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

Stérilisation des produits de santé — 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

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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

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

This second edition cancels and replaces the first edition (ISO 25424:2009), which has been technically revised. The main changes compared to the previous edition are as follows:

— alignment with EN 14180:2014;

— alignment with ISO 14937:2009;

— alignment of definitions with ISO 11139:2018;

— addition of relevant literature.

Any feedback or questions on this document should be directed to the user’s national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

A sterile medical device is one that is free of viable microorganisms. International Standards that specify requirements for validation and routine control of sterilization processes require, when it is necessary to supply a sterile medical device, that adventitious microbiological contamination of a medical device prior to sterilization be minimized. Even so, medical devices produced under standard manufacturing conditions in accordance with the requirements for quality management systems (see, for example, ISO 13485) could, prior to sterilization, have microorganisms on them, albeit in low numbers. Such medical devices are non-sterile. The purpose of sterilization is to inactivate the microbiological contaminants and thereby transform the nonsterile medical devices into sterile ones.

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

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

Generic requirements of the quality management system for design and development, production, installation and servicing are given in ISO 9001 and particular requirements for quality management systems for medical device production are given in ISO 13485. The standards for quality management systems recognise that, for certain processes used in manufacturing, the effectiveness of the process cannot be fully verified by subsequent inspection and testing of the product. Sterilization is an example of such a process. For this reason, sterilization processes are validated for use, the performance of the sterilization process is monitored routinely and the equipment is maintained.

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

a) the microbiological status of incoming raw materials and/or components;

b) the validation and routine control of any cleaning and disinfection procedures used on the medical device;

c) the control of the environment in which the medical device is manufactured, assembled and packaged;

d) the control of equipment and processes;

e) the control of personnel and their hygiene;

f) the manner and materials in which the medical device is packaged;

g) the conditions under which the medical device is stored.

The type of contamination on a medical device to be sterilized varies, and this influences the effectiveness of a sterilization process. Medical devices that have been used in a health care setting and that are being presented for resterilization in accordance with the manufacturer's instructions

(see ISO 17664) should be regarded as special cases. There is the potential for such medical devices to possess a wide range of contaminating microorganisms and residual inorganic and/or organic contamination in spite of the application of a cleaning process. Hence, particular attention has to be given to the validation and control of the cleaning and disinfection processes used during reprocessing.

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

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 document have been grouped together and are presented in a particular order, this document does not require that the activities be performed in the order that they are presented. The activities required are not necessarily sequential, as the programme of development and validation can be iterative. The responsibility for carrying out the activities required by this document will vary from case to case. This document requires that the responsibilities of the various parties be defined (see 4.3) but does not specify to whom the responsibilities are allocated. Annex C provides guidance on allocation of responsibility.

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

Sterilization of health care products — 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 document specifies requirements for the development, validation and routine control of a low temperature steam and formaldehyde (LTSF) sterilization process for medical devices using a mixture of low temperature steam and formaldehyde as sterilizing agent and which operates below ambient pressure.

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

1.1.2 This document 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 ISO 14937:2009, Table E.1).

1.2 Exclusions

1.2.1 This document does not specify requirements for the 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 ISO 22442-1, ISO 22442-2 and ISO 22442-3.

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

1.2.3 This document 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 document 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 ISO 13485) that control all stages of production or reprocessing of medical devices including the sterilization process. Further guidance is given in E.4 of ISO 14937:2009.

1.2.4 This document 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 IEC 61010-2-040.

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

1.2.5 This document 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 regulations specifying limits for the level of formaldehyde residues on medical devices and products.

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

NOTE For reprocessable medical devices, the manufacturer(s) of these devices can supply information on the preparatory measures (see ISO 17664).

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 11138-1, *Sterilization of health care products — Biological indicators — Part 1: General requirements*

ISO 11138-5:2017, *Sterilization of health care products — Biological indicators — Part 5: Biological indicators for low-temperature steam and formaldehyde sterilization processes*

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

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

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

3 Terms and definitions

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

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at https://www.electropedia.org/

— ISO Online browsing platform: available at https://www.iso.org/obp

3.1
bioburden
population of viable microorganisms on or in *product* (3.25) and/or sterile barrier system

[SOURCE: ISO 11139:2018, 3.23]

3.2
biological indicator
BI
test system containing viable microorganisms providing a specified resistance to a specified *sterilization process* (3.39)

[SOURCE: ISO 11139:2018, 3.29, modified — "BI" has been added.]

3.3
calibration
operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by the measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication

[SOURCE: ISO/IEC Guide 99:2007, 2.39, modified — The notes to entry have been deleted.]

3.4
change control
assessment and determination of the appropriateness of a proposed alteration to *product* (3.25), process or equipment

[SOURCE: ISO 11139:2018, 3.39]

3.5
chemical indicator
test system that reveals change in one or more pre-defined *process variables* (3.24) based on a chemical or physical change resulting from exposure to a process

Note 1 to entry: An indicator intended to be used only in combination with a specific test load is also termed an indicator (both together becoming an indicator system).

[SOURCE: ISO 11139:2018, 3.43, modified — Note 1 to entry has been added.]

