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Sterilization of health care products — Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives — Requirements for characterization, development, validation and routine control of a sterilization process for medical devices

Stérilisation des produits de santé — Agents stérilisants chimiques liquides pour dispositifs médicaux non réutilisables utilisant des tissus animaux et leurs dérivés — Exigences pour la caractérisation, le développement, la validation et le contrôle de routine d'un procédé de stérilisation de 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 of 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 www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 204, *Sterilization of medical devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This third edition cancels and replaces the second edition (ISO 14160:2011), which has been technically revised.

The main changes compared to the previous edition are as follows:

— aligned definitions with those used in other standards for development, validation and routine control of sterilization processes and added new definitions;

— incorporated defined terms consistently throughout the document;

— updated cross-references;

— revised informative Annex A to follow the order of the normative body of the standard;

— added clarification to normative Annex B in regard to applying the overkill approach.

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 which 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) have microorganisms on them prior to sterilization, albeit in low numbers. The purpose of sterilization is to inactivate the microbiological contaminants and thereby transform the non-sterile 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 can generally best be described by an exponential relationship between the numbers of microorganisms surviving and the extent of treatment with the sterilizing agent; inevitably this means that there is always a finite probability that a microorganism 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 of items 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.

Attention also has to be given to a number of factors, including the microbiological status (bioburden) of incoming raw materials and/or components and their subsequent storage, and to the control of the environment in which the product is manufactured, assembled and packaged (see also ISO 13485).

Requirements for quality management systems for medical device production are given in ISO 13485. The standards for quality management systems recognize 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.

Animal tissues and their derivatives are used as constituents of certain medical devices to provide performance characteristics that present advantages over the characteristics provided by non-animal-based materials. The range and quantities of materials of animal origin in medical devices vary; such materials can comprise a major part of the device, can be a product coating or impregnation, or can be used in the manufacturing process for the medical device.

This document describes requirements that, if met, will provide a liquid chemical sterilization process that has appropriate microbicidal activity for single-use medical devices containing materials of animal origin or their derivatives. The sterilizing agents used most frequently for medical devices are moist heat, dry heat, irradiation and ethylene oxide. While some devices containing animal tissues can be compatible with these commonly applied methods of sterilization (historically, for example, catgut sutures have been sterilized by irradiation), other devices, such as biological heart valves or tissue patches, are not compatible with conventional sterilization processes. It has been recognized that other sterilizing agents could have to be used in these exceptional circumstances. Liquid chemical sterilization is normally chosen over other sterilization processes in order that the medical devices present the desired physical properties of the tissue after sterilization. Sterilization by liquid chemicals of medical devices made in whole or in part from tissues of animal origin represents a special case in terms of establishing an effective sterilization process. In common with the other sterilization methods, the efficacy of a liquid chemical sterilization process needs to be demonstrated and recorded before it is adopted for routine use.

Liquid chemical sterilization requires determination of types of microorganisms comprising the bioburden and their resistance to the sterilization process in order to establish the appropriate reference microorganism, whether that be a recognized biological indicator or an isolate from the bioburden. Compliance with the requirements of this document ensures that the microbicidal activity of the liquid chemical 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 product after sterilization. Specification of this probability is a matter for regulatory authorities and can vary among regions or countries (see for example, EN 556-1 and ANSI/AAMI ST67).

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

a) the source and harvesting conditions of the tissue;

b) the microbiological status of incoming raw materials or components, or both;

c) the routine control of any cleaning and disinfection procedures used on the product;

d) the control of the environment in which the product is manufactured, assembled and packaged;

e) the control of equipment and processes;

f) the control of personnel and their hygiene;

g) the manner and materials in which the product is packaged; and

h) the conditions under which product is stored.

Sterilization of health care products — Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives — Requirements for characterization, development, validation and routine control of a sterilization process for medical devices

1 Scope

This document specifies requirements for the characterization of a liquid chemical sterilizing agent and for the development, validation, process control and monitoring of sterilization by liquid chemical sterilizing agents of single-use medical devices comprising, in whole or in part, materials of animal origin.

This document covers the control of risks arising from contamination with bacteria and fungi by application of a liquid chemical sterilization process. Risks associated with other microorganisms can be assessed using other methods (see NOTE 1).

This document is not applicable to material of human origin.

This document does not describe methods for the validation of the inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents (see NOTE 2 and NOTE 3).

This document does not describe methods for validation of the inactivation or elimination of protozoa and parasites.

The requirements for validation and routine control described in this document are only applicable to the defined sterilization process of a medical device, which is performed after the manufacturing process, and do not take account of the lethal effects of other bioburden reduction steps (see NOTE 4).

This document does not specify tests to establish the effects of any chosen sterilization process upon the fitness for use of the medical device (see NOTE 5).

This document does not cover the level of residual sterilizing agent within medical devices (see NOTE 6).

Guidance for the characterization of a liquid chemical sterilizing agent and for the development, validation, process control and monitoring of sterilization by liquid chemical sterilizing agents of single-use medical devices comprising, in whole or in part, materials of animal origin is provided in informative Annex A.

NOTE 1 The prior application of risk management principles to medical devices utilizing animal tissues, as described in ISO 22442-1 is important. ISO 18362 provides information on control of microbial risks during processing of cell-based health-care products.

NOTE 2 Liquid chemical sterilizing agents traditionally employed to sterilize animal tissues in medical devices might not be effective in inactivating the causative agents of TSE such as bovine spongiform encephalopathy (BSE), or scrapie. Satisfactory validation in accordance with this document does not necessarily demonstrate inactivation of infective agents of this type. Risk controls related to sourcing, collection and handling of animal materials are described in ISO 22442-2.

NOTE 3 The validation of the inactivation, elimination, or elimination and inactivation of viruses and TSE agents is described in ISO 22442-3.

NOTE 4 Manufacturing processes for medical devices containing animal tissues frequently include exposure to chemical agents which can significantly reduce the bioburden on the medical device. Following the manufacturing process, a medical device is exposed to a specified sterilization process.

NOTE 5 Such testing is a crucial part of the design and development of a medical device.

NOTE 6 ISO 10993-17 specifies a method to establish allowable limits for residues of sterilizing agents.

NOTE 7 Standards for quality management systems (see ISO 13485) can be used in the control of all stages of manufacture including the sterilization process.

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 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

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

ISO 13408 (all parts), *Aseptic processing of health care products*

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 http://www.electropedia.org/

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

3.1
batch
defined quantity of product, intended or purported to be uniform in character and quality produced during a defined cycle of manufacture

[SOURCE: