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Sterilization of medical devices — Low temperature steam and formaldehyde — Requirements for development, validation and routine control of a sterilization process for medical devices

Stérilisation des dispositifs médicaux — Formaldéhyde et vapeur à faible température — Exigences pour le développement, la validation et le contrôle de routine d'un procédé de stérilisation pour dispositifs médicaux

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Foreword

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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 25424 was prepared by CEN (as EN 15424:2007) and is submitted for approval under a special “fast-track procedure”, by Technical Committee ISO/TC 198, *Sterilization of health care products*, in parallel with its approval by the ISO member bodies.

For the purposes of this International Standard, the CEN annex regarding the fulfilment of European Council Directives has been removed.

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Foreword

This document (EN 15424:2007) has been prepared by Technical Committee CEN/TC 204 “Sterilization of medical devices”, the secretariat of which is held by BSI.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by October 2007, and conflicting national standards shall be withdrawn at the latest by October 2007.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive(s).

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland and United Kingdom.

Introduction

A sterile medical device is one which is free of viable microorganisms. European Standards, which specify requirements for validation and routine control of a sterilization process 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 EN ISO 13485) 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 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.

This standard describes requirements which will enable the demonstration that a low temperature steam and formaldehyde sterilization 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. This standard does not specify the maximal value to be taken by this probability; specification of this probability is given in EN 556-1.

Requirements of the quality management system for medical device design/development, production, installation and servicing are given in EN ISO 13485. The standard for quality management systems recognizes that, for certain processes used in manufacturing or reprocessing, the effectiveness cannot be fully verified by subsequent inspection and testing of the product. Sterilization is an example of such a process. For this reason, sterilization processes are validated for use, the performance of the sterilization process monitored routinely and the equipment maintained.

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

g) the conditions under which the product is transported and 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 re-sterilization in accordance with the manufacturer's instructions (see EN ISO 17664) should be regarded as a special case. There is the potential for such products to possess a wide range of contaminating microorganisms and residual inorganic and/or organic contamination in spite of the application of a cleaning process. Hence, particular attention has to be given to the validation and control of the cleaning and disinfection processes used during reprocessing.

The requirements are the normative parts of this standard 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 as well as methods that are accepted as being suitable means for complying with the requirements. Approaches other than those given in the guidance may be used, if they are effective in achieving compliance with the requirements of this European Standard.

The development, validation and routine control of a sterilization process comprise a number of discrete but interrelated activities, for example calibration, maintenance, product definition, process definition, installation qualification, operational qualification, and performance qualification. While the activities required by this standard have been grouped together and are presented in a particular order, this European Standard does not require that the activities be performed in the order that they are presented. The activities required are not necessarily sequential, as the programs 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 European Standard does not specify the particular individuals or organizations to carry out the activities.

Activities required by this standard might also give rise to an environmental burden that should be considered and minimized, e.g. by utilizing flexibility in planning. Environmental aspects are addressed in Annex D of this standard.

Sterilization of medical devices — Low temperature steam and formaldehyde — Requirements for development, validation and routine control of a sterilization process for medical devices

1 Scope

1.1 Inclusions

1.1.1 This European Standard specifies requirements for the development, validation and routine control of a Low Temperature Steam and Formaldehyde (LTSF) sterilization process for medical devices.

NOTE Although the scope of this standard is limited to medical devices it specifies requirements and provides guidance that may be applicable to other products and equipment.

1.1.2 This European Standard is intended to be applied by process developers, manufacturers of sterilization equipment, manufacturers of medical devices to be sterilized and the organizations with responsibility for sterilizing medical devices. (See EN ISO 14937:2000, Table E.1)

1.1.3 This European Standard covers sterilization processes which use a mixture of low temperature steam and formaldehyde as sterilant, and which are working below ambient pressure only.

1.2 Exclusions

1.2.1 Sterilization processes validated and controlled in accordance with the requirements of this 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.

1.2.2 This standard does not specify requirements for designating a medical device as “STERILE”. Such requirements are given in EN 556-1.

1.2.3 This standard 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 standard to have a complete quality management system during manufacture or reprocessing, but those elements of such a system that are required are normatively referenced at appropriate places in the text. Attention is drawn to the standards for quality management systems (see EN ISO 13485) that control all stages of production or reprocessing of medical devices including the sterilization process. Further guidance is given in E.2 of EN ISO 14937:2000.

1.2.4 This standard does not specify requirements for occupational safety associated with the design and operation of LTSF sterilization facilities.

NOTE 1 Safety requirements for sterilizers are specified in EN 61010-2-040.

NOTE 2 Attention is also drawn to the existence in some countries of regulations stipulating safety requirements.

1.2.5 This European Standard does not cover analytical methods for determining levels or residues of formaldehyde and/or its reaction products.

NOTE 1 Attention is drawn to EN 14180.

NOTE 2 Attention is drawn to the possible existence in some countries of statutory regulation specifying limits for the level of formaldehyde residues on medical devices and products.

1.2.6 This European Standard does not cover preparatory measures that may be necessary before sterilization such as cleaning, disinfection and packing.

NOTE For re-sterilizable medical devices, the manufacturer(s) of these devices should supply information on the preparatory measures (see EN ISO 17664).

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.

EN 14180:2003, *Sterilizers for medical purposes — Low temperature steam and formaldehyde sterilizers — Requirements and testing*

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

EN ISO 11138-5:2006, *Sterilization of health care products — Biological indicators — Part 5: Biological indicators for low-temperature steam and formaldehyde sterilization processes (ISO 11138-5:2006)*

EN ISO 11140, *Sterilization of health care products — Chemical indicators* (Parts as appropriate)

EN ISO 11737-1, *Sterilization of medical devices — Microbiological methods — Part 1: Determination of a population of microorganisms on products (ISO 11737-1:2006)*

EN ISO 11737-2, *Sterilization of medical devices — Microbiological methods — Part 2: Tests of sterility performed in the validation of a sterilization process (ISO 11737-2:1998)*

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

3 Terms and definitions

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

3.1
adjustment
correction of a measurement device or system to indicate the value as established by calibration

3.2
aeration
part or parts of the sterilization process in which defined conditions are used such that formaldehyde and its reaction products are desorbed from the medical device, and which can be performed within the sterilizer, within a separate room or chamber, or by a combination of the two

[3.3 of EN 14180:2003]

3.3
air removal
removal of air from the sterilizer chamber and sterilization load to facilitate sterilant penetration

[3.3 of EN 14180:2003]

3.4
bioburden
population of viable microorganisms on or in product and/or sterile barrier system

[2.2 of ISO/TS 11139:2006]

3.5
biological indicator (BI)
test system containing viable microorganisms inoculated onto a carrier and contained within a primary pack, ready for use and providing defined resistance to a specified sterilization process under defined reference conditions

3.6
calibration
set of operations that establish, under specified conditions, the relationship between values 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

[2.4 of ISO/TS 11139:2006]

3.7
change control
assessment and determination of the appropriateness of a proposed alteration to product or procedure

[2.5 of ISO/TS 11139:2006]

3.8
chemical indicator
test system that reveals change in one or more predefined process variables based on a chemical or physical change resulting from exposure to a process

[2.6 of ISO/TS 11139:2006]

3.9
conditioning
treatment of product within the sterilization cycle, but prior to the holding time, to attain a predetermined temperature and humidity throughout the sterilization load

[3.7 of EN 14180:2003]

3.10
desorption
removal of the sterilant from the chamber and the load at the end of the exposure time

[3.11 of EN 14180:2003]

3.11
***D* value**
time or dose required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions

[2.11 of ISO/TS 11139:2006]

NOTE For LTSF sterilization the D value is given in minutes.