3.6
conditioning
treatment of *product* (3.25) prior to the *exposure phase* (3.10) to attain a specified temperature, relative humidity, or other *process variable* (3.24) throughout the *load* (3.16)

[SOURCE: ISO 11139:2018, 3.58]

3.7
desorption
removal of the *sterilizing agent* (3.40) from the chamber and the *load* (3.16) at the end of the *exposure phase* (3.10)

[SOURCE: ISO 11139:2018, 3.78]

3.8
***D* value**
D_{10} value
time or dose required under stated conditions to achieve inactivation of 90 % of a population of the test microorganisms

Note 1 to entry: For LTSF *sterilization* (3.37) the *D* value is given in minutes.

[SOURCE: ISO 11139:2018, 3.75, modified — Note 1 to entry has been added]

3.9
establish
determine by theoretical evaluation and confirm by experimentation

[SOURCE: ISO 11139:2018, 3.107]

3.10
exposure phase
cycle stage between the introduction of the sterilizing or disinfecting agent into the chamber and when the agent is removed

[SOURCE: ISO 11139:2018, 3.111]

3.11
fault
situation in which one or more of the process or cycle parameters is/are outside its/their specified tolerance(s)

[SOURCE: ISO 11139:2018, 3.116]

3.12
F_{BIO} value
expression of the resistance of a *biological indicator* (3.2) calculated as the product of the logarithm of the initial population of microorganisms and the *D value* (3.8)

Note 1 to entry: The F_{BIO} value can be used to express the "total resistance" of the biological indicator.

[SOURCE: ISO 11139:2018, 3.113.2, modified — Note 1 to entry has been added.]

3.13
holding time
period during which *process parameters* (3.23) are maintained, within their specified tolerances

[SOURCE: ISO 11139:2018, 3.133]

3.14
inoculated carrier
supporting material on or in which a specified number of viable test microorganisms has been deposited

[SOURCE: ISO 11139:2018, 3.144]

3.15
installation qualification
IQ
process of *establishing* (3.9) by objective evidence that all key aspects of the process equipment and ancillary system installation comply with the approved specification

[SOURCE: ISO 11139:2018, 3.220.2]

3.16
load
product (3.25), equipment or materials to be processed together within an operating cycle

[SOURCE: ISO 11139:2018, 3.155]

3.17
LTSF-equilibration time
period which elapses between the attainment of the sterilization temperature at the *reference measurement point* (3.27) and the attainment of the sterilization temperature at all points within the *load* (3.16)

[SOURCE: EN 14180:2014, 3.18]

3.18
medical device
instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use or calibrator, software, material or other similar related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific medical 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 by means of *in vitro* examination of specimens derived from the human body;

and does not achieve its primary intended action by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

Note 1 to entry: Products which can be considered to be medical devices in some jurisdictions, but not in others include:

— items specifically intended for cleaning or *sterilization* (3.37) of medical devices;

— pouches, reel goods, sterilization wrap, and reusable containers for packaging of medical devices for sterilization;

— disinfection substances;

— aids for persons with disabilities;

— devices incorporating animal and/or human tissues;

— devices for *in vitro* fertilization or assisted reproduction technologies.

[SOURCE: ISO 13485:2016, 3.11, modified — The first two list items in Note 1 to entry have been added.]

3.19
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[SOURCE: ISO 11139:2018, 3.220.3]

3.20
parametric release
declaration that *product* (3.25) is *sterile* (3.35) based on records demonstrating that the *process variables* (3.24) were delivered within specified tolerances

[SOURCE: ISO 11139:2018, 3.193]

3.21
performance qualification
PQ
process of *establishing* (3.9) by objective evidence that the process, under anticipated conditions, consistently produces a *product* (3.25) which meets all predetermined requirements

[SOURCE: ISO 11139:2018, 3.220.4]

3.22
process challenge device
PCD
item providing a defined resistance to a cleaning, disinfection, or *sterilization process* (3.39) and used to assess performance of the process

Note 1 to entry: The device is so constituted that a biological or *chemical indicator* (3.5) can be put in the place which is the most difficult to reach by *sterilizing agent(s)* (3.40) and does not interfere with the function of the process challenge device.

[SOURCE: ISO 11139:2018, 3.205, modified — Note 1 to entry has been added.]

3.23
process parameter
specified value for a *process variable* (3.24)

Note 1 to entry: The specification for a process includes the process parameters and their tolerances

[SOURCE: ISO 11139:2018, 3.211]

3.24
process variable
chemical or physical attribute within a cleaning, disinfection, packaging, or *sterilization process* (3.39), changes in which can alter its effectiveness

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

[SOURCE: ISO 11139:2018, 3.213]

3.25
product
tangible result of a process

EXAMPLE Raw material(s), intermediate(s), sub-assembly(ies), health care product(s).

[SOURCE: ISO 11139:2018, 3.217]

3.26
recognized culture collection
depository authority under the Budapest Treaty on *The International Recognition of the Deposit of Microorganisms for the Purposes of Patent and Regulation*

[SOURCE: ISO 11139:2018, 3.222]

3.27
reference measurement point
location of the sensor controlling the operating cycle

[SOURCE: ISO 11139:2018, 3.227]

3.28
reference microorganism
microbial strain obtained from a *recognized culture collection* (3.26)

[SOURCE: ISO 11139:2018, 3.228]

3.29
requalification
repetition of part or all of *validation* (3.42) for the purpose of confirming the continued acceptability of a specified process

[SOURCE: ISO 11139:2018, 3.220.5]

3.30
residues challenge device
item used to assess the effectiveness of *desorption* (3.7)

[SOURCE: ISO 11139:2018, 3.232]

3.31
services
supplies from an external source needed for the function of equipment

[SOURCE: ISO 11139:2018, 3.252]

3.32
specify
stipulate in detail within an approved document

[SOURCE: ISO 11139:2018, 3.259]

3.33
sterilant
chemical or combination of chemicals used to generate a *sterilizing agent* (3.40)

Note 1 to entry: The sterilant usually contains stabilizers, e.g. alcohols.

[SOURCE: ISO 11139:2018, 3.268, modified — Note 1 to entry has been added.]

3.34
sterilant/sterilizing agent injection
introduction of sterilant/sterilizing agent into the evacuated chamber until the set operating pressure has been attained or the specified quantity of sterilant/sterilizing agent has been delivered

[SOURCE: ISO 11139:2018, 3.269]

3.35
sterile
free from viable microorganisms

[SOURCE: ISO 11139:2018, 3.271]

3.36
sterility
state of being free from viable microorganisms

Note 1 to entry: In practice, no such absolute statement regarding the absence of microorganisms can be proven.

[SOURCE: ISO 11139:2018, 3.274, modified — Note 1 to entry has been added.]

3.37
sterilization
process used to render *product* (3.25) free from viable microorganisms

Note 1 to entry: In a *sterilization process* (3.39), 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.

[SOURCE: ISO 11139:2018, 3.277]

3.38
sterilization cycle
predetermined sequence of stages performed in a sterilizer to achieve *product* (3.25) free of viable microorganisms

[SOURCE: ISO 11139:2018, 3.279]

3.39
sterilization process
series of actions or operations needed to achieve the specified requirements for *sterility* (3.36)

Note 1 to entry: This series of actions includes pre-treatment of *product* (3.25) (if necessary), exposure under defined conditions to the *sterilizing agent* (3.40) and any necessary post treatment. The sterilization process does not include any cleaning, disinfection or packaging operations that precede sterilization.

[SOURCE: ISO 11139:2018, 3.284]

3.40
sterilizing agent
physical or chemical entity, or combination of entities, having sufficient microbicidal activity to achieve *sterility* (3.36) under defined conditions

[SOURCE: ISO 11139:2018, 3.288]

3.41
inactivation curve
graphical representation of inactivation of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions

[SOURCE: ISO 11139:2018, 3.137]

3.42
validation
confirmation process, through the provision of objective evidence that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The objective evidence needed for a validation is the result of a test or other form of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The word "validated" is used to designate the corresponding status.

Note 3 to entry: The use conditions for validation can be real or simulated.

[SOURCE: ISO 9000:2015, 3.8.13, modified — "process" has been added to the definition.]

4 Quality management system elements

4.1 General

To ensure the consistent quality of the processes described in this document, the implementation of a quality management system, such as ISO 13485, is advised.

Although a management system needs to be considered as a whole, the following elements should be regarded as indispensable: documentation, management responsibility, product realization, control of non-conforming product.

4.2 Documentation

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

4.2.2 Documents and records required by this document shall be reviewed and approved by designated personnel (see 4.3.1). Documents and records shall be controlled in accordance with an established quality management system, such as ISO 13485.

4.3 Management responsibility

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

4.3.2 If the requirements of this document are undertaken by different organizations with separate quality management systems, the responsibilities and authority of each party shall be specified.

4.4 Product realization

4.4.1 Procedures for purchasing shall be specified. These procedures shall conform to an established quality management system, such as ISO 13485.

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

NOTE ISO 13485 details requirements for design reviews.

4.4.3 Procedures conforming to established quality management system such as ISO 13485 shall be specified for the calibration or adjustment of equipment, including instrumentation for test purposes used in meeting the requirements of this document.

4.5 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 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 are well known after decades of practical use and development[22][23][24][25][26][31]. Development of new processes can 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 ISO 13485).

5.2 Sterilizing agent

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

NOTE 1 For further guidance see EN 14180:2014, 10.3.

NOTE 2 The LTSF-sterilization process is a modified steam sterilization process[26]. A formaldehyde solution (sterilant) 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 the literature[22][23][24][25][31][32].

NOTE Manufacturers of sterilizers can be requested to make 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 (see, for example, References [19], [20], [21], [28], [29] and [30]). However, when new materials are introduced, the effects of sterilizing agent exposure with respect to material compatibility and formaldehyde residue levels after processing shall be assessed (repeated when applicable) and documented (see also 7.4, 7.5 and 7.8).

