
**Sterilization of health care products —
Moist heat —**

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

Stérilisation des produits de santé — Chaleur humide —

*Partie 1: Exigences pour le développement, la validation et le contrôle
de routine d'un procédé de stérilisation des 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

Published in Switzerland

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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 17665-1 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This first edition of ISO 17665-1 cancels and replaces ISO 11134:1994 and ISO 13683:1997 both of which have been technically revised.

ISO 17665 consists of the following parts, under the general title *Sterilization of health care products — Moist heat*:

- *Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*
- *Part 2: Guidance on the application of ISO 17665-1*

Introduction

A sterile medical device is one which is free of viable microorganisms. International standards that specify requirements for validation and routine control of sterilization processes require, when it is necessary to supply a sterile medical device, that adventitious microbiological contamination of a medical device prior to sterilization be minimized. Even so, medical devices produced under standard manufacturing conditions in accordance with the requirements for quality management systems (see, for example, ISO 13485) may, prior to sterilization, have microorganisms on them, albeit in low numbers. Such 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 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 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 is defined in terms of the probability of there being a viable microorganism present on a product item.

ISO 17665 describes requirements that, if met, will provide a moist heat sterilization process intended to sterilize medical devices, which has appropriate microbicidal activity. Furthermore, compliance with the requirements ensures this activity 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 product after sterilization. Specification of this probability is a matter for regulatory authorities and may vary from country to country (see, for example, EN 556-1 and ANSI/AAMI ST67).

Generic requirements of the quality management 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 the product is sterile and, in this regard, suitable for its intended use. Attention is therefore 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 product;
- c) the control of the environment in which the product 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 product is packaged;
- g) the conditions under which product is stored.

The type of contamination on a product to be sterilized varies and this has an impact upon the effectiveness of a sterilization process. It is preferable that products 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) be regarded as special cases. 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 has to be given to the validation and control of the cleaning and disinfection processes used during reprocessing.

This part of ISO 17665 describes the requirements for ensuring that the activities associated with the process of moist heat sterilization are performed properly. These activities are described in documented work programmes designed to demonstrate that the moist heat sterilization process will consistently yield sterile products on treatment with process variables falling within the predetermined limits.

The requirements are the normative parts of this part of ISO 17665 with which compliance is claimed. The guidance given in the informative annexes is not normative and is not provided as a checklist for auditors. The guidance provides explanations and methods that are regarded as being suitable means for complying with the requirements. Methods other than those given in the guidance may be used, if they are effective in achieving compliance with the requirements of this part of ISO 17665.

The development, validation and routine control of a sterilization process comprise a number of discrete but interrelated activities, e.g. calibration, maintenance, product definition, process definition, installation qualification, operational qualification and performance qualification. While the activities required by this part of ISO 17665 have been grouped together and are presented in a particular order, this part of ISO 17665 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 may be iterative. It is possible that performing these different activities will involve a number of separate individuals and/or organizations, each of whom undertake one or more of these activities. This part of ISO 17665 does not specify the particular individuals or organizations to carry out the activities.

Sterilization of health care products — Moist heat —

Part 1:

Requirements for the development, validation and routine control of a sterilization process for medical devices

1 Scope

1.1 Inclusions

1.1.1 This part of ISO 17665 specifies requirements for the development, validation and routine control of a moist heat sterilization process for medical devices.

NOTE Although the scope of this part of ISO 17665 is limited to medical devices, it specifies requirements and provides guidance that may be applicable to other health care products.

1.1.2 Moist heat sterilization processes covered by this part of ISO 17665 include but are not limited to:

- a) saturated steam venting systems;
- b) saturated steam active air removal systems;
- c) air steam mixtures;
- d) water spray;
- e) water immersion.

NOTE See also Annex E.

1.2 Exclusions

1.2.1 This part of ISO 17665 does not specify requirements 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.

1.2.2 This part of ISO 17665 does not apply to those sterilization processes that are based on a combination of moist heat with other biocidal agents (e.g. formaldehyde) as the sterilizing agent.

1.2.3 This part of ISO 17665 does not detail a specified requirement for designating a medical device as “sterile.”

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

1.2.4 This part of ISO 17665 does not specify a quality management system for the control of all stages of production of medical devices.

NOTE It is not a requirement of this part of ISO 17665 to have a complete quality management system during manufacture, but the elements of a quality management system that are the minimum necessary to control the sterilization process are normatively referenced at appropriate places in the text (see, in particular, Clause 4). Attention is drawn to the standards for quality management systems (see ISO 13485) that control all stages of production of medical devices, including the sterilization process. Regional and national regulations for the provision of medical devices might require implementation of a complete quality management system and the assessment of that system by a third party.

1.2.5 This part of ISO 17665 does not specify requirements for occupational safety associated with the design and operation of moist heat sterilization facilities.

NOTE Requirements for operational safety are specified in IEC 61010-2-040. Additionally, safety regulations exist in some countries.

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

ISO 11138-3, *Sterilization of health care products — Biological indicators — Part 3: Biological indicators for moist heat sterilization processes*

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

ISO 11140-3, *Sterilization of health care products — Chemical indicators — Part 3: Class 2 indicator systems for use in the Bowie and Dick steam penetration test*

ISO 11140-4, *Sterilization of health care products — Chemical indicators — Part 4: Class 2 indicators as an alternative to Bowie and Dick test for detection of steam penetration*

ISO 11140-5, *Sterilization of health care products — Chemical indicators — Part 5: Class 2 indicators for Bowie and Dick air removal test sheets and packs*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 11607-2, *Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes*

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

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

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

ISO 17664, *Sterilization of medical devices — Information to be provided by the manufacturer for the processing of resterilizable medical devices*

3 Terms and definitions

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

3.1

air detector

device designed to detect the presence of non-condensable gases in a stream of steam and condensate or in the sterilizer chamber

3.2

automatic controller

〈sterilization〉 device that, in response to pre-determined operating cycle variables, operates the sterilizer sequentially through the required stages of the operating cycle(s)

3.3

bioburden

population of viable microorganisms on and/or in a product and/or sterile barrier system

[ISO/TS 11139:2006, definition 2.2]

3.4

biological indicator

test system containing viable microorganisms providing a defined resistance to a specified sterilization process

[ISO/TS 11139:2006, definition 2.3]

3.5

calibration

set of operations that establish, under specified conditions, the relationship between values of a quantity indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards

[VIM:1993, definition 6.11]

3.6

chemical indicator

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]

3.7

contained product

product for which the environment within the sterilizer during any stage of the sterilization process does not come into direct contact with the product

NOTE The environment within the sterilizer is used for heating and cooling purposes only, not for achieving the sterilization effect; e.g. a solution in a sealed bottle.

3.8

correction

action to eliminate a detected nonconformity

NOTE A correction can be made in conjunction with a corrective action.

[ISO 9000:2005, definition 3.6.6]

3.9

corrective action

action to eliminate the cause of a detected nonconformity or other undesirable situation

NOTE 1 There can be more than one cause for a nonconformity.

NOTE 2 Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence.

NOTE 3 There is a distinction between correction and corrective action.

[ISO 9000:2005, definition 3.6.5]

3.10

D value

D₁₀ value

time or dose required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions

[ISO/TS 11139:2006, definition 2.11]

NOTE For the purposes of this part of ISO 17665 *D*-value refers to the exposure necessary to achieve 90 % reduction.

3.11

development

act of elaborating a specification

[ISO/TS 11139:2006, definition 2.13]

3.12

environmental control

application of engineering and/or procedural systems to maintain conditions in defined areas within specified limits

NOTE Such systems can include air and fluid filters, surface disinfection, protective clothing and administrative procedures.

[ISO/TS 11139:2006, definition 2.16]

3.13

equilibration time

period which elapses between the attainment of the sterilization temperature at the reference measuring point and the attainment of the sterilization temperature at all points within the sterilization load

3.14

establish

determine by theoretical evaluation and confirm by experimentation

[ISO/TS 11139:2006, definition 2.17]

3.15

exposure time

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

[ISO/TS 11139:2006, definition 2.18]

3.16

fault

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

[ISO/TS 11139:2006, definition 2.19]

3.17 **F_0 value**

microbiological lethality of a sterilization process expressed in terms of the equivalent time, in minutes, at a temperature of 121,1 °C with reference to microorganisms with a z value of 10 °C

3.18**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]

3.19**holding time**

⟨sterilization⟩ period for which the temperatures at the reference measurement point and at all points within the sterilization load are continuously within the sterilization temperature band

3.20**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]

3.21**load configuration**

specified configuration within the sterilization chamber of the items of fixed chamber parts and the numbers, types, distribution and orientation of product presented for sterilization

3.22**maintenance**

⟨sterilization⟩ combination of all technical and associated administrative actions intended to retain an item at/or restore it to a state in which it can perform its required function

3.23**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 was developed by the Global Harmonization Task Force (GHTF 2002).

3.24

measuring chain

series of elements of a measuring instrument or measuring system, which constitutes the path of the measurement signal from the input (quantity subject to measurement) to the output (the result of the measurement)

3.25

microorganism

entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

NOTE A specific standard might not require demonstration of the effectiveness of the sterilization process in inactivating all types of microorganism identified in the definition above, for validation and/or routine control of the sterilization process.

[ISO/TS 11139:2006, definition 2.26]

3.26

moist heat

thermal energy in the presence of moisture provided as steam or liquid water for the purpose of achieving microbial lethality

3.27

non-condensable gas

air and/or other gas which will not liquefy under the conditions of a saturated steam processes

3.28

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]

3.29

operating cycle

complete set of stages of the process, carried out in a specified sequence

[IEC 61010-2-040:2005]

3.30

packaging system

combination of the sterile barrier system and protective packaging

[ISO/TS 11139:2006, definition, 2.28]

3.31

performance qualification

PQ

process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification

[ISO/TS 11139:2006, definition 2.30]

3.32**preventive action**

action to eliminate the cause of a potential nonconformity or other undesirable potential situation

NOTE 1 There can be more than one cause for a potential nonconformity.

NOTE 2 Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence.

[ISO 9000:2005, definition 3.6.4]

3.33**plateau period**

equilibration time plus the holding time

3.34**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]

3.35**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]

3.36**process variable**

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

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

[ISO/TS 11139:2006, definition 2.35]

3.37**product**

result of a process

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

[ISO/TS 11139:2006, definition 2.36]

3.38**product family**

⟨sterilization⟩ groups or subgroups of product characterized by similar attributes such as mass, material, construction, shapes, lumens, packaging system and which present a similar challenge to the sterilization process

3.39**reference challenge device**

device having a known thermal relationship to the contained product or sterilization load

3.40**reference load**

specified sterilization load(s) created to represent difficult combinations of items to be sterilized

3.41

reference measuring point

point where the temperature sensor used for the operating cycle control is located

3.42

reference microorganism

microbial strain obtained from a recognized culture collection

[ISO/TS 11139:2006, definition 2.39]

3.43

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]

3.44

saturated steam

water vapour in a state of equilibrium between condensation and evaporation

3.45

services

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

EXAMPLE Electricity, water, compressed air, drainage.

[ISO/TS 11139:2006, definition 2.41]

3.46

specification

document stating requirements

[ISO 9000:2005, definition 3.7.3]

3.47

specify

stipulate in detail within an approved document

[ISO/TS 11139:2006, definition 2.42]

3.48

sterile

free from viable microorganisms

[ISO/TS 11139:2006, definition 2.43]

3.49

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** (3.51)].

[ISO/TS 11139:2006, definition 2.45]

3.50**sterility assurance level****SAL**

probability of a single viable microorganism occurring on an item after sterilization

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

[ISO/TS 11139:2006, definition 2.46]

3.51**sterilization**

validated process used to render product free from viable microorganisms

NOTE In a sterilization process, the nature of microbial inactivation is exponential and thus, the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero [see **sterility assurance level** (3.50)].

[ISO/TS 11139:2006, definition 2.47]

3.52**sterilization load**

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

[ISO/TS 11139:2006, definition 2.48]

3.53**sterilization process**

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

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

[ISO/TS 11139:2006, definition 2.49]

3.54**sterilization temperature**

minimum temperature of the sterilization temperature band

3.55**sterilization temperature band**

range of temperatures, expressed as the sterilization temperature and the maximum permissible temperature which may prevail throughout the sterilization load during the holding time

3.56**sterilizer chamber**

part of the sterilizer which receives the sterilization load

3.57**sterilizing agent**

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

[ISO/TS 11139:2006, definition 2.50]

3.58**thermal energy**

energy in the form of heat

3.59

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]

3.60

validation

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

[ISO/TS 11139:2006, definition 2.55]

3.61

***z* value**

temperature change required to effect a ten fold change in *D* value

4 Quality management system elements

4.1 Documentation

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

4.1.2 Documents and records required by this part of ISO 17665 shall be reviewed and approved by designated personnel (see 4.2.1). Documents and records shall be controlled in accordance with the applicable clauses of ISO 13485.