3.12
environmental control
engineering and/or procedural systems to maintain conditions in defined areas within specified limits

NOTE Such systems may include air and fluid filters, surface disinfection, personnel attire and administrative procedures [2.16 of ISO/TS 11139:2006].

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 load

[3.13 of EN 14180:2003]

3.14
establish
determine by theoretical evaluation and confirm by experimentation

[2.17 of ISO/TS 11139:2006]

3.15
exposure time
time between introducing the sterilant into the chamber and start of the desorption phase

[3.14 of EN 14180:2003]

3.16
fault
one or more of the process parameters which lies outside of its/their specified tolerance(s)

[2.19 of ISO/TS 11139:2006]

3.17
F_{BIO} value
product of the logarithm of the initial population of microorganisms and the D value

NOTE The F_{BIO} value may be used to express the "total resistance" of the biological indicator.

3.18
holding time
period for which the temperature, the steam pressure and the formaldehyde concentration of steam are held within pre-set values and their tolerances to achieve the required inactivation efficacy in the sterilizer chamber

NOTE The holding time follows immediately after the equilibration time [3.15 of EN 14180:2003].

3.19
inoculated carrier
supporting material on or in which a defined number of test microorganisms have been deposited

3.20
installation qualification [IQ]
process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

[2.22 of ISO/TS 11139:2006]

3.21
medical device
instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:

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

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

— investigation, replacement, 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

[EN ISO 13485]

3.22
microbicidal solution
aqueous solution containing formaldehyde to feed the vaporizer for generating sterilant in the sterilizer

[3.20 of EN 14180:2003]

NOTE The microbicidal solution usually contains stabilizers i.e. alcohols.

3.23
operational qualification (OQ)
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[2.27 of ISO/TS 11139:2006]

3.24
parametric release
declaration that a product is sterile, based on records demonstrating that the process parameters were delivered within specified tolerances

[2.29 of ISO/TS 11139:2006]

3.25
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 pre-determined criteria and thereby yields product meeting its specification

[2.30 of ISO/TS 11139:2006]

3.26
process challenge device (PCD)
item designed to constitute a defined resistance to a sterilization process and used to assess performance of the process

[2.33 of ISO/TS 11139:2006]

NOTE The device is designed so that an inoculated carrier or chemical indicator can be put in the place which is the most difficult to reach by sterilizing agent(s). The indicator should not interfere with the function of the process challenge device.

3.27
process parameter
specified value for a process variable

[2.34 of ISO/TS 11139:2006]

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

3.28
process variable
condition within a sterilization process, changes in which alter microbicidal effectiveness

EXAMPLE Time, temperature, pressure, concentration, humidity, wavelength. [2.35 of ISO/TS 11139:2006].

3.29
product
result of a process

[EN ISO 9000]

NOTE For the purposes of sterilization standards, product is tangible and can be raw material(s), intermediate(s), sub-assembly (ies) and health care product(s) [2.36 of ISO/TS 11139:2006].

3.30
recognized culture collection
depository authority under the Budapest Treaty on The International Recognition of the Deposit of Microorganisms for the purpose of Patent and Regulation

[2.38 of ISO/TS 11139:2006]

3.31
reference measuring point
point where the temperature sensor for the sterilization cycle control is located

[3.29 of EN 14180:2003]

3.32
reference microorganism
microbial strain obtained from a recognized culture collection

[2.39 of ISO/TS 11139:2006]

3.33
requalification
repetition of part of validation for the purpose of confirming the continued acceptability of a specified process

[2.40 of ISO/TS 11139:2006]

3.34
residues challenge device
item used to assess the desorption efficacy of the sterilization cycle

3.35
services
supplies from an external source, necessary for the correct function of sterilizing equipment

EXAMPLE Electricity, water, compressed air, drainage [2.41 of ISO/TS 11139:2006].

3.36
specify
stipulate in detail within an approved document

[2.42 of ISO/TS 11139:2006]

3.37
sterilant
microbicidal agent composed of steam containing formaldehyde

[3.31 of EN 14180:2003]

NOTE Sterilant is generated by vaporizing the microbicidal solution and feeding it into the sterilizer chamber.

3.38
sterilant injection
single or repeated stage beginning with the introduction of sterilant into the evacuated sterilizer chamber and ending when the set operating pressure has been attained

[3.32 of EN 14180:2003]

3.39
sterile
free from viable microorganisms

[2.43 of ISO/TS 11139:2006]

3.40
sterility
state of being free from viable microorganisms

NOTE In practice, no such absolute statement regarding the absence of microorganisms can be proven [ISO/TS 11139:2006, 2.45]

3.41
sterilization
validated process used to render a product free from viable microorganisms

NOTE In a sterilization process, the nature of microbial inactivation is described by an exponential function. Therefore the presence of a viable microorganism(s) on any 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 [2.47 of ISO/TS 11139:2006].

3.42
sterilization cycle
predetermined sequence of operating stages performed in a sterilizer for the purpose of sterilization and desorption

[3.37 of EN 14180:2003]

3.43
sterilization load
product to be, or that has been, sterilized together using a given sterilization process

[2.48 of ISO/TS 11139:2006]

3.44
sterilization process
series of actions or operations to achieve the specified requirements for sterility and for reduction of sterilant residues to an acceptable level

[2.49 of ISO/TS 11139:2006]

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 necessary operations preceding the sterilization process, such as cleaning, disinfection or packaging.

3.45
sterilizing agent
physical or chemical entity, or combination of entities having sufficient microbicidal activity to achieve sterility under defined conditions

[2.50 of ISO/TS 11139:2006]

NOTE The sterilizing agent is the condensate film, generated by condensation of the sterilant on the surface of the medical devices to be sterilized.

3.46
survivor curve
graphical representation of the inactivation of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions

[2.51 of ISO/TS 11139:2006]

3.47
validation
documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product conforming to predetermined specifications

[2.55 of ISO/TS 11139:2006]

4 Quality management system elements

4.1 Documentation

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

4.1.2 Documents and records required by this European Standard shall be reviewed and approved by designated personnel (see 4.2.1). Documents and records shall be controlled in accordance with an established quality management system, such as EN ISO 13485.

4.2 Management responsibility

4.2.1 The responsibility and authority for implementing and performing the procedures described in this European Standard shall be specified. Responsibility shall be assigned to competent personnel in accordance with an established quality management system, such as EN ISO 13485.

4.2.2 If the requirements of this European Standard are undertaken by different 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 conform to an established quality management system, such as EN ISO 13485

4.3.2 Procedures for identification and traceability of product shall be specified. These procedures shall conform to an established quality management system, such as EN ISO 13485.

NOTE EN ISO 13485 details requirements for design reviews.

4.3.3 Procedures conforming to EN ISO 13485 shall be specified for the calibration or adjustment of equipment, including instrumentation for test purposes used in meeting the requirements of this European Standard.

4.4 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 conform to an established quality management system, such as EN ISO 13485.

5 Sterilizing agent characterization

5.1 General

The purpose of this activity is to define the sterilizing agent, demonstrate its microbicidal effectiveness, identify the factors which influence microbicidal effectiveness, assess the effects that exposure to the sterilizing agent has on materials and identify requirements for safety of personnel and protection of the environment.

NOTE 1 The characteristics of LTSF processes and of low temperature steam and formaldehyde are well known after decades of practical use and development. Development of new processes may however necessitate new studies.

NOTE 2 If characterization studies of a sterilizing agent with a non-traditional formaldehyde mixture is necessary, these studies can be undertaken under formal design and development controls (see EN ISO 13485).

5.2 Sterilizing agent

A specification for the microbicidal solution and for the process to generate the sterilizing agent shall be generated. This shall include, if appropriate, conditions for storage to maintain the microbicidal solution within its specification for the duration of any stated shelf life.

NOTE 1 For further guidance see EN 14180:2003, 10.3.

NOTE 2 The LTSF-sterilization process is a modified steam sterilization process. A formaldehyde solution (microbicidal solution) is evaporated into a gas mixture containing steam and formaldehyde. The microbicidal activity is achieved by the condensate film on the surface of the medical devices to be sterilized.

5.3 Microbicidal effectiveness

Data shall be available to demonstrate the microbicidal effectiveness of the sterilizing agent in the process. The microbicidal effectiveness of LTSF and its use in processes has been comprehensively documented and is available in literature.

NOTE Manufacturers of sterilizers should have these data available for their customers.

5.4 Material effects

The effects of low temperature steam and formaldehyde on materials, both in the sterilizer and in products, are generally well known after decades of practical use. However, when new materials are introduced the effects of sterilizing agent exposure (repeated when applicable) shall be assessed and documented.

5.5 Environmental considerations

The potential impact on the environment of the use of formaldehyde in the sterilization process shall be assessed and measures to protect the environment shall be identified. This assessment, including potential impact (if any) and measures for control (if identified), shall be documented.

NOTE 1 See CEN Guide 4, *Guide for the inclusion of environmental aspects in product standards*.

NOTE 2 See also Annex D.

NOTE 3 Attention is also drawn to the existence in some countries of regulations laying down environmental requirements.

6 Process and equipment characterization

6.1 General

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

6.2 Process

6.2.1 The load shall be exposed to the sterilizing agent under defined and controlled conditions. 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 yielding acceptable product.

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

NOTE See EN 14180:2003, Clause 5.

6.2.3 The quality of steam used throughout the sterilization cycle shall be specified. It shall be suitable for its intended use with regard to equipment and products.

NOTE See EN 14180:2003, 10.4.

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

6.2.5 The sterilization cycle shall include:

a) air removal;

b) conditioning;

c) sterilant injection;

d) equilibration time and holding time;

e) desorption;

f) air admission to atmospheric pressure.

NOTE For further information see EN 14180:2003, Figure 4.

6.3 Equipment

6.3.1 The equipment to be used for LTSF sterilization shall be specified.

6.3.2 The specification shall include but is not limited to: description of the sterilizer equipment, its installation, its accessories, its consumables and other related items as specified in the information provided in accordance with Clause 9 of EN 14180:2003.

6.3.3 The conditions for storage of formaldehyde solution prior to and during use shall conform to the specification, see 5.2.

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

NOTE For information see EN ISO 13485.

6.3.5 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.

NOTE 1 This may be achieved either by the use of independent systems for control and monitoring, or a crosscheck between values for process variables derived from control and monitoring, which identifies any discrepancies and indicates a fault.

NOTE 2 EN 14180 requires independent control and recording systems.

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 the product is packaged and presented for sterilization.

7.2 Product definition activities shall be performed before application of the sterilization process to a new or altered product, package or loading pattern.

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

NOTE Conforming to this requirement could necessitate appropriate written information to be provided to the organization undertaking the sterilization process by the manufacturer of the medical device (see EN ISO 17664) and/or the manufacturer of the sterilization equipment and/or the manufacturer of packaging materials.

7.3 Product and packaging shall be designed to allow removal of air and facilitate penetration of sterilant. The location within the product at which sterilization is most difficult to achieve shall be identified.

7.4 It shall be demonstrated by assessment or tests, as applicable, that the specified sterilization process does not affect the materials used for and/or the correct functioning of the product and its packaging.

NOTE After decades of practical use substantial experience is available regarding material compatibility to LTSF.

7.5 For resterilization of products, the effects of repeated processing on the product and its packaging shall be evaluated (See also EN ISO 17664).

7.6 A system shall be defined, documented and maintained to ensure that the condition of the product, whenever presented for sterilization, is controlled and does not compromise the effectiveness of the sterilization process.

7.7 The effectiveness of the system defined in accordance with 7.6 shall be demonstrated. For medical devices to be supplied for single use, this demonstration shall include estimation of bioburden in accordance with EN ISO 11737-1. For reusable medical devices, this demonstration shall include assessment of the effectiveness of preparatory measures such as cleaning and, if applicable, disinfecting. This may also include an assessment of any organic and inorganic contamination.

NOTE Standards for equipment for cleaning and disinfecting medical devices prior to sterilization have been published (see EN ISO 15883). These standards will include methods to demonstrate the effectiveness of a cleaning and disinfecting process.

7.8 The medical device manufacturer shall evaluate the formaldehyde retention characteristics of product compared to that of the desorption efficacy indicator as specified in C.5 of EN 14180:2003. The results evaluation shall consider the limit values referred to in Annex E of EN 4180:2003 as well as other available toxicological data.

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) to achieve the required microbicidal efficacy, without compromising the safety, quality and performance of that product.

8.2 The sterilization process applicable for defined product shall be established by demonstrating the attainment of process parameters by measurements, if practical; and

a) demonstrating an overkill by using the method described in Annex B, or

b) delivering the sterilizing agent under conditions so designed that process provides less lethality than the intended sterilization process to defined product (see Annex A).

NOTE Procedure b) can only be used under experimental conditions.

8.3 Biological indicators or inoculated carriers used as a part of the establishment of the sterilization process shall:

a) conform to EN ISO 11138-1 and, if the method described in Annex B is used, B.2.2.

NOTE For disposal of biological indicators attention should be paid to instructions provided by its manufacturer.

b) be placed in product at positions determined to be most difficult to achieve sterilizing conditions or in a PCD (see EN 867-5).

8.4 If chemical indicators are used as part of the establishment of the sterilization process, these shall conform to EN ISO 11140-1.

NOTE For disposal of chemical indicators attention should be paid to instructions provided by its manufacturer.

8.5 If tests of sterility are performed during the establishment of the sterilization process such tests shall conform to EN ISO 11737-2.

8.6 Sterilization process establishment shall include methods to bring residual levels in product down to levels not higher than those specified in 6.2 of EN 14180:2003. The parameters for this treatment shall be based on the most challenging process conditions with regard to residues.

NOTE 1 The choice of process parameters may affect the residue levels.

NOTE 2 The disposal and handling of chemicals and indicators used at sterilization process development should be considered.

8.7 Product shall meet its specified requirements for safety, quality and performance after being subjected to the most challenging sterilization process parameters identified.

When the manuals for a reprocessable medical device contain detailed sterilization requirements and these requirements are fulfilled, the requirements for safety, quality and performance are deemed to be met (See EN ISO 17664).

8.8 The established sterilization process shall be defined, specified and documented.

9 Validation

9.1 General

9.1.1 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 sequential stages; installation qualification; operational qualification; and performance qualification.

NOTE For re-qualification see 12.3.

9.1.2 Test equipment for validation shall be specified.

NOTE Annex C of EN 14180:2003 gives guidance on this subject.

9.1.3 Upon installation, but prior to installation qualification, the calibration and adjustment of instrumentation (including any test instruments) used for monitoring, controlling, indicating or recording shall be confirmed (see 4.3.3).

9.1.4 Prior to validation at least the following information or documentation shall be checked for validity and applicability:

— standard operation procedures for the sterilization process, including documentation for routine operation, process control, monitoring, product release, and for scheduled maintenance of the equipment;

— qualification and training status of personnel;

— validated efficacy of the cleaning and disinfecting process for the products to be sterilized;

— user manual and technical documentation of the LTSF sterilizer and its accessories;

— verification that supplies and consumables for the sterilizer conform to their specifications;

— compatibility of the products and their packaging to LTSF sterilization processes;

— packaging lists and configuration schemes of the products used for routine operation;

— configuration schemes of products intended to be used for performance qualification.

9.2 Installation qualification

9.2.1 General

Installation qualification shall be undertaken to demonstrate that the sterilization equipment and any ancillary items have been supplied and installed in accordance with their specification (see C.9.2.)

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 service required (see EN 14180:2003, Clause 10). 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 Instructions for the safe storage of the microbicidal solution to ensure that its quality and composition remain within specification shall be available.

9.2.2.4 Drawings of the equipment as installed, plumbing, and any ancillary equipment shall be finalized during Installation Qualification.

9.2.2.5 There shall be no leaks or unintended effluent or emissions.

9.2.3 Equipment

9.2.3.1 The conformance of the sterilizer and any ancillary items to specification shall be verified.

Requirements for the information to be provided are specified in Clause 9 of EN 14180:2003, and for marking and labelling in Clause 8 of EN 14180:2003.

9.2.3.2 Equipment safety in accordance with criteria stated in the sterilizer specification shall be verified.

NOTE EC Declaration of conformity or corresponding certifications may be used for verification.

9.2.3.3 It shall be verified that appropriate operating procedures for the equipment are available.

9.3 Operational qualification

9.3.1 Operational qualification shall be carried out using specified test loads and shall demonstrate that the installed equipment is capable of delivering the sterilization process within defined tolerances (see C.9.3.4).

NOTE The disposal and handling of chemicals and indicators used at sterilization process development should be considered.

9.3.2 Results of the installation qualification shall be available prior to operational qualification (see 9.2).

9.3.3 Operational qualification shall be carried out in accordance with a specified test program. The program shall define requirements to be verified, test equipment and procedures, and acceptance criteria.

NOTE 1 Guidance for a test programme is given in Table B.1 of EN 14180:2003. Specifications for suitable test loads and test procedures for operational qualification tests are given in Annex A of EN 14180:2003.

NOTE 2 These tests should be performed in combination in order to reduce overall time, effort and environmental burden.

9.3.4 Reproducibility of the supply, control and monitoring of sterilant within the established values and tolerances stated by the manufacturer shall be verified (For further guidance see C.9.3.5).

9.4 Performance qualification

9.4.1 General

9.4.1.1 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.

9.4.1.2 Results of the operational qualification shall be available prior to performance qualification (see 9.3).

9.4.1.3 Performance qualification shall be carried out in accordance with a specified test program. The program shall define requirements to be verified, test equipment and procedures, and acceptance criteria.

9.4.1.4 For establishments that have widely varying load configurations (e.g. hospitals), the most challenging load configuration(s) in compliance with the instructions for use shall be defined.

Factors that shall be considered when defining the most challenging load configuration(s) include but are not limited to:

— sterilant consumption;

— air removal and sterilant penetration;

— sterilant desorption;

— wrapping;

— thermal characteristics of the product, e.g. slow warm-up.

9.4.1.5 The manner of presenting the product for sterilization and the packaging shall be equivalent to the manner specified for routine use (See 9.4.1).

9.4.1.6 Reproducibility of the cycle shall be demonstrated by performing at least three exposures of product.

NOTE 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 successful runs. Examples of this type of failure include, but are not limited to power failure, loss of service, or failure of external monitoring equipment.

9.4.1.7 Physical, microbiological and desorption performance qualification shall be carried out, separately or in combination.

9.4.1.8 If chemical indicators are used in performance qualification, they shall conform to EN ISO 11140-1 and any subsequent parts of EN ISO 11140 which are applicable to the process.

NOTE For disposal of chemical indicators attention should be paid to instructions provided by its manufacturer.

9.4.2 Performance qualification – physical

9.4.2.1 The physical performance qualification shall verify that those physical parameters given in the sterilization process specification are achieved when using representative challenging load configurations.

NOTE For thermometric tests A.3.2 of EN 14180:2003 and for pressure profile test A.3.4 of EN 14180:2003 may be used for guidance.

9.4.2.2 Reproducibility of the supply, control and monitoring of sterilant within the established values and tolerances stated by the manufacturer shall be verified (For further guidance see C.9.3.5).