NOTE The manufacturer of the sterilizer or of the product can be requested to supply information about any restriction or limitation of application of the process on specific product with respect to product integrity and residue levels of sterilizing agent (see also ISO 17664).

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 also Annex D.

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

NOTE Minimum requirements for LTSF-sterilizers can be found in EN 14180:2014, 6.1.

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

NOTE See EN 14180:2014, 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 product.

NOTE See EN 14180:2014, 10.4.

6.2.4 Any treatment of product that is 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.

NOTE Minimum requirements for the performance of the desorption and drying phase of the cycle can be found in EN 14180:2014, 6.2 and 6.3.

6.2.5 The sterilization cycle shall include:

a) air removal;

b) conditioning;

NOTE Conditioning can be carried out fully using sterilizing agent.

c) sterilant injection;

d) LTSF-equilibration time and holding time;

e) desorption;

f) air admission to atmospheric pressure.

NOTE For further information, see EN 14180:2014, 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;

— other related items specified as provided with the sterilizer.

NOTE EN 14180:2014, Clause 9, specifies information to be supplied by the manufacturer of the sterilizer.

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 process shall be prepared in accordance with a quality management system that provides documented evidence (see 4.2.2) that the software meets its design intention.

NOTE Attention is drawn to ISO/IEC 90003.

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 can 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 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 sterilizing agent. 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[28][29][30].

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

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

7.7 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 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 can also include an assessment of any organic and inorganic contamination.

NOTE The ISO 15883 series on equipment for cleaning and disinfecting medical devices prior to sterilization includes 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.

NOTE 1 EN 14180:2014, C.5, specifies the desorption efficacy indicator as a paper disc.

The results evaluation shall consider the available toxicological data.

NOTE 2 EN 14180:2014, Annex E., specifies a limit.

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 the process provides less lethality than the intended sterilization process to defined product as described in Annex A.

NOTE Procedure b) can only be used under experimental conditions during the development of a novel LTSF sterilization process.

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

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

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

NOTE For disposal of biological indicators instructions provided by its manufacturer can be applied.

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

NOTE For disposal of chemical indicators, refer to instructions provided by the manufacturer.

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

8.6 Sterilization process establishment shall include methods to bring residual levels in product down to acceptable levels. 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 can affect the residue levels.

NOTE 2 EN 14180:2014, 6.2, specifies an acceptable level.

NOTE 3 The disposal and handling of chemicals and indicators are aspects to be considered during sterilization process development.

8.7 Product shall meet its specified requirements for safety, quality and performance after being subjected to the most challenging combination of 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 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 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 EN 14180:2014, Annex C, 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 4.4.3).

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. Any special precautions and provisions shall be identified (for example, safety equipment).

NOTE EN 14180:2014, Clause 10, provides information on services required.

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 sterilant 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 conformity of the sterilizer and any ancillary items to specification shall be verified.

NOTE Requirements for the information to be provided are specified in EN 14180:2014, Clause 9, and for marking and labelling in EN 14180:2014, Clause 8.

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 can 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 in an empty chamber or using specified test loads and shall demonstrate that the installed equipment is capable of delivering the sterilization process within defined tolerances (see C.9.3.3).

NOTE The disposal and handling of chemicals and indicators used at sterilization process development could require specific consideration.

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 programme. The programme shall define requirements to be verified (see 6.2.1 and 6.3.2), test equipment and procedures, and acceptance criteria.

NOTE 1 Guidance for a test programme is given in EN 14180:2014, Table B.1. Specifications for suitable test loads and test procedures for operational qualification tests are given in EN 14180:2014, Annex A.

NOTE 2 These tests can 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 sterilizing agent within the established values and tolerances stated by the manufacturer shall be verified.

NOTE For further guidance, see C.9.3.4.

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 programme. The programme 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, used to generate the sterilizing agent,

— air removal and sterilizing agent penetration,

— desorption of sterilizing agent,

— sterile barrier systems, and

— 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 C.9.4.1).

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

NOTE If failure can be attributed to factors not relevant to the effectiveness of the process being validated, this test can 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 ISO 11140-1.

NOTE For disposal of chemical indicators, refer to instructions provided by the 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 EN 14180:2014, A.3.2, and for pressure profile test EN 14180:2014, A.3.4, can be used for guidance.

9.4.2.2 Reproducibility of the supply, control and monitoring of sterilizing agent within the established values and tolerances stated by the manufacturer shall be verified.

NOTE For further guidance, see C.9.3.4.

Results from operational qualification (see 9.3) may be used for this verification. The rationale for the use of operational qualification results 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. EN 14180:2014, Table B.1, can be used for guidance.

NOTE 3 For disposal of biological indicators, refer to instructions provided by the 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 Methods for residues evaluation are given in EN 14180:2014, Annexes A, D and E.

9.4.4.2 Drying

Drying performance shall be verified by visual inspection.

NOTE The test is intended to verify that no part of the sterile barrier system in the sterilized load is wet when unloading, and that any remaining water droplets of the inner side of the sterile barrier system are evaporated within 5 min (see also EN 14180:2014, 6.3).

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 4.2.2). 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) sterilizing agent exposure data as declared by the sterilizer manufacturer to govern the generation and supply of sterilizing agent to the chamber, e.g.
   - the amount of sterilant used,
   - the chamber pressure versus time profile,
   - the chamber and load temperature, and
   - 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;

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.

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.

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 ISO 11138-5:2017, Clauses 5 and 9. The number of indicators and the use of process challenge devices (PCDs) shall be justified and documented. The results of testing shall be documented.

NOTE 1 Attention is drawn to EN 867-5 specifying a hollow-load PCD.

NOTE 2 For disposal of biological indicators instructions provided by its manufacturer can be applied.

10.3 Chemical indicators

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

NOTE 1 Ineffective desorption can affect the performance of chemical indicators.

NOTE 2 For disposal of chemical indicators, refer to instructions provided by the manufacturer.

10.4 Records

10.4.1 All records related to 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 sterilizing agent or consumption of sterilant.

11 Product release from sterilization

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

a) conformity of the process parameters to the sterilization process specification (see 6.2 and 8.8),

b) if BIs or PCDs containing BIs are used as part of product release, complete colour change of these (see 8.4 and 10.3),

c) if BIs are used as a part of product release, acceptable results from culture of these (see 8.3 and 10.2), and

d) any other indication specified by the manufacturer of the sterilizer (see 6.2, 6.3, 8.3 and 8.4).

NOTE Sterilizers in conformity with EN 14180 are deemed to allow parametric release.

11.2 Product shall be considered as non-conforming and handled in accordance with documented procedures (see 4.5) if any of the criteria for designating conformity 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 4.4.3.

12.2 Maintenance of equipment

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

NOTE EN 14180:2014, in 9.2 and 9.5, specifies data that can be used 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 4.2.2).

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 can 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 4.2.2).

12.3.3 Requalification data shall be reviewed against specified acceptance criteria in accordance with documented procedures. Records shall be retained (see 4.2.2) 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 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, PCD, 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. As indicated in 8.3, this packed, inoculated product shall meet the requirements of ISO 11138-1.

NOTE 1 For disposal of biological test material, refer to instructions provided by the manufacturer.

Pack the challenge, created in accordance with the list above, in the same manner as products produced routinely and included within the load. Expose the 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 inactivation curve test method as described in 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 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 can 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 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, and

— 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 health care 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 sterilizing agent 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.

If biological indicators cannot be located in product at positions determined to be the most difficult to achieve sterilizing conditions, then it might be necessary to inoculate these locations with a suspension of the reference microorganism (see B.2.2). The retrieval and recovery processes for the BIs and reference microorganism shall be validated. Alternatively, a PCD containing BIs that conforms with the requirements in B.2.2 can be used. The PCD shall present a challenge to the sterilization process that is equivalent to or greater than the challenge presented by the natural bioburden at the most difficult to sterilize location within the product. Furthermore, the sterile barrier system shall be considered, as the sterile barrier system can obstruct penetration of the sterilizing agent, 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

An F_{BIO} value of (33 ± 3) min at 60 °C for the 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 ISO 11138-5.

B.2.3 Test systems

Define the most difficult penetration location in accordance with B.1.2

— if feasible, put a BI at this location,

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

NOTE Hollow load PCDs in accordance with EN 867-5 are considered suitable.

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

Package these test systems in the same manner as the products sterilized routinely and include them within the 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 used to generate sterilizing agent,

— air removal,

— sterile barrier systems, and

— 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 BIs that conform with B.2.2. Place the BIs in accordance with B.2.3 and distribute in sufficient numbers throughout the load to achieve statistically valid data to demonstrate the required microbicidal lethality 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 and check the biological indicators for growth. For culturing BI, follow the specific procedures described in ISO 11138-5.

No surviving microbiological indicators shall be detected.

For disposal of biological indicators, refer to instructions provided by the manufacturer.

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

Annex C
(informative)

Guidance on application of this document

NOTE 1 The guidance given in this annex is not intended as a checklist for assessing conformity with this document. This guidance is intended to assist a uniform understanding and implementation of this document, by providing explanations and acceptable methods for achieving conformity with specified requirements. It highlights important aspects and provides examples. Methods other than those given in the guidance can be used, providing their performance achieves conformity with this document.

NOTE 2 The main headings in this annex follow the chapter headlines and numbering in the main document. Below the main headings the subheadings and their numbering are not consistent with the subheadings and the numbering in the main document.

C.1 Scope

No guidance offered.

C.2 Normative references

No guidance offered.

C.3 Terms and definitions

No guidance offered.

C.4 Quality management system elements

Reference is made to ISO 14937:2009, E.4.

C.5 Sterilizing agent characterization

C.5.1 General

No guidance offered.

C.5.2 Sterilizing agent

Formaldehyde in aqueous solution has been demonstrated to have a high level of antimicrobial activity. In LTSF sterilizers, a formaldehyde solution (sterilant) 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 is achieved and microbial inactivation can already start. 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.5.3 Microbicidal effectiveness sterilizing agent

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. Semi-logarithmic plots of microbial counts versus exposure time are linear, providing there is proper air removal and sterilizing agent penetration of the product to be sterilized, and the temperature and formaldehyde concentration at product surfaces are constant. This makes it possible to define the kinetics of the microbial inactivation and to calculate the theoretical probability of a microorganism surviving.