4.2 Management responsibility

4.2.1 The responsibility and authority for implementing and meeting the requirements described in this part of ISO 17665 shall be specified. Responsibility shall be assigned to competent personnel in accordance with the applicable clauses of ISO 13485.

4.2.2 If the requirements of this part of ISO 17665 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) ISO 13485 or ISO 10012 shall be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this part of ISO 17665.

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 Sterilizing agent

5.1.1 For the purposes of this part of ISO 17665 the sterilizing agent shall be moist heat.

5.1.2 Contaminants contained within the sterilizing agent shall not impair the safety of the product for its intended use.

5.2 Microbicidal effectiveness

If moist heat is used outside of the range of conditions that are widely recognised, then the microbicidal effectiveness shall be established and documented.

NOTE The microbicidal effectiveness of moist heat and its use in sterilization processes has been comprehensively documented and is available in the published literature.

5.3 Materials effects

The effect of the sterilizing agent on materials shall be assessed in accordance with the requirements of Clauses 6 and 7.

5.4 Environmental consideration

Moist heat is not normally considered as having a significant environmental effect; however, the potential impact on the environment of the operation of the sterilization process shall be assessed and any measures necessary to protect the environment shall be identified. This assessment, including potential impact (if any) and measures for control (if identified), shall be documented.

6 Process and equipment characterization

6.1 Process

6.1.1 General

All sterilization processes shall be specified. The specification shall include:

- a) a description of the operating cycle;
- b) the process parameters and their tolerances;
- c) the product family(ies) that can be sterilized;
- d) requirements for the conditioning of product prior to sterilization, if such conditioning is necessary to ensure the efficacy of the sterilization process;
- e) the location of the reference measuring point;
- f) the minimum and maximum pressure that can occur in an empty sterilizer chamber (including fixed chamber parts);
- g) the rate of change of falling and rising pressure and tolerances for each stage of the process;
- h) the maximum quantity of each contaminant that could be present in any liquid, air, gas or steam admitted to the sterilizer chamber if the contaminant could adversely affect the product;

- i) the process variables that are measured and used to verify that the sterilization process will be delivered;
- j) the load configuration;
- k) any restrictions on the size and/or mass of the sterilization load;
- l) periodic test(s) and acceptance criteria (where applicable) to be used to verify that the sterilization process remains reproducible;
- m) the location and defined acceptance criteria for biological indicators (8.5 or 8.6), if used;
- n) the location and defined acceptance criteria for chemical indicators (8.8), if used;
- o) the minimum cycle lethality achieved throughout the sterilization load, and the means by which such lethality was determined for the sterilization load for which the sterilization process was designated, if microbiological methods were used to establish the effectiveness of the sterilization process;
- p) the post operating cycle treatment if such treatment is included in the sterilization process.

6.1.2 Saturated steam processes

In addition to the requirements in 6.1.1, the specification for a saturated steam sterilization process in which the steam admitted to the sterilizer is the sterilizing agent, shall include:

- a) the holding time and the minimum and maximum temperatures (and their locations) measured during this time in an empty sterilizer chamber (including fixed chamber parts);
- b) during the holding time, the maximum difference between the temperature measured at the reference measuring point and the theoretical steam temperature determined from steam table values for the measured sterilizer chamber pressures;
- c) where the product family(ies) identified in 6.1.1 c) consist of materials known to restrict the penetration of steam by virtue of their design or load configuration or, unless otherwise justified, a description of the steam penetration test used to verify that the level of non-condensable gases carried into the sterilizer chamber in the steam supply, by air leakage into the chamber during periods of vacuum or remaining as a result of an inadequate air removal stage of the operating cycle, does not prevent the presence of saturated steam on the surfaces to be sterilized;
- d) if water can cause an adverse effect on the integrity of the sterilized product and its packaging system, the maximum amount of water that could be suspended in saturated steam entering the sterilizer chamber;
- e) the reference load(s) to be used to confirm or judge the effectiveness of the sterilization process for a sterilization load identified in 6.1.1 c), 6.1.1 j) and 6.1.1 k);
- f) a description of the monitoring device, its location, and how to interpret results if one is used to check delivery of the specified sterilization process;
- g) dryness of the reference load determined by mass change or perceptible moisture.

6.1.3 Contained product processes

In addition to the requirements in 6.1.1, the sterilization process specification shall include the following information for a sterilization load comprising a product(s) that is assigned to the product family(ies) identified in 6.1.1 c) and for a load configuration known to be the one that is most difficult to sterilize:

- a) details of the product(s) and its container(s) or, if applicable, reference product(s);
- b) the size of the sterilization load and its location, orientation and support system within the sterilizer chamber;

- c) the temperature profiles and the locations from which they were determined for the period of the operating cycle for which lethality is claimed, measured in both an empty sterilizer chamber and in the free space surrounding the sterilization load;
- d) for the period of the operating cycle for which lethality is claimed, the maximum and minimum temperature and rates of change;
- e) the method for establishing the location where the maximum and minimum temperature can be measured.

6.2 Equipment

6.2.1 Equipment used to deliver the sterilization process shall be specified. The specification shall include:

- a) the equipment, together with any necessary ancillary items;
- b) the materials of construction of any part of the equipment and ancillary items that are used to contain and transport steam or any other gas or liquid into the sterilizer chamber (see 6.1.1 h);
- c) for each measuring chain used to control, indicate, monitor and provide an electronic or permanent record of the sterilization process:
 - 1) a description of the measuring chain;
 - 2) the characteristics and location of the sensor;
 - 3) method of verification of calibration of the measuring chain traceable to a national calibration standard.
- d) the maximum rate of change of pressure;
- e) the fault(s) recognised by the sterilizing equipment, together with any visual, audio or recorded warnings;
- f) the safety features, including those for the control of personnel or for environmental protection;
- g) a statement of conformity to local, regional, or national regulations for emissions into the environment from the equipment;
- h) if vacuum is used during the operating cycle, a description and acceptance criteria for the test to be used to determine the level of air leakage into the sterilizer chamber;
- i) if fitted, a description of the device, (e.g. air detector) including its settings used to detect non-condensable gas (including air) that could be present in steam supplied to the sterilizer chamber or remain in the sterilizer chamber after the air removal stage of the sterilization process.

