirm that it has the services and infrastructure necessary to operate the sterilizing equipment.

d) 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 manufacturer include instructions for cleaning and disinfection, and 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 its data on the effectiveness of its cleaning processes and confirms they are adequate for the particular device(s) and sterilization process.

e) Process definition

The sterilizer manufacturer and the medical device manufacturer have collaborated to define the sterilization process for these 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.

f) Validation

The health care facility agrees, by contract with the sterilizer manufacturer, to undertake installation qualification and operational qualification, in accordance with documented procedures. The health care facility undertakes performance qualification and then reviews and approves the validation exercise.

g) Routine monitoring and control

The health care facility undertakes the routine control and monitoring in accordance with its documented procedures.

h) Product release from sterilization

The health care facility undertakes the product release from sterilization in accordance with its documented procedures.

i) Maintaining process effectiveness

The health care facility accepts responsibility for maintaining process effectiveness. It agrees by contract 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 its cleaning and disinfection processes.

E.2.1.3 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 might be as follows.

a) Quality system

Each party has its own quality system. The limits of responsibility of each party are laid down in formal contracts.

b) Sterilizing agent characterization

The sterilizer manufacturer has undertaken the sterilizing agent characterization and made the data available to the medical device manufacturer.

c) 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.

d) Product definition

The medical device manufacturer is responsible for the specification of the product and its manufacture.

e) 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. These studies are conducted using experimental sterilization equipment.

f) 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.

g) Routine control and monitoring

This is carried out by the medical device manufacturer in accordance with documented procedures.

h) Product release from sterilization

This is carried out by the medical device manufacturer in accordance with documented procedures.

i) Maintaining process effectiveness

This is carried out by the medical device manufacturer in accordance with documented procedures.

E.2.1.4 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 might be as follows:

a) Quality system

Each party has its own quality system. The limits of responsibility of each party are laid down in formal contracts.

b) Sterilizing agent characterization

The sterilization subcontractor has licensed the sterilization process from a separate organization who 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.

c) 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.

d) Product definition

The medical device manufacturer is responsible for the specification of the product and its manufacture.

e) Process definition

The medical device manufacturer defines a process for the particular medical device(s) to be sterilized. The medical device manufacture undertakes the biological safety assessments and product compatibility studies. In this case, these studies are conducted using experimental sterilization equipment.

f) Validation

The sterilization subcontractor undertakes installation qualification and operational qualification in accordance with documented procedures. The medical device manufacturer then undertakes performance qualification 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.

g) 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.

h) 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 contact laboratory.

i) 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 product prior to sterilization and takes responsibility for requalification; the sterilization subcontractor carries out any necessary repetition of part or all of installation qualification or operational qualification.

E.2.2 Personnel

The level of qualification, training and experience required by personnel at various levels will depend upon the activities being performed. General guidance on training as part of the overall system of quality assurance 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 performance qualification; routine sterilizer operation; calibration; process design; equipment specification.

E.3 Sterilizing agent characterization

E.3.1 Neutralization

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

a) dilution of the sterilizing agent,

b) removal of the sterilizing agent by filtration, or

c) inactivation of the sterilizing agent by reaction with a neutralizing 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. Cytotoxity controls also should be included to determine the effect of the sterilizing agent on the cell culture system used for detection of test organisms. In addition, 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 (approximately 10) of microorganisms will 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 system should be demonstrated prior to the commencement of inactivation studies.

E.3.2 Studies of microbial inactivation

E.3.2.1 General

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 microbial inactivation studies are to

— provide definition of the sterilizing agent and the associated process and equipment sufficient to establish and maintain reproducible conditions for microbial inactivation studies. This activity should be documented;

— develop and validate methods for the growth of microorganisms and their inoculation onto 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 E.3.1);

— define the microbicidal activity of the sterilizing agent against different types of microorganisms;

— identify a highly resistant microorganism(s) appropriate for detailed microbial inactivation studies;

— with the highly resistant microorganism(s), characterize the microbicidal activity of the sterilizing agent in regard to concentration/potency, exposure time/dose, and/or other variables that could affect the microbicidal activity;

— using the inactivation data obtained with the highly resistant microorganism(s), define the kinetics of microbial inactivation and demonstrate that the attainment of a probability of a microorganism surviving a defined treatment can be calculated. Confirm that the lethal action can be extrapolated validly to predict the probability of a microorganism surviving exposure to a defined treatment.

E.3.2.2 Sterilizing agent and associated equipment

E.3.2.2.1 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 the associated process(es) and equipment is required in order to ensure reproducible conditions for microbial inactivation studies.

E.3.2.2.2 Consideration should be given to 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 overall system. For example, inactivation studies with a liquid chemical sterilizing agent performed in a "test tube" will be, by nature, much less complex than those with a gas plasma agent.

E.3.2.2.3 Regardless of the complexity of the process, the set-up for each study should be documented; any changes to the set-up and their impact 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 documented together with the microbiological and any other test measurements.

E.3.2.3 Development of microbiological methods and their validation

E.3.2.3.1 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. Residual microorganism inactivation due to delay in testing arising, for example, from transport of test material to a contract laboratory, should also be considered. Development of the test methods and/or their performance may be carried out in-house or a contract laboratory.