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 EN 14180:2014, 6.2). Further reduction is needed prior to incubation and is achieved by use of neutralizing chemical agents and the procedures described in ISO 11138-5:2017, A.3.

Studies on defined and reproducible sterilizing agent generation and sterilizing agent characterization can 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, should be identified.

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.

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

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

For biological indicators for use with LTSF sterilization, reference is made to ISO 11138-5 and B.2.2.

Guidance on development of microbiological test methods and their validation can be found in ISO 11737-1 and ISO 11737–2.

C.5.4 Material effects

No guidance offered.

C.5.5 Environmental considerations

No guidance offered.

C.6 Process and equipment characterization

No guidance offered.

C.7 Product definition

C.7.1 The LTSF sterilization process can adversely affect the integrity of medical devices and their packages. These effects should be evaluated.

Some design characteristics of the product can 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. According to ISO 17664, information about suitable packaging and sterilization processes of the product have to be provided.

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.7.1.1 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 No guidance offered.

C.7.3 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 an unacceptable effect (e.g. absorption and/or chemical reaction) on overall product quality. Packaging considerations are addressed in more detail in the ISO 11607 series and the EN 868 series.

C.7.4 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.

C.7.5 The effects of multiple exposures to the sterilization process should be studied and evaluated. When necessary, the maximum allowable number of exposures should be stated.

C.7.6 No guidance offered.

C.7.7 No guidance offered.

C.7.8 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.

The biocompatibility of materials after exposure to the sterilization process should be assessed.

C.8 Process definition

C.8.1 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 From the range of values for the process variables studied in 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 an inactivation curve, which is extrapolated to enable the process to be fully defined. The form of the inactivation curve can be different from that observed during earlier characterization studies. For instance, the inactivation curve observed during characterization can 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 might not be fully achieved at the 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.

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.

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 *Geobacillus stearothermophilus* has been identified as a suitable microorganism for testing LTSF-sterilizers (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.

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 the 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.8.4 No guidance offered.

C.8.5 No guidance offered.

C.8.6 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[19][20][21].

C.8.7 No guidance offered.

C.8.8 No guidance offered.

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.

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.9.1.2 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, for example, EN 14180:2014, Annex C).

C.9.1.3 No guidance offered.

C.9.1.4 No guidance offered.

C.9.2 Installation qualification (IQ)

C.9.2.1 IQ should be based on written requirements and valid certifications. The first step for new equipment is to 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.

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

C.9.2.2 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;

— availability of the documentation to be provided by the supplier;

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

— provision and proper supply of all services as specified. Special attention should be paid to the quality of water and of the sterilant supplied;

— installation site facilities and provisions as required by safety or environmental aspects in accordance with the specification.

NOTE EN 14180:2014, Clauses 8, 9 and 10 provide specifications which can be used to verify the above listed items.

C.9.2.3 No guidance offered.

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. To perform OQ, standardized test procedures, test equipment,

test loads, indicators and test cycles should be applied (see e.g. EN 14180:2014, Annexes A and C and Table B.1).

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

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

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

C.9.3.2 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 can be replaced by spot checks.

C.9.3.3 At least the following tests could be part of the OQ:

— vacuum leak test;

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

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

— verification of air removal and sterilizing agent 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.9.3.4 The quality of steam and reproducibility of the supply of the sterilizing agent 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 sterilant used.

C.9.4 Performance qualification (PQ)

C.9.4.1 General

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).

At least the following tests should be part of the PQ:

— pressure and temperature profile tests;

— verification of air removal and sterilizing agent 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 can be performed in combination to reduce overall time, effort and environmental burden.

C.9.4.2 Performance qualification — Physical

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.

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 can 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.9.4.3 Performance qualification — Microbiological

No guidance offered.

C.9.4.4 Performance qualification — Desorption and drying

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 sterile barrier system material and the number of layers of sterile barrier system 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 can serve as a residue challenge device.

The disposal and handling of chemicals and indicators used in 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 sterilizing agent below required levels for residues after sterilization;

— the product range, loading configurations, loading equipment to be used, as well as material and kind of sterile barrier system 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 sterilizing agent 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, and

— 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 programme 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 can become subject to inspection and conformity assessment by the manufacturer's notified body or governmental authorities.

C.10 Routine monitoring and control

C.10.1 General

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 can 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.

C.10.2 Biological indicators

No guidance offered.

C.10.3 Chemical indicators

No guidance offered.

C.10.4 Records

No guidance offered.

C.11 Product release from sterilization

C.11.1 Information on the suitability of the product and packaging for resterilization, and the effect of repeated exposures to the sterilization process on product functionality should be available (see ISO 17664). If product is sterilized again because the initial exposure to the sterilization process was outside its specification, records of the initial sterilization process should be included or referenced in the records of the subsequent sterilization process for that product.