6.2.2 The operating procedures for the equipment and ancillary items shall be specified. The specification shall include:

- a) the operating cycle(s) programmed into the automatic controller, and the means by which changes to the programmes can be made;
- b) step-by-step operating instructions;
- c) the method by which failure to attain a process parameter can be identified and the actions to be taken in such a case;
- d) calibration and maintenance instructions;
- e) the means by which an error in the results of a measurement for control, indication or recording can be identified;
- f) the contact for technical support.

6.2.3 The location in which the equipment is to be installed shall be specified. The specification shall include:

- a) the location, space and the environment in which the equipment is to be installed;
- b) installation instructions;
- c) details of each service necessary for the correct function of the equipment, including (if applicable);
 - 1) means of isolation;
 - 2) minimum and maximum pressure;
 - 3) maximum temperature;
 - 4) minimum flow;
 - 5) filtration;
 - 6) minimum and maximum voltage and maximum volt amperes;
 - 7) maximum level of non-condensable gas and liquid water in saturated steam;
 - 8) maximum quantity of each contaminant;
- d) the load bearing structures that are to support the principal heavy components of the equipment;
- e) the materials of construction for the parts that transport steam, gas, air and water into the space into which the sterilizer is to be installed;
- f) documentation of conformity to local, regional, or national regulations regarding emissions into the environment from the equipment.

6.2.4 The sterilization load support system in the sterilizer chamber shall not inhibit the uniform attainment of the sterilizing conditions or cause damage to the product and/or its packaging.

6.2.5 Means shall be provided to ensure that failure to attain specified process parameters does not lead to an ineffective sterilization process appearing to be effective.

6.2.6 The equipment manufacturer shall establish documented procedures for the validation of the application of software and changes to such software and/or its application for production that could affect conformity of the equipment to its specification.

7 Product definition

7.1 Product to be sterilized shall be specified.

7.2 Product packaging systems (if used) shall be specified and shall conform to ISO 11607-1 and ISO 11607-2.

7.3 The product family assigned to the product and its packaging system shall be specified.

7.4 The criteria for assigning the product family shall be specified.

7.5 If a process challenge device (PCD) is identified as a challenge that can be used to represent the product and its packaging system, it shall be defined.

7.6 The limiting value(s) shall be specified for each process variable to which the product and its packaging system (if used) can be exposed. Limiting values shall be identified for all materials and combination of materials used. The worst case effects of exposure or repeated exposure (when applicable) to the sterilizing agent under any combination of process parameters on the physical and chemical characteristics and biocompatibility of the product shall be identified.

Examples of some process variables include:

- temperature;
- dwell time at the limit values;
- pressure;
- rate of change of pressure;
- rate of change of temperature.

NOTE Limiting values for these process parameters are specified, because exceeding the specified values could have an adverse effect on the performance of the product and/or its packaging.

7.7 If the level of moisture present in the product and/or its packaging system prior to sterilization could affect the efficiency of the sterilization process, the limiting value(s) shall be specified.

7.8 The stability and potency of a contained product shall not be adversely affected when exposed to the proposed sterilization temperature and exposure time(s).

7.9 If the integrity of the product can be affected by a contaminant(s) remaining on the product after sterilization, the contaminant and the maximum acceptable limit shall be specified.

7.10 A system shall be specified to ensure that the condition of the product and/or its packaging system presented for sterilization will not compromise the effectiveness of the sterilization process. This system shall include at least the following elements:

- a) effective cleaning and disinfection (if reprocessing is intended) including re-usable packaging systems, when used (e.g. rigid sterilization containers);
- b) integrity of the packaging system before and after exposure to the sterilization process;
- c) environmental control in areas that could have an impact on the product bioburden;
- d) when process parameters are determined using a bioburden-based method, an estimation of the bioburden in accordance with ISO 11737-1.

8 Process definition

8.1 The sterilization process, including process parameters and their limits, shall be defined. During the establishment of this process, physical process parameters shall be measured and used, as appropriate, to confirm reproducibility.

8.2 The minimum level of sterility assurance, SAL, to be achieved by the sterilization process on and/or within a product shall be specified.

8.3 The sterilization process shall not expose the product and its packaging system (if used) to process parameters exceeding the levels identified in 7.6 and also to the contaminant(s) identified in 7.9.

8.4 If a product is to be sterilized by saturated steam, the level of residual air and non-condensable gas at the commencement of the holding time shall not prevent the contact of saturated steam on all surfaces of the product, including the surfaces in cavities, lumens and tubing.

8.5 If biological indicator systems are used as part of the establishment of the sterilization process according to the method described in 8.11 a) they shall comply with ISO 11138-1 and ISO 11138-3. The microorganism, population, resistance and method of presentation shall be identified and shall take into account the nature of the sterilization process to be used and the expected or established bioburden.

The method of presentation may include inoculated product or the placement of inoculated carrier(s) within the product.

8.6 If biological indicator systems are used as part of the establishment of a saturated steam sterilization process according to the method described in 8.11 b), c) and/or d), these shall comply with ISO 11138-1 and ISO 11138-3.

8.7 For contained product, the effect of the product and its packaging system on the lethality of the test microorganism when exposed to the proposed sterilization process shall be known.

8.8 If chemical indicators are used as part of the establishment of the sterilization process, they shall comply with the applicable parts of the ISO 11140 series and shall not adversely affect the medical device by reaction, contamination and/or transfer before, during or after the defined sterilization process.

8.9 If a PCD is to be used to assess the efficiency of the specified sterilization process for processing the product identified in Clause 7, the validity of the PCD, test methodology(ies) and acceptance criteria shall be established and documented.

8.10 The sterilization process shall be established from at least one of the following:

- data supplied by the medical device manufacturer, and/or packaging material manufacturer and/or the sterilizer manufacturer (see ISO 17664);
- similarity with a product that is already assigned to a product family;
- development of an operating cycle that will deliver the specified SAL.

8.11 The SAL attained on and/or within the product during the sterilization process shall

- a) be established by knowledge of the bioburden (see Annexes B and C) or
- b) be determined by an 'overkill' method (see Annex D) or
- c) be defined by demonstrating that during the holding time all parts of the product are exposed to process parameters selected from an official national or regional pharmacopoeia or
- d) be deemed to be equal to or to exceed the requirements specified in c), provided that the product is assigned to a product family for which a sterilization process is specified and that the equilibration time does not exceed the maximum for products assigned to the same product family.