NOTE Results from operational qualification (see 9.3.4) might be used for this verification if equivalence can be demonstrated. In this case demonstration of equivalence should be documented.

9.4.3 Performance qualification – microbiological

Microbiological performance studies shall be carried out in accordance with Annex B.

NOTE 1 The method described in Annex B is the only method known to be commonly used at this time for microbiological performance qualification of LTSF-processes.

NOTE 2 The appropriate number and location of BIs to be used depends on the number and character of items in the load under study. Table B.1 of EN 14180:2003 may be used for guidance.

NOTE 3 For disposal of biological indicators, attention should be paid to instructions provided by its manufacturer.

9.4.4 Performance qualification – desorption and drying

9.4.4.1 Desorption

The capability of the process to reduce the residue levels below the specified limits shall be verified during desorption studies.

The rationale shall be given for the number and types of test items to be used.

NOTE Pertinent method for residues evaluation are given in EN 14180:2003, Annexes A, D and E.

9.4.4.2 Drying

Drying performance shall be verified by visual inspection (see A.3.6 of EN 14180:2003).

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 Documented information gathered or produced during installation qualification and operational qualification shall be reviewed for acceptability (see also 4.1.2). The results of this review shall be documented.

9.5.3 Performance qualification shall be documented and reviewed. Records shall at least include the following:

a) preparations made before sterilization such as:

- packing of items and packing material used;
- loading equipment used;
- loading configuration within the sterilizer;

b) the combinations of product (load) and cycle tested;

c) sterilant exposure data as declared by the sterilizer manufacturer to govern the generation and supply of sterilant to the chamber e.g.:

- the amount of microbicidal solution used;
- the chamber pressure versus time profile;
- the chamber and load temperature;

— other time periods;

— direct analysis data;

d) results of the evaluation of the physical parameters in accordance with 9.4.2;

e) results of the microbiological studies in accordance with 9.4.3;

f) results of the desorption studies as required by 9.4.4.1:

— formaldehyde residues measured as described in Annex D and/or E of EN 14180:2003;

g) results of the drying studies as required by 9.4.4.2.

The records generated for combinations of product (load) and process shall be reviewed for acceptance. A justification for acceptance of each combination shall be documented.

9.5.4 A validation report including data, considerations and decisions based upon the activities as required by 9.5.2 and 9.5.3 shall be generated. The report shall be approved and signed in accordance with 4.1 and 4.2 in this document.

10 Routine monitoring and control

10.1 General

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

10.1.2 There shall be evidence through physical measurements, supplemented as necessary by results from residual, biological and/or chemical indicator testing, that the LTSF sterilization process was delivered within the defined tolerances.

NOTE The frequency of testing should be based on evidence of the reproducibility of the process.

10.1.3 Routine sterilization shall be carried out in accordance with the limitations established during performance qualification, e. g. for type of products and packaging.

10.1.4 Pressure-temperature-time diagrams shall be recorded and it shall be verified that all process variables were within specification.

10.2 Biological indicators

If biological indicators are used in routine monitoring, these indicators, and the recovery media and culture conditions used, shall conform to EN ISO 11138-1 and, when applicable, B.2.2. The number of indicators and the use of process challenge devices (PCD) shall be justified and documented. The results of testing shall be documented.

NOTE 1 When the method in Annex A is used, A.2.b might not be applicable.

NOTE 2 Attention is drawn to EN 867-5 specifying a hollow-load PCD.

NOTE 3 For disposal of biological indicators attention should be paid to instructions provided by its manufacturer.

10.3 Chemical indicators

If chemical indicators are used in routine monitoring, they shall conform to EN ISO 11140-1. The results shall be documented.

NOTE 1 Effective desorption, as required by EN 14180, may affect the performance of chemical indicators.

NOTE 2 For disposal of chemical indicators attention should be paid to instructions provided by its manufacturer.

10.4 Records

10.4.1 All records related to the routine monitoring and control shall be retained in accordance with 4.1.

10.4.2 Data shall be retained for each sterilization cycle to demonstrate that the sterilization process conforms to its specification. These data shall include at least the following:

a) records of temperature and pressure in the chamber throughout the sterilization cycle measured from a representative position within the chamber;

b) records of data concerning the supply of sterilant.

11 Product release from sterilization

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

a) conformance to the process variables and their parameters established by the sterilization process specification (see 8.8),

b) if chemical indicators are used as part of product release, complete colour change of these (see 10.3),

c) if BI are used as a part of product release, acceptable results from culture of these (see 10.2),

d) any other indication specified by the manufacturer of the sterilizer.

11.2 Sterilizers in compliance with EN 14180 are deemed to allow parametric release.

11.3 Product shall be considered as non-conforming and handled in accordance with documented procedures (see 4.4) if any of the criteria for designating conformance given in 11.1 is not met.

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 7.6) shall be demonstrated.

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

12.2 Maintenance of equipment

12.2.1 Maintenance shall be planned and performed in accordance with documented procedures.

NOTE 9.2 and 9.5 of EN 14180:2003 specify data that should be available when planning maintenance.

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

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

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

12.3 Requalification

12.3.1 Requalification of a sterilization process shall be carried out for defined product and specified equipment at defined intervals and in accordance with the result of the assessment of any change (see 12.4). The intervals for and the extent of requalification shall be justified and documented.

NOTE National regulations may state specific requirements regarding the extent of and intervals for requalification.

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

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

12.4 Assessment of change

A change to equipment, product, packaging or presentation of product for sterilization shall be assessed for its 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.

Annex A
(normative)

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

A.1 General

This approach has been referred to as the “combined biological indicator/bioburden method”. Guidance on this approach can be found in EN ISO 14161. Due to the variability of the bioburden in health care facilities, the variability of product and the limited availability of microbiological testing, this method is not likely to be used in health care facilities.

A.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) placing an inoculated carrier at position(s) where sterilizing conditions are most difficult to achieve;

c) inoculating the position(s) within product where sterilizing conditions are most difficult to achieve with reference organisms. When the product is inoculated in this manner, it becomes the supporting material and hence the packed product meets the definition of a biological indicator. Subclause 8.3 requires this packed, inoculated product to meet the requirements of EN ISO 11138-1.

NOTE 1 For disposal of biological test material attention should be paid to instructions provided by its manufacturer.

Pack 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 a most probable number technique or by direct enumeration.

NOTE 2 The survivor curve test method as described in EN ISO 11138-1 can be used only in case the formaldehyde concentration over time is predictable.

Calculate the rate of inactivation of the reference microorganisms.

From knowledge of the bioburden (see EN ISO 11737-1) and the rate of inactivation of the reference microorganisms, determine the extent of treatment required to achieve the specified requirements for sterility.