If biological indicators are to be used in product release, records of the physical sterilization process parameters and results of indicator testing are reviewed to demonstrate the efficacy of the sterilization process. Consequently, product should only be released after the biological indicators show no growth. Guidance on use and interpretation of results of biological indicators is given in ISO 14161.

C.11.2 Parametric release is the declaration of adequacy of sterilization of product based solely on the direct measurement and evaluation of physical parameters within the chamber and the load. Parametric release is considered a design aspect of a sterilization process that can be fully characterized.

The appropriateness of parametric release should be demonstrated during the development and validation of the sterilization process. For parametric release to be applicable, all process parameters have to be identified and their values known. Parametric release should be supported by extensive experience of the sterilization process. For LTSF, one of the most important requirements for parametric release is a full understanding and control of the concentration of the injected steam and formaldehyde mixture.

If a sterilization cycle operating within specified tolerances has been demonstrated to be both effective and reproducible during OQ and PQ, confirmation that all critical process parameters were within specification limits is taken as evidence of the reliability of the cycle.

C.11.3 Failure to conform to the specification for the process, or failure indicated by any biological or chemical indicator, should lead to the load being placed in quarantine and the cause of failure investigated. The investigation should be documented.

The product should be handled in accordance with non-conforming product procedures. The decision reached as to the disposition of the product should be documented.

C.12 Maintaining process effectiveness

C.12.1 General

No guidance offered.

C.12.2 Maintenance of equipment

No guidance offered.

C.12.3 Requalification

C.12.3.1 To guard against unreported or inadvertent changes, consideration should be given to periodic repetition of all or part of installation, operational and performance qualification. The interval between periodic requalifications should be determined by the nature of the sterilization process and by the amount of process data documented. The interval can be varied, taking into account historical data that demonstrate process reproducibility and conformity with established specifications for process

parameters. The decision to perform requalification can be event-related or time-related. Commonly, a requalification period of one year is considered to be adequate for health care facilities.

Typically, requalification would be performed for the most challenging load configuration defined in 9.4.1.4. However, if requalification detects a significant deviation from the previous performance qualification results, performance qualification should be performed again for all load configurations.

C.12.3.2 Previous validation and requalification results should be considered in establishing the requalification protocol. In general, single requalification cycles are considered sufficient.

C.12.3.3 Data from requalification should be compared with records of the original validation (and any subsequent requalification) to confirm that the specified performance has been retained. This comparison is facilitated by a common format for validation and requalification reports.

C.12.4 Assessment of change

A change control system should be employed to establish when operational or performance qualification testing or parts thereof should be repeated. Qualification is recommended if significant changes are made in the sterilization equipment (hardware or software), process, product or packaging, that could influence sterilization effectiveness. The following are examples (not necessarily all-inclusive) of changes that could necessitate performance qualification unless data are available to establish equivalency.

— Product tolerance: a change in the product material, assembly, construction or design tolerances that could affect attainment of sterilizing conditions. When a PCD is used for the process it should be verified to be applicable also for the changed product.

— Product design: significant change in product design including product materials composition that could influence the effectiveness of the sterilization process.

— Packaging: a change in packaging design that could significantly affect properties of the package and attainment of sterilizing conditions.

— Equipment: changes that could affect the ability to maintain specified process parameters or a modification to the sterilizing agent and/or its presentation.

— Process: alterations in the process that could substantially change the manner in which process parameters are achieved and controlled (e.g. changes in process control software).

— Product loading: changes in the previously validated loading configurations that could affect sterilizing agent penetration into the load (e.g. increasing the maximum load).

Annex D
(informative)

Environmental aspects regarding development, validation and routine control of low temperature steam and formaldehyde processes

D.1 General

Environmental aspects covered by this document are summarized in Table D.1.

D.2 Formaldehyde (brief description)

Formaldehyde is a colourless, toxic gas, highly soluble in water and commercially available as a 35 % solution called formalin. Formalin solution is a clear, colourless liquid, with a highly irritating smell and "burning" taste that effects mucous membranes.

In addition to its industrial use, formaldehyde solutions are used in medical environments for sterilization, autopsies, in surgical and pathology departments, and to some extent in dermatology and radiotherapy departments[27].

The fact that formaldehyde is highly soluble in water enables it to be diluted into suitable concentrations of sterilant to form an efficient sterilizing agent, as well as to dilute residuals in process water before disposal, into concentrations regarded as less harmful to the environment.

D.3 Environmental impact of formaldehyde

Formaldehyde represents the primary environmental burden caused by activities described in this document. Although formaldehyde is an unstable chemical compound and not enriched in the human body or nature, precautions should be considered to minimize effects of short and long-term exposure.

Formaldehyde occurs naturally in most living creatures and is a vital part of our ecology. Commercially formaldehyde is widely used in different materials. It is produced from methanol and is environmentally bio-degradable in accordance with the following formula chain:

CH_3OH(methanol) – HCHO(formaldehyde) – HCOOH(formic acid) – $CO_2 + H_2O$(carbon dioxide + water).

Formaldehyde solutions are known to be toxic, irritating and allergenic. They are also suspected to have carcinogenic effect on humans at long term exposure.