8.12 For a sterilization process established by microbiological methods, the following apply.

- bioburden determination shall be performed in accordance with ISO 11737-1;
- tests of sterility shall be performed in accordance with ISO 11737-2;
- product used in establishing the process shall be representative of that to be produced routinely;
- equipment used shall be capable of reproducibly delivering a combination of process parameters with less lethality than the sterilization process, such that the level of inactivation of microorganisms results in a population that allows interpolation with regard to the total result.

8.13 If, after exposure to the sterilization process, treatment of the product and its packaging is required in order to maintain sterility, this treatment shall be specified.

9 Validation

9.1 General

9.1.1 Each stage of validation shall be carried out in accordance with a documented procedure.

9.1.2 It shall be verified that each item of fixed and portable equipment used during validation complies with its specification.

9.1.3 Any modifications to product, equipment, or sterilization process carried out during validation shall be recorded and justified, and the specification(s) changed accordingly (see also 12).

9.1.4 The measuring chain for each test instrument used for validation shall have:

- calibration traceable to a national standard;
- a valid maintenance certificate (if appropriate);
- a calibration status verified according to the technical and applicable management requirements;
- verification of calibration carried out at a value(s) used to control the sterilization process and judge the results of the test in which the measuring chain is used.

9.1.5 The correlation between readings indicated and recorded by instruments fitted to the sterilizer and readings registered by independent test instruments having sensors in similar locations shall be verified.

9.1.6 It shall be verified during installation qualification (IQ), operational qualification (OQ) or performance qualification (PQ), as applicable, that fault recognition systems function and comply with their performance specifications.

9.1.7 If an existing sterilizer and sterilization process is to be used to process a new product, the IQ and OQ stages of validation may be omitted, provided that changes are not made to the equipment or to existing sterilizer load(s) that could affect delivery of the existing sterilization process.

9.1.8 The validity of the proposed periodic test(s) shall be verified [see 6.1.1 I) and 10.3].

9.2 Installation qualification (IQ)

9.2.1 Equipment

It shall be verified that the equipment and documentation comply with 6.2.1, 6.2.2 and 6.2.3 and that services comply with 6.2.3.

9.2.2 Installation

It shall be verified that the installation complies with 6.2.3.

9.2.3 Function

It shall be verified that the equipment and operational safety systems detailed in 6.2.1 function in accordance with their specifications, the operating cycle(s) is in accordance with 6.1.1 a), and that there is no evidence of leakage from the services or the equipment.

9.3 Operational qualification (OQ)

9.3.1 Operational qualification shall demonstrate that installed equipment will deliver the sterilization process defined in 8, and shall establish data for each requirement (if applicable) listed in 6.1.

9.3.2 The rationale for the number and locations of the temperature sensors used to demonstrate that requirements are met for temperature distribution in an empty sterilizer chamber (including fixed chamber parts), and also with a test load (if used), shall be documented.

9.4 Performance qualification (PQ)

9.4.1 Performance qualification shall demonstrate that product has been exposed to the specified sterilization process by the equipment to be used for routine sterilization.

9.4.2 Rationale shall be documented for the number and locations of temperature sensors used to demonstrate that requirements are met in the sterilization load.

9.4.3 Checks shall include and verify that:

- a) documentation confirms successful IQ and OQ;
- b) the test sterilization load comprises product that will be routinely processed and that is assigned to a product family(ies) compatible with the one(s) assigned to the sterilization process or that represents the product families presenting the greatest challenge to the sterilization process;
- c) the packaging system is identical to that intended for routine production or reprocessing;
- d) pre-conditioning is compliant with 6.1.1 d);
- e) the load configuration complies with 6.1.1 j) and is known to be the most difficult to sterilize;
- f) the size and/or mass of the sterilization load comply with 6.1.1 k).

9.4.4 For each of the following, studies shall establish;

- a) conformity to the sterilization process identified in Clause 8 and the limiting process values identified in 7.6;
- b) data as required in 6.1.3, if applicable;
- c) the exposure profile(s) on and throughout product located in the position(s) identified in 6.1.1 e), 6.1.1 m) and 6.1.1 n);
- d) the holding time and the minimum and maximum temperatures and their locations, measured during this time in the sterilization load for processes identified in 6.1.2;
- e) the temperature profiles during the plateau period of the sterilization processes identified in 6.1.2 a):
 - measured at the reference measuring point;
 - measured on or within the sterilization load;
 - determined from the sterilizer chamber pressure;

NOTE Attention is drawn to national or regional requirements when defining the maximum permissible difference between measured and calculated temperatures. See, for example, EN 285.

- f) the response of chemical indicators, when used (see 8.8);

- g) the response of the PCD, when used;
- h) the integrity of the packaging system when used.

9.4.5 If, in addition to the measurement of physical parameters, the sterilization process is to be based on bioburden, or verified by microbiological methods, biological indicators (see 8.5 or 8.6) shall be positioned in and/or on the product in locations identified in 9.4.4, and then exposed to one of the following:

- a treatment that is reduced relative to that in the sterilization process; the outcome of this treatment is extrapolated to demonstrate that, on application of the sterilization process, the specified requirements for minimum microbicidal effectiveness are met;
- the full extent of the treatment at the lower tolerances of the sterilization process parameters, the outcome of this treatment is used to confirm a prediction that, on the application of the sterilization process, the specified requirements for minimum microbicidal effectiveness are met; or
- an “overkill” process.

NOTE See Annexes B, C and D.

9.4.6 PQ shall include a series of at least three consecutive exposures of the sterilization load to the sterilization process, which demonstrate compliance with the sterilization process specification and the reproducibility of the sterilization process.

9.4.7 Non-compliance with the sterilization process specification during PQ shall be reviewed and corrected.

If a failure can be attributed to factors not relevant to the effectiveness of the sterilization process being validated (see example below), the test may be documented as unrelated to the performance of the sterilization process without requiring three further consecutive exposures.

EXAMPLE Power failure, loss of services and failure of external monitoring equipment.

9.5 Review and approval of validation

9.5.1 Information gathered or produced during IQ, OQ and PQ shall be reviewed for conformity to the acceptance criteria specified for each stage of the validation process. The outcome of this review shall be documented and approved (see 4.1.2).

9.5.2 A sterilization process specification, including the process parameters and their tolerances, shall be confirmed. This specification shall include the criteria for designating the sterilization process used for a particular sterilizer load as conforming, and shall document at least the following:

- a) the product family(ies) that can be processed;
- b) the load configuration(s);
- c) the size of the sterilization load and/or its mass;
- d) the procedures for any pre-conditioning of product;
- e) a description of the packaging system and methods;
- f) the distribution of medical devices within a package containing multiple medical devices, if applicable;
- g) the periodic tests (see 10.3);
- h) the process challenge device and the product family(ies) for which it is relevant;
- i) the bioburden, if applicable.