Annex B
(normative)

Process definition based on inactivation of reference microorganisms

B.1 General

B.1.1 Overkill approach

This approach to the definition of the process has been widely employed; particularly for products to be re-processed in health care facilities. Qualifying a sterilization process for such products employs an approach different from that adopted with most virgin products. This is because the challenge to the sterilization process is difficult to define and pre-treatments such as cleaning are sometimes difficult to validate and control. Therefore, sterilization processes applied in these situations are conservative and employ a treatment that may exceed the minimum requirements to achieve sterility. This approach has been referred to as the "overkill approach". Guidance on this approach can be found in EN ISO 14161.

B.1.2 Penetration characteristics into medical devices

The range of medical devices to be exposed to LTSF sterilization represents designs of different complexity. Several design characteristics of medical devices can provide a penetration challenge that should be considered. Such design characteristics include, but are not limited to:

— contacting sliding surfaces;

— mated surfaces;

— screws;

— long lumens, e.g. hollow devices;

— lubricated areas.

Specific attention has to be paid to verifying the presence of sterilizing agent at the worst case locations of such designs.

Long narrow lumen devices are commonly re-sterilized in healthcare facilities and are therefore likely to be chosen as a worst case penetration challenge. They have large interior surface areas and low interior volumes. The sterilant is absorbed by condensate or adsorbed at the surfaces starting from the entrance. Worst case locations are generally in the middle part of tubes open at both ends or at the end of dead-ended tubes.

In case biological indicators cannot be placed in the worst-case locations it may be necessary to inoculate these locations with reference germ suspensions (see B.2.2). In that case, the retrieval process shall be validated. Alternatively, to prevent expensive and time-consuming inoculation processes, a PCD loaded with biological indicators in accordance with B.2.2 may be used. If so, the PCD shall present at least the penetration challenge of the original device. Furthermore, the packaging shall be taken into consideration since wrapping may obstruct sterilant penetration as well, especially when wet.

B.2 Test procedure

B.2.1 General

LTSF-sterilization processes usually consist of air removal and conditioning (phase 1) followed by the holding time (phase 2). Both phases together contribute to microbial inactivation. Additionally, microbial inactivation continues during desorption. Therefore it is difficult to define and perform a reduced cycle.

B.2.2 Biological indicators

A F_{BIO}-value of (33 ± 3) min at 60 °C for BI is considered adequate for performance qualification and process definition purposes to demonstrate overkill using a full process.

NOTE The minimum value is based upon the requirements given in EN ISO 11138-5.

B.2.3 Test systems

Define the most difficult penetration location in accordance with B.1

— if feasible put biological indicator (BI) at this location or

— use PCD(s) (B.1.2) and place BI inside or

NOTE Hollow load PCD in accordance with EN 867-5 are considered suitable as a penetration challenge device.

— inoculate the medical device directly at the worst case location and assure that it conforms to B.2.2

Package in the same manner as the products sterilized routinely and include them within the sterilization load.

B.2.4 Load configuration

Define the most challenging load configuration in compliance with the instructions for use.

Factors that shall be considered include but are not limited to:

— sterilant consumption;

— air removal;

— wrapping;

— thermal characteristics of the product, e.g. slow warm-up.

B.2.5 Testing

B.2.5.1 Use the load configuration as defined in B.2.4 and use BI in accordance with B.2.2. Place them in accordance with B.2.3 and distribute the BIs in sufficient number to achieve statistically relevant data and to demonstrate sufficient microbicidal efficacy throughout the load.

NOTE A minimum of 10 indicators up to 100 l and 5 indicators more for each additional 50 l is considered to be adequate.

B.2.5.2 Carry out the sterilization process, or a reduced cycle process if applicable, and check the biological indicators for growth. For culturing BI follow the specific procedures described in EN ISO 11138-5.

No surviving microbiological indicators shall be detected.

NOTE For disposal of BI attention should be paid to instructions provided by its manufacturer.

B.2.5.3 Repeat the sterilization process at least twice to achieve results of 3 cycles in total to prove reproducibility of the process.

Annex C
(informative)

Guidance on application of this European Standard

The guidance given in this annex is not intended as a checklist for assessing compliance with this European Standard. This guidance is intended to assist 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 European Standard.

The main headings in this annex follow the chapter headlines and numbering in the main document. Below the main headlines the sub headlines and their numbering are not consistent with the sub headlines and the numbering in the main document.

C.1 Scope

No further guidance given.

C.2 Normative references

No further guidance given.

C.3 Terms and definitions

No further guidance given.

C.4 Quality management system elements

Reference is made to E.2 of EN ISO 14937:2000.

C.5 Sterilizing agent characterization

C.5.1 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 residuals into the recovery system.

For LTSF sterilization in accordance with the specifications given in EN 14180 significant dilution is achieved by the desorption phase of the sterilization cycle (see 6.2 of EN 14180:2003). Further reduction is needed prior to incubation and is achieved by use of neutralizing chemical agents and the procedures described in EN ISO 11138-5:2006, A.3.

C.5.2 Studies of microbial inactivation

C.5.2.1 General

C.5.2.1.1 Formaldehyde in aqueous solution has been demonstrated to have a high level of antimicrobial activity. In LTSF sterilizers a formaldehyde solution (microbicidal solution) is evaporated into a gas mixture containing steam and formaldehyde. This principle has been successfully used for more than 30 years. The microbicidal activity is achieved by the condensate film on the surface of the medical devices to be sterilized. Before the commencement of the holding time equilibrium between the gas phase and liquid phase will be achieved and microbial inactivation may already have started. Sterilization temperatures between 48 °C and 80 °C and formaldehyde concentrations of the sterilizing agent between 2 % and more than 35 % have been applied. Different kinds of LTSF sterilization processes have been established to achieve the required inactivation rate.

C.5.2.1.2 Spores of G. stearothermophilus have been found to be highly resistant to LTSF sterilization processes, and proved to be appropriate for inactivation studies and for biological indicators for process validation and routine monitoring. Providing proper air removal and sterilizing agent penetration of the product to be sterilized and in addition constant temperature and formaldehyde concentration at product surfaces, semi-logarithmic plots of microbial counts versus exposure time are linear. This makes it possible to define the kinetics of the microbial inactivation and to calculate the theoretical probability of a surviving microorganism.

C.5.2.2 Sterilizing agent and associated equipment

C.5.2.2.1 Studies on defined and reproducible sterilant generation and sterilizing agent characterization may be performed with laboratory equipment, prototype or routine production-type equipment. The process details and any associated equipment should be specified. In addition all cycle parameters, that could affect the microbicidal activity, need to be identified.

C.5.2.2.2 The reproducibility of the set-up and operation of equipment and the monitoring and control of all relevant variables should be considered. Written procedures should be prepared prior to operation of the equipment and performance of the studies.

C.5.2.2.3 The set-up and results of each study should be documented and retained to enable re-evaluation.