The low level of airborne concentration needed to detect formaldehyde at inhalation normally limits the possibility of unconscious exposure to harmful concentrations.

EXAMPLE

— 0,06 mg/m^3 can normally be smelled;

— 0,012 mg/m^3 to 0,15 mg/m^3 can irritate the eyes;

— 0,06 mg/m^3 to 0,15 mg/m^3 can irritate the nose;

— 0,6 mg/m^3 is regarded in some countries as a full-day working limit [i.e. maximum allowed concentration (MAC)];

— 1,2 mg/m^3 is regarded in some countries as a maximum level for 15 min;

— 4,8 mg/m^3 normally causes lachrymation.

National regulations can specify limits for the exposure of humans to airborne formaldehyde concentrations.

D.4 Other environmental burdens

Other essential environmental burdens caused by the activities described in this document include but cannot be limited to

— the use and disposal of other chemicals, e.g. at determination of residuals,

— the use and disposal of packaging material,

— the use and disposal of biological and chemical indicators, and

— the use of other resources, e.g. energy, water, etc.,

— exaggerated testing and use of resources caused by poor planning of validation.

Appropriate planning of the activities that are mentioned in this document minimizes the environmental burdens.

Table D.1 — Environmental aspects addressing clauses of this document

Environmental aspects (inputs and outputs)	Product life-cycle			
	Production and reproduction Stage A	Distribution (including packaging) Stage B	Use Stage C	End of life Stage D
	Addressed in clause	Addressed in clause	Addressed in clause	Addressed in clause
1 Resource use	Introduction 5.5 C.9.3.4 C.9.4.4	—	Introduction 5.5 C.9.3.4 C.9.4.4	1
2 Energy consumption	Introduction 5.5 C.9.3.4 C.9.4.4	—	Introduction 5.5 C.9.3.4 C.9.4.4	2
3 Emission to air	Introduction 5.1 5.5 6.3.3 8.6 9.3.1 9.3.3 9.4.2.2 C.9.3.4 C.9.4.4	—	Introduction 5.1 5.5 6.3.3 8.6 9.3.1 9.3.3 9.4.2.2 C.9.3.4 C.9.3.4	—

Table D.1 *(continued)*

Environmental aspects (inputs and outputs)	Product life-cycle			
	Production and reproduction Stage A	Distribution (including packaging) Stage B	Use Stage C	End of life Stage D
	Addressed in clause	Addressed in clause	Addressed in clause	Addressed in clause
4 Emission to water	Introduction 5.1 5.5 8.6 9.3.1 9.3.3 9.4.2.2 C.9.3.4 C.9.4.4	—	Introduction 5.1 5.5 8.6 9.3.1 9.3.3 9.4.2.2 C.9.3.4 C.9.4.4	—
5 Waste	Introduction 5.1 5.5 8.3 8.4 8.6 9.3.1 9.3.3 9.4.1.8 9.4.2.2 9.4.3 10.2 10.3 B.2.5.2	—	Introduction 5.1 5.5 8.3 8.4 8.6 9.3.1 9.3.3 9.4.1.8 9.4.2.2 9.4.3 10.2 10.3 B.2.5.2	—
6 Noise	—	—	—	—

Table D.1 *(continued)*

Environmental aspects (inputs and outputs)	Product life-cycle			
	Production and reproduction Stage A	Distribution (including packaging) Stage B	Use Stage C	End of life Stage D
	Addressed in clause	Addressed in clause	Addressed in clause	Addressed in clause
7 Migration of hazardous substances	Introduction 4.3.3 5.1 5.2 5.5 6.3.3 7.8 8.3 8.4 8.6 9.2.2.5 9.3.1 9.4.2.2 9.4.3 10.2 10.3 A.2 B.2.5.2 C.9.3.4 C.9.4.4	—	Introduction 4.3.3 5.1 5.2 5.5 6.3.3 7.8 8.3 8.4 8.6 9.2.2.5 9.3.1 9.4.2.2 9.4.3 10.2 10.3 A.2 B.2.5.2 C.9.3.4 C.9.4.4	—
8 Impacts on soil	5.5 8.6 9.3.1 9.3.3 9.4.2.2	—	5.5 8.6 9.3.1 9.3.3 9.4.2.2	—

Table D.1 *(continued)*

Environmental aspects (inputs and outputs)	Product life-cycle			
	Production and reproduction Stage A	Distribution (including packaging) Stage B	Use Stage C	End of life Stage D
	Addressed in clause	Addressed in clause	Addressed in clause	Addressed in clause
9 Risks to the environment from accidents or misuse	Introduction 4.3.3 5.1 5.2 5.5 6.1 6.2.4 6.3.3 7.8 8.6 9.2.2.3 9.3.1 C.9.3.4	—	Introduction 4.3.3 5.1 5.2 5.5 6.1 6.2.4 6.3.3 7.8 8.6 9.2.2.3 9.3.1 C.9.3.4	—

NOTE Clause references in the Stage A column are invariably repeated in the Stage C column, as this document requires testing procedures during both stages of the life cycle.

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