10 Routine monitoring and control

10.1 Routine monitoring and control shall be performed on each operating cycle.

10.2 Evidence of successful maintenance and requalification (if applicable) shall be verified.

10.3 The operational status of the equipment (if applicable) shall be verified by evidence from periodic tests of factors such as (but not limited to) the following:

- a) air leakage into the sterilizer chamber;
- b) quality of saturated steam or heat transfer media admitted to the sterilizer chamber (which may include checks for non-condensable gas, conductivity of feed water, contaminant(s), moisture content);
- c) automatic control (e.g., a test to verify that the operating cycle continues to function correctly);
- d) steam penetration;
- e) sterilization process (e.g., a test to verify that the sterilization process remains reproducible).

10.4 Delivery of the sterilization process shall be verified from the results of chemical indicators (see 8.8) or biological indicator systems (see 8.5 or 8.6), if used, and by confirming that within specified tolerances, recorded data from routine monitoring match data from validation.

10.5 For saturated steam processes, the data shall include (if applicable):

- a) sterilization temperature, chamber pressure and theoretical steam temperature during the plateau period;
- b) duration of the plateau period;
- c) the chamber temperature and the chamber pressure for at least each stage of the operating cycle;
- d) the results obtained from a process challenge device;
- e) temperatures and/or pressures in a process monitoring system, if used as part of process control.

10.6 For contained product processes, the data shall include (if applicable):

- a) the temperature(s) measured in the reference challenge device, if used as part of process control;
- b) the chamber temperature and the chamber pressure profiles for heating, exposure and cooling;
- c) the temperature profiles for heating, exposure and cooling in product located in positions identified in 9.4.4 c), if used as part of process control;
- d) the plateau period or holding time;
- e) the value(s) for the process parameter(s) for homogeneity of the heating media in the sterilizer chamber;
- f) results of inspection of the sterilization load to confirm dryness and integrity of the packaging system.

10.7 All records shall be retained in accordance with 4.1.2.

11 Product release from sterilization

11.1 Procedures for the review of records and product release from the sterilization process shall be specified. The procedure(s) shall define the requirements (see 9.5.2 and 10.3 as appropriate) for designating a sterilization process as conforming. If a requirement is not met, product shall be designated as non-conforming and handled in accordance with 4.4.

11.2 A system shall be specified to ensure that processed and non-processed items are clearly differentiated.

12 Maintaining process effectiveness

12.1 Demonstration of continued effectiveness

12.1.1 Product presented for sterilization shall comply with

- a) the product definition in Clause 7;
- b) the load configuration as defined in 6.1.1 j);
- c) the size and mass criteria defined in 6.1.1 k).

12.1.2 Successful completion of periodic tests, calibrations, maintenance tasks and requalification carried out at specified intervals shall be verified.

12.1.3 The quality of the environment in which the product is prepared and/or packaged shall be periodically verified.

12.1.4 Requirements for the health, cleanliness and clothing of personnel in the manufacturing and/or packaging area shall be specified and enforced.

12.1.5 If the sterilization process makes use of a vacuum, an air leakage test shall be carried out at specified intervals.

12.1.6 If the sterilization process relies on the removal of air from the sterilizer chamber in order to achieve rapid and even penetration of steam into the sterilizer load, a steam penetration test shall be carried out each day before the sterilizer is used.

The steam penetration test is carried out using a device having a defined challenge to air removal and steam penetration for the process. For industrial applications, if the saturated steam process uses consistent, defined sterilization loads known not to inhibit the penetration of steam, alternative methods may be used based on specified physical measurements and a risk assessment of the likelihood of process failure.

12.1.7 Product shall conform to bioburden requirements, if applicable.

12.2 Recalibration

The accuracy and reliability of each measuring chain used to control, indicate, or record the sterilization process shall be verified periodically in accordance with 4.3.3.

12.3 Maintenance of equipment

12.3.1 Preventative maintenance shall be planned and performed in accordance with documented procedures.

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

12.3.3 The maintenance plan, maintenance procedures and maintenance records shall be retained (see 4.1.2) and reviewed at specified intervals by a designated person. The results of the review shall be documented.

12.4 Requalification

12.4.1 Requalification of a sterilization process shall be carried out for defined product and specified equipment, at defined intervals and after the assessment of any change (see 12.5). The extent to which requalification is carried out shall be justified.

12.4.2 Requalification procedures shall be specified and records of requalification 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 action taken.

12.5 Assessment of change

Any change shall be assessed for its impact on the effectiveness of the sterilization process. Changes to be considered (if applicable) shall include:

- a) replacement of a part which could cause a process parameter to change;
- b) replacement of a part which could cause an increase in leakage into the sterilizer chamber;
- c) variation of homogeneity in the sterilizer chamber;
- d) new or modified software and/or hardware;
- e) any change to a process parameter;
- f) any change to services and the outcome of maintenance on a service;
- g) any change of packaging and/or packaging procedure;
- h) any change of load configuration;
- i) any change of product materials, source of materials or design.

The outcome of this assessment, including the rationale for the decisions reached and the extent of changes made to the sterilization process, product or requalification requirements (if applicable), shall be documented.

Annex A **(informative)**

Guidance

NOTE 1 The guidance given in this annex is not intended as a checklist for assessing compliance with this part of ISO 17665. This guidance is intended to assist in obtaining a uniform understanding and implementation of this part of ISO 17665 by providing explanations and acceptable methods for achieving compliance with specified requirements. Methods other than those given in the guidance may be used. However, the use of alternative methods has to be demonstrated to be effective in achieving compliance with this part of ISO 17665.

NOTE 2 For ease of reference the numbering in this annex corresponds to that in the normative part of this part of ISO 17665.

A.1 Scope

A.1.1 Inclusions

No guidance offered.

A.1.2 Exclusions

A.1.2.1 No guidance offered.

A.1.2.2 No guidance offered.

A.1.2.3 No guidance offered.

A.1.2.4 The effective implementation of defined and documented procedures is necessary for the development, validation and routine control of a sterilization process for medical devices. Such procedures are commonly considered to be elements of a quality management system. This part of ISO 17665 identifies and specifies those elements of a quality management system that are essential for the effective control of sterilization by normative reference to the quality management system standard for medical devices, ISO 13485. This part of ISO 17665 does not require that a complete quality management system complying with ISO 13485 be implemented, nor does it require that those quality management system elements that are specified be subject to third party assessment. Attention is drawn to the existence of national and regional regulatory requirements for quality management systems in the manufacture of medical devices and for third party assessment of such systems.

A.1.2.5 No guidance offered.

A.2 Normative references

The requirements of documents included as normative references are requirements of this part of ISO 17665 only to the extent that they are cited in a normative part; the citation may be to an entire standard or limited to specific clauses.

A.3 Terms and definitions

No guidance offered.

A.4 Quality management system elements

NOTE See also A.1.2.4.

A.4.1 Documentation

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

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

A.4.2 Management responsibility

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

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

The development, validation and routine control of a sterilization process can involve a number of separate parties, each of whom is responsible for certain elements. This part of ISO 17665 requires that the party accepting particular responsibilities be defined and that this definition of responsibilities be documented. This definition of authority and responsibility is documented within the quality management system(s) of the identified parties. The party accepting responsibilities for defined elements is required to assign these elements to competent personnel, with competence demonstrated through appropriate training and qualification.

A.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.

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

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

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

A.4.4 Measurement, analysis and improvement — Control of nonconforming product

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

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

A.5 Sterilizing agent characterization

The purpose of this activity is to characterize the sterilizing agent, demonstrate its 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 should be relatable to the experimental studies undertaken using any such test or prototype system.

A.6 Process and equipment characterization

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

A sterilization process is established for a specified product family(ies) and loading configuration(s). This specification should include the process parameters that define the exposure profile throughout the operating cycle and the process parameters used to verify reproducibility. The portion of the exposure over which lethality is established should be identified, and the upper and lower limits of each process parameter that can affect both this lethality and the performance of the product are defined. The specification for the sterilization process and the equipment that delivers the process should contain sufficient detail for them to be considered in the section discussing process definition (see Clause 8) as an option when a new product or loading configuration is proposed.

A.7 Product definition

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

The combination of materials used to construct and package the product should withstand the process parameters that are typical in moist heat processes. Any restrictions resulting from the design of the product and the materials used should be defined.

A.8 Process definition

The purpose of this activity is to define a detailed specification for the sterilization process to be applied to defined product without compromising the safety, quality and performance of that product.

The sterilization process may be identified from equipment that has been validated and known to process product assigned to the same product family. It may be identified by the product manufacturer or developed for the product family assigned to the product. In all cases the limits on process parameters and restrictions on exposure identified in product definition should be observed.

Examples of operating cycles are illustrated in Annex E.

A.9 Validation

The purpose of validation is to establish that the sterilization process developed in process definition 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. Conformity to the equipment, services and installation specifications is established during installation qualification. Delivery of the prescribed sterilization process is established during operational qualification and the attainment of the required SAL in and/or on product is established during performance qualification.

A.10 Routine monitoring and control

The purpose of routine monitoring and control is to ensure that the validated sterilizing process has been delivered to the product. This is evidenced from data obtained during the sterilization process and from periodic tests used to verify that the specified sterilization process can be delivered.

A.11 Product release from sterilization

The purpose of product release from sterilization is to confirm that the product has been successfully exposed to the specified sterilization process and can be released for use.

A.12 Maintaining process effectiveness

The purpose of this activity is to identify and implement the periodic checks and tests necessary to predict the specified sterilization process should continue to be delivered to product during routine processing.

Any change that raises doubt about the lethality that will be delivered to the sterilization load should initiate a review. The responsible party for each element of validation and routine monitoring is indicated in Table A.1.

Table A.1 — Elements of sterilizing agent characterization and sterilization process development, validation and routine control

Elements	Purpose	Components	Responsible party
Quality system	To provide a structure to control all stages of the sterilization process	Management responsibility, design control, product realization, measurement, analysis and improvement	All parties with respect to the elements undertaken
Sterilizing agent characterization	To define the sterilizing agent and its microbicidal effectiveness	Sterilizing agent definition, microbicidal effectiveness, material effects	Developer of the sterilization process
Sterilization process/equipment characterization	To define the overall sterilization process and the equipment necessary to carry it out	Sterilization process description, equipment specification, ancillary equipment, and service definition, safety and environment	Sterilizer manufacturer, in collaboration with the developer of the sterilization process, if appropriate
Product definition	To define the product to be sterilized	Product specification, packaging materials, product quality prior to sterilization	Manufacturer of product to be sterilized (and sterilizer manufacturer, depending on claims made for sterilizing equipment)
Sterilization process definition	To define the sterilization process in order to achieve sterility for identified product whilst maintaining safety and performance of the product	Development, biological safety, process residuals, product compatibility, limits on re-sterilization	Manufacturer of product to be sterilized, in collaboration with the sterilizer manufacturer and, if appropriate, the health care facility
Validation	To demonstrate that the defined sterilization process can be delivered effectively and reproducibly to the sterilization load	Installation Qualification, Operational Qualification, Performance Qualification, review, and approval of validation	Organization with responsibility for sterilizing the product (either product manufacturer or reprocessing facility), in collaboration with the sterilizer manufacturer, if appropriate; product manufacturer or reprocessing facility, in collaboration with the organization sterilizing the product, if appropriate
Routine monitoring and control	To demonstrate that the validated sterilization process has been delivered within defined tolerances to all products within a sterilization load	Sterilization load, configuration, sterilization process monitoring, record generation, periodic testing, record retention	Product manufacturer or reprocessing facility
Product release from sterilization	To review records of routine control procedures and determine the disposition of a particular sterilization load	Record review, indicator testing (if any), product disposition, corrective action (if any)	Product manufacturer or reprocessing facility
Maintaining sterilization process effectiveness	To ensure the continued acceptability of the validated sterilization process		Sterilizer manufacturer, product manufacturer or reprocessing facility, together with organization sterilizing the product, if appropriate

Annex B

(informative)

Process definition based on inactivation of the microbial population in its natural state (bioburden-based method)

B.1 General

Guidance and discussion on this method are given in the literature such as Halverson and Zeigler 1932^[37], Pflug and Holcomb 1983^[44], PDA 1978^[42] and Pflug 1999^[43].

The method requires extensive knowledge of the naturally occurring bioburden. Bioburden of representative production should be determined in accordance with ISO 11737-1. It may be necessary to screen isolates for heat resistance.