E.3.2.3.2 Selection of test microorganisms for microbial inactivation studies should be justified. Methods to be validated may include

a) growth, maintenance and enumeration of the selected test organism,

b) inoculation of samples of the selected microorganisms onto carriers for exposure to the sterilizing agent,

   Microorganisms inoculated onto carriers should be prepared in a defined and reproducible manner. The effects of drying of 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 agent upon the inoculated microorganisms.

c) 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.

   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 survival to extent of treatment.

NOTE 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.

E.3.2.4 Microbial inactivation studies

E.3.2.4.1 Studies of microbial inactivation are both qualitative and quantitative in nature. The qualitative studies test the activity of the candidate sterilizing agent against a range of microorganisms. The purpose of these studies is two-fold:

a) to demonstrate that a range of different types of microorganisms are sensitive, to some degree, to the action of the sterilizing agent;

b) to identify one or more highly resistant microorganisms for more quantitative inactivation studies.

E.3.2.4.2 If, during these studies, bacterial spores are found to be essentially insensitive to the action of the candidate sterilizing agent, its use for sterilization applications is not permissible although other antimicrobial uses may exist (e.g low-level disinfection).

E.3.2.4.3 The quantitative microbial inactivation studies demonstrate that the sterilizing agent, when applied in a defined manner, can reliably yield a calculable probability of a surviving microorganism. 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 probability of survivors occuring, 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 microorgansm lower than this limit is inferred by extrapolation. In situations where the survival curve is log-linear, i.e. a plot on semi-log paper yields a straight line, this extrapolation is readily performed. A curve that is concave in relation to the x-axis can yield a somewhat conservative estimate of the extent of treatment. Caution has to 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.

E.3.2.4.4 Further information can be found in the references cited in the Bibliography.

E.4 Product definition

E.4.1 General

This clause describes product considerations that are addressed when evaluating a sterilization process. These considerations ensure that the sterilization process will result in a safe and functional product. 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.

E.4.2 Design considerations for medical devices intended for sterilization

E.4.2.1 Product function

Product can be subjected to various environmental stresses during sterilization, such as vacuum and pressure changes, elevated temperature, and changes in relative humidity. Product also could react with the sterilizing agent and/or any diluent(s). The product design has to ensure that functionality and safety are not compromised by exposure to the anticipated range of sterilization conditions. Typically, the maximum conditions would represent the most severe challenge to the product including the package. If applicable, the effects of multiple exposures to the sterilization process are evaluated.

E.4.2.2 Design tolerances and configuration

Design tolerances and configuration are important in ensuring effective delivery of the sterilizing agent and its distribution. If fitments are intended to maintain sterility, they are designed to avoid inadvertent contamination of surfaces intended to be sterile.

E.4.2.3 Materials composition

It is important to select materials that exhibit adequate resistance during sterilization to chemical and physical changes caused by the sterilizing agent 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, embrittlement and phase separation should be determined, and resistant materials specified. Materials should also allow sufficient sterilizing agent, transmission or permeation to ensure that target surfaces and materials are sterilized. The materials should allow

aeration (if applicable) within a reasonable time and retain biocompatibility. Methods for determining residuals of the sterilizing agent should be selected and validated during product development. If applicable, the effects of exposure to multiple sterilization processes are evaluated.

E.4.3 Packaging considerations

E.4.3.1 General

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).

Packaging considerations are addressed in more detail in ISO 11607.

E.4.3.2 Primary packaging

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. If penetration is required, the permeability of the package to the particular sterilizing environment is of utmost importance. For nonpermeable packaging (e.g. vials, ampoules, flexible pouches), the material and design permit adequate transfer of the sterilizing agent to the product. If air removal is part of the sterilization process, the package also permits air evacuation without damage or rupture. It is recommended that preliminary evaluation of the maintenance of primary package integrity be conducted before final selection of a sterilization cycle.Those portions of the primary package or product components intended to maintain product sterility (e.g. closures) should be demonstrated to maintain their integrity during and following exposure to the sterilization process.

E.4.3.3 Secondary packaging

The ability of the secondary packaging 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 . Additionally, the effect of the materials from which the secondary packaging is made on the attainment of sterilizing conditions during the process is established, together with the effect of resterilization (if applicable) on the secondary packaging.

E.5 Process definition

E.5.1 General

Process definition is undertaken to define the process parameters for a sterilization process, which will achieve the specified requirements for sterility for a defined product without adversely affecting product performance. Therefore process definition includes at least two bodies of work; one directed at assessing the impact (if any) of a range of candidate values for the process variables on the product and packaging and the other directed at defining the process parameters which will achieve the specified requirements for sterility for the product.

E.5.2 Influence on product and packaging

As sterilization does not typically improve product performance, a careful selection of values and tolerances for each process variable should be undertaken during process definition. In general, those variables which, when increased, significantly improve sterilization effectiveness without adversely affecting product performance should be maximized during this stage. Conversely, those variables which, when increased, adversely impact product performance without significantly improving sterilization effectiveness should be minimized during this stage. In addition, if there is a threshold value observed during these studies above which significant adverse effects on product or packaging are observed, it should be documented.