C.5.2.2.4 In case changes to the set-up have been made, their impact on the outcome of microbial inactivation studies should be assessed and documented.

C.5.2.2.5 For biological indicators for use with LTSF sterilization, reference is made to EN ISO 11138-1 and B.2.2.

C.5.2.2.6 Guidance on development of microbiological test methods and their validation can be found in D.3.2 in EN ISO 14937:2000.

C.6 Process and equipment characterization

No further guidance given.

C.7 Product definition

C.7.1 General

The LTSF sterilization process can adversely affect the integrity of medical devices and their packages. These effects need to be evaluated.

Some design characteristics of the product may inhibit full air removal and penetration of the sterilizing agent. Some packaging materials and devices could impede the sterilization process or the desorption of formaldehyde. The manufacturer of the product is required to provide information about suitable packaging and sterilization processes (EN ISO 17664).

C.7.2 Design considerations for medical devices intended for sterilization

C.7.2.1 Product function

The product is subjected to various environmental stresses during LTSF sterilization, such as pressure, temperature and relative humidity. The product might also chemically react with the sterilizing agent. The product design has to ensure that functionality and safety are not compromised by exposure to the anticipated range of cycle variables. The minimum and maximum values for process variables and their rate of change should be considered when establishing the most severe challenge to the product including the package. The effects of multiple exposures to the sterilization process should be evaluated.

C.7.2.2 Design configuration and tolerances

Design configuration and tolerances are important for air removal, delivery and penetration of the sterilizing agent and its distribution onto the surfaces to be sterilized. Effective desorption of the sterilizing agent needs to be ensured. If fitments are intended to maintain sterility, they should be designed to prevent inadvertent contamination of surfaces intended to be sterile.

C.7.2.3 Materials composition

C.7.2.3.1 It is important to select materials with adequate resistance to chemical and physical changes caused by the sterilizing agent over the anticipated range of cycle variables. Properties such as physical strength, permeability, dimensions and resilience should be 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. The effects of multiple exposures to the sterilization process need to be studied and evaluated. When necessary, the maximum allowable number of exposures shall be stated.

C.7.2.3.2 The biocompatibilty of materials after exposure to the sterilization process should be assessed.

C.7.2.3.3 If the retention characteristics of the actual products are lower than those of the desorption efficacy indicator, this indicator is an acceptable challenge device for this product. If the product has higher retention characteristics than the desorption efficacy indicator, this product should either be used itself for desorption testing or a new desorption challenge device needs to be chosen.

C.7.3 Packaging considerations

The major function of a package for a sterilized medical device is to ensure that the product remains sterile until used. During sterilization, the package is intended to withstand the process conditions without a negative effect (e.g. absorption and/or chemical reaction) on overall product quality.

Packaging considerations are addressed in more detail in EN ISO 11607 and EN 868.

C.8 Process definition

C.8.1 General

Process definition is undertaken to define the process parameters and their tolerances. It includes at least two parts; one assessing the impact of a range of candidate process parameters on the product and packaging, and the other defining those process parameters, that will achieve the specified requirements for sterility of the product.

C.8.2 Influence on product and packaging

As sterilization could influence product performance, a careful selection of values and tolerances for each process parameter should be undertaken during process definition. In general, those parameters which, when increased, significantly improve sterilization effectiveness without adversely affecting product performance should be maximized during this stage. Conversely, those parameters 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. To provide a safety margin for the process, the operating parameter concerned should be sufficiently below this threshold level.

C.8.3 Determination of process effectiveness

C.8.3.1 General

The sterilization process will be defined based on the inactivation of microorganisms. These microorganisms could be either the natural contamination on the product or reference microorganisms that present at least as great a challenge as does the bioburden on the product. A number of stages in the determination of process effectiveness should be performed to have confidence in the selection of the process parameters. When biological indicators are to be used, these stages include:

— selection of the biological indicator,

— determination of the location most difficult to sterilize,

— assessment of lethality at this location, and

— evaluation of the influence of packaging and load configuration.

C.8.3.2 Selection of biological indicator

Geobacillus stearothermophilus has been identified as a suitable micro-organism for testing LTSF-sterilizers (EN ISO 11138-5). If a process is being developed (in industry) based on the actual bioburden, the biological indicator should have a relatively high resistance to the sterilization process when compared to other microorganisms evaluated. The challenge presented by the biological indicator should be compared to that of the product bioburden and, if the challenge is greater than that of the product bioburden, it can be considered as appropriate for process definition and subsequent validation studies. While it is not necessary to determine the D-value for each bioburden isolate, it is important to assess the more resistant portion of the bioburden population. Relative inactivation can be assessed via graded exposures to the sterilizing agent.

C.8.3.3 Placement of the biological indicator

Once the biological indicator has been selected, an appropriate location within the product has to be established. This location can be established based on an expert understanding of the process and a documented rationale for why a given location will be the most difficult to sterilize. If this cannot be done with certainty, then a number of locations that are likely to be difficult to sterilize should be evaluated. A biological indicator should be placed at each of these locations within product and the product exposed to a fraction of the sterilization process. The location which consistently yields the greatest number of survivors should be chosen.

C.8.3.4 Selecting the process parameters

From the range of values for the process variables studied in C.8.2, a single value with its tolerance should be defined for all but one of the process variables. Usually the process variable that is not defined is time. A series of studies is performed to generate a survivor curve, which is extrapolated to enable the process to be fully defined. The form of the survivor curve can be different from that observed during earlier characterization studies. For instance, the survivor curve observed during characterization may have been a straight line. This might be expected when the process parameters are fully achieved at process start, and fully depleted at the end of the process. When measuring inactivation at the most difficult to sterilize location, however, the process parameters may not be fully achieved at start of the holding time or fully depleted at the end of the process. In such cases, the effectiveness of the sterilizing agent will increase with time. Conversely, if the process parameters decay with time, the microbicidal effects of the sterilizing agent will deteriorate. In this case, there is greater risk in predicting end points, and it is recommended that other values for the process variables be evaluated.

C.8.3.5 Process residues

It is widely known from experience that residual (para)formaldehyde will remain on product after exposure to LTSF. Therefore, a desorption phase after exposure is part of a LTSF-process. EN 14180 specifies a test method for residues of (para)formaldehyde.

C.9 Validation

C.9.1 General

C.9.1.1 A validation study has at least the four main elements described in C.9.2 to C.9.5.

C.9.1.2 Any test equipment used for measurement of physical parameters needs to be adjusted to the required accuracy. This accuracy needs to be confirmed by valid calibration documentation in accordance with the applicable standards (see e.g. EN 14180:2003, Annex C).

C.9.1.3 Documented results of type testing or production testing (in accordance with EN 14180) can be used as additional data for qualification providing these results were obtained under a specified quality system.

C.9.2 Installation qualification (IQ)

C.9.2.1 establish and document purchase, design and installation requirements. As soon as installation permits, the established construction and installation should be assessed, and it should be verified that the written requirements are met.

This verification should focus on those properties that might be affected by improper production, delivery and installation, including at least:

— unique identification and complete labelling of the equipment (see EN 14180:2003, Clause 8);

— availability of the documentation to be provided by the supplier (see EN 14180:2003, Clause 9);

— completeness of the installation including all functional components and ancillary items;

— provision and proper supply of all services as specified in Clause 10 of EN 14180:2003. Special attention should be taken to the quality of water and of the microbicidal solution supplied:

— installation site facilities and provisions as required by safety or environmental aspects in accordance with 10.8 of EN 14180:2003 and, if applicable, by European Directives and national legislation.

C.9.2.2 IQ should be documented. Reference should be made to existing documentation.

C.9.2.3 IQ should be reviewed and approved by a designated person prior to operational qualification of the equipment.

C.9.3 Operational qualification (OQ)

C.9.3.1 OQ consists of documented testing of the equipment over its defined and installed operating range to verify consistent operation.

C.9.3.2 To perform OQ, standardized test procedures, test equipment, test loads, indicators and test cycles should be applied (see e.g. EN 14180:2003, Annexes A, C and Table B.1).

C.9.3.3 Prior to OQ calibration of all instrumentation used for process control, monitoring, indication and recording should be performed in order to confirm adjustment as specified. If adjustment has already been confirmed recently (within a justified time span) and has been properly documented, e.g. in the course of final production tests or routine maintenance, full recalibration may be replaced by spot checks.

C.9.3.4 At least the following tests should be part of the OQ:

— vacuum leak test;

— check of all essential functions of the sterilizer;

— temperature measurement of the empty chamber walls as preheating test;

— pressure and temperature profile tests of the usable space including the reference measuring point (small or full load);

— verification of air removal and sterilant penetration by use of suitable process challenge devices with specified indicators as part of the load;

— microbiological test (small or full load);

— desorption test (small load);

— drying test (small or full load).

Evaluation of the test results should verify that the relevant process parameters and process control switch points are within the limits specified by the manufacturer.

These tests should be performed in combination in order to reduce overall time, effort and environmental burden.

C.9.3.5 In order to fulfil the requirements in 9.3.4 the quality of steam and reproducibility of the supply of the sterilant to the process in sufficient amount should be verified. Information that can be used for this purpose includes, but may not be limited to:

— temperature and pressure profiles,

— information delivered by the process control and monitoring system, and

— amount of microbicidal solution used.

C.9.3.6 OQ should also include verification and functional checks that the process monitoring system is functioning properly.

C.9.3.7 Built-in alarm and other safety functions should be verified.

C.9.3.8 OQ should be documented and then reviewed and approved by a designated person prior to performance qualification of the process.

C.9.4 Performance qualification (PQ)

C.9.4.1 When product used for PQ is presented to sterilization and packaged equivalent to the most challenging load configuration in compliance with the instructions for use, any less challenging load configuration is considered to be validated as well (See B.2.4).

C.9.4.2 Foreseeable changes in product or process in routine production should be considered when defining the most challenging conditions to be tested in PQ. Otherwise change control will become applicable, see C.12.1.

C.9.4.3 In order to demonstrate reproducibility for a specific sterilization cycle, at least three runs of that cycle should be performed with product as load. Variation in load size and load configuration for these runs may allow a better assurance of reproducibility. In each of these runs all cycle parameters should be measured and demonstrated to be within their specified tolerances. Between these runs other sterilization cycles could be run, but not the specific cycle under study.

C.9.4.4 At least the following tests should be part of the PQ:

— pressure and temperature profile tests;

— verification of air removal and sterilant penetration capability of the process e.g. by use of suitable process challenge devices with specified indicators as part of the load;

— microbiological tests;

— drying test;

— desorption test.

As far as possible these tests may be performed in combination to reduce overall time, effort and environmental burden.

C.9.4.5 Microbiological PQ tests

See Annex B. Annex A is a possible alternative mainly for industrial use.

C.9.4.6 Desorption PQ tests

When widely varying loads occur in normal use it could raise practical difficulties to evaluate residues for each load. One possible method of evaluation is:

a) identify worst case load with regard to desorption;

The type of material of products, the type of wrapping material and the number of layers of wrapping material influence desorption efficacy.

b) select a residues challenge device and verify that the retention characteristics of the residues challenge device is at least as high as the worst case load items (see also 7.8);

This can be done either by referring to existing data/information or performing comparative testing.

A medical device itself may serve as a residue challenge device.

The disposal and handling of chemicals and indicators used at sterilization process development should be considered.

C.9.5 Documentation and approval of validation

C.9.5.1 The validation report summarizes the results of IQ, OQ and PQ. The report includes a critical review of the results and provides evidence for acceptability.

C.9.5.2 The report should confirm at least that:

— the sterilizer to be used for routine production is identified, installed and connected to services in accordance with the specifications, it is calibrated, tested and delivers the defined sterilization process as well as removal of the sterilant below required levels for residues after sterilization;

— the product range, loading configurations, loading equipment to be used, as well as material and kind of wrapping is identified and the appropriate sterilization processes are stated;

— defined sterilizing conditions have been attained in product or test load;

— the sterilization process parameters (including their tolerances) and the parameters governing the supply of sterilant to the process are identified and stated, and that these ensure minimum microbicidal efficacy for the defined sterilization conditions at the product.

C.9.5.3 The report should further provide or refer to requirements or statements on:

— provisions for recording routine monitoring and control parameters of the process;

— criteria or parameters (including their tolerances) that are to be used to justify release of the product;

— routine tests using physical, chemical or biological indicators or procedures to be performed to establish continuing reproducibility of the sterilization process;

— criteria for repeating of IQ, OQ, PQ or parts thereof (requalification).

C.9.5.4 This validation report should be duly signed by the person(s) responsible for performing the validation program and release of the report as well as by the person(s) designated in the quality system of the product manufacturer/hospital to approve the validation report. This report may become subject to inspection and conformity assessment by the manufacturer's Notified Body or governmental authorities.

C.10 Routine monitoring and control

Routine monitoring and control of LTSF sterilization processes is based primarily on measurements of time, temperature, pressure and the conditions for the supply of the sterilizing agent. EN 14180 gives adequate information on the minimum monitoring and control systems for LTSF-sterilizers. Supplementing these measurements by the use of biological or chemical indicators may be needed if not all critical process parameters for sterilization can be adequately controlled and monitored.

Procedures for routine monitoring and control are required to ensure that the process parameters of the sterilization cycle are within limits specified by the manufacturer and verified during the performance qualification. These procedures should include the tests and checks (e.g. leak test), and the frequency with which these tests and checks should be performed. The appropriateness of any process challenge devices that are used and their locations should be demonstrated.