B.2 Sampling

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

B.3 Procedure

B.3.1 Product should be exposed to the sterilizing agent in predetermined increment(s) of the anticipated sterilization process.

B.3.2 The required accuracy and precision of increments should be established, and the delivery of the sterilizing agent should be controlled and monitored to meet defined limits.

B.3.3 Following exposure to the sterilizing agent, the product should be subjected individually to tests of sterility (see ISO 11737-2).

B.3.4 Knowledge of the relationship between the proportion of product exhibiting no growth in tests of sterility and the extent of exposure to the sterilizing agent should be used to define the sterilization process.

B.3.5 The level of treatment identified should be carried out in triplicate to demonstrate reproducibility.

B.4 Follow up

The continued appropriateness of the sterilization process should be confirmed at defined intervals using product representative of routine production.

The method requires on-going monitoring of and control over the bioburden.

Annex C (informative)

Process definition based on the inactivation of a reference microorganism and a knowledge of bioburden on product items to be sterilized (combined bioburden/biological indicator based method)

C.1 General

Guidance and discussion on this method can be found in ISO 14161^[10] and also in the literature such as Halverson and Zeigler 1932^[37], Pflug and Holcomb 1983^[44], PDS 1978^[42] and Pflug 1999^[43].

C.2 Procedure

C.2.1 The location within the product at which sterility is most difficult to achieve should be established.

C.2.2 A challenge to the sterilization process comprising a known number of microorganisms with known resistance to the sterilizing agent should be created by either:

- a) placing biological indicators within the product at position(s) or representative of positions where sterilizing conditions are most difficult to achieve, or
- b) inoculating the product with reference microorganisms at position(s) within the product where sterilizing conditions are most difficult to achieve.

NOTE An inoculated product can be considered to be a biological indicator. (See 8.5 and ISO 11138-1.)

C.2.3 The challenge should be packaged the same as routinely produced product and should be included within the sterilization load in the location where it is most difficult to achieve sterilizing conditions.

C.2.4 The sterilization load should be exposed to the sterilizing agent under conditions selected to deliver less lethality than is delivered during routine sterilization, so that not all reference microorganisms will be inactivated.

C.2.5 The level of treatment identified should be carried out in triplicate in order to demonstrate reproducibility.

C.2.6 The number of microorganisms surviving should either be determined by direct enumeration or estimated by the most probable number technique.

C.2.7 The rate of inactivation of the reference microorganisms should be calculated.

C.2.8 From a knowledge of the bioburden (established in accordance with 8.11 a) and the rate of inactivation of the reference microorganisms, the extent of treatment required to achieve the specified requirements for sterility should be determined.

Annex D (informative)

Conservative process definition based on inactivation of reference microorganisms (overkill method)

D.1 General

D.1.1 This annex describes the process of overkill based on the inactivation of reference microorganisms. This process is widely employed and is often used to sterilize re-usable items. Qualifying a sterilization process for such products requires an approach different from that used for virgin product, because the challenge to the sterilization process is difficult to define and pre-sterilization treatments (such as cleaning) are difficult to validate and control. A sterilization process in this situation is often conservative and designed to deliver a treatment exceeding that required to achieve the specified requirements for sterility. This type of treatment, which is often referred to as “overkill”, can be determined either mathematically based on an empirical microorganism (full cycle approach) or from a reduced level of treatment delivered to a defined microorganism (partial cycle approach).

D.1.2 The overkill method is best suited to sterilization processes where linear inactivation kinetics can be demonstrated.

D.1.3 Guidance and discussion on the overkill method are given in, ISO 14161^[10] and in literature, such as Halverson and Zeigler 1932^[37], Pflug and Holcomb 1983^[44], PDA 1978^[42], and Pflug 1999^[43].

D.2 Procedure

D.2.1 The location within the product at which sterility is most difficult to achieve should be established.

D.2.2 A challenge to the sterilization process should be created by either:

- a) placing biological indicators within the product at position(s) or representative of positions where sterilizing conditions are most difficult to achieve, or
- b) inoculating the product with reference microorganisms at position(s) within the product where sterilizing conditions are most difficult to achieve.

NOTE An inoculated product can be considered to be a biological indicator. (See 8.5 or 8.6 and ISO 11138-1.)

D.2.3 The challenge should be packaged the same as routinely produced product and included within the sterilization load in the location where it is most difficult to achieve sterilizing conditions.

D.3 Partial cycle approach

D.3.1 The sterilization load should be exposed to the sterilizing agent under conditions designed to deliver a reduced level of treatment.

D.3.2 The extent of treatment needed to inactivate 10^6 microorganisms on a biological indicator that complies with ISO 11138-3 should be confirmed.

D.3.3 The level of treatment identified should be carried out in triplicate to demonstrate reproducibility.

D.3.4 If the inactivation of 10^6 viable microorganisms is confirmed, determine the extent of treatment for the sterilization process by extrapolation to a predicted probability of survival 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.

D.3.5 The extent of treatment can be defined conservatively as twice that used by the reduced level of treatment.

D.4 Full cycle approach

D.4.1 The sterilization load should be exposed to the sterilizing agent under conditions designed to deliver a level of treatment that will inactivate a biological indicator complying with ISO 11138-3.

D.4.2 The nominal population on the biological indicator should exceed by at least $0,5 \times \log$ to the base 10 of the population, calculated from F_{bio}^{12} and the certified D_{121} value for the biological indicator. This takes into account variations in microbiological manipulations and changes in D value for the test microorganism, which can be caused by contact with the product or a contaminating material.

F_{bio} is determined from the equation:

$$F_{\text{bio}} = D_{121}(\log N_0 - \log N) \quad (\text{D.1})$$

where:

D_{121} is the D value of the biological indicator at an exposure temperature of 121 °C;

N_0 is the pre-exposure viable population of the biological indicator;

N is the post-exposure viable population of the biological indicator.

D.4.3 Examples of microorganisms that demonstrate high resistance to moist heat and which are suitable for use in this approach are *G. stearothermophilus*, *B. coagulans*, *C. sporogenes* and *B. atrophaeus*.

D.4.4 Variations in delivered lethality that may occur within the sterilizer chamber and the probability that this could result in a positive test piece should be included in the calculation to determine the target F_0 .

D.4.5 The sterilization load should be exposed to the sterilizing agent for the target F_0 to confirm that there are no survivors. If the results of the test establish that this level of treatment is acceptable, then two further repeats should be done to demonstrate reproducibility and to confirm the defined treatment to be delivered by the sterilization process.