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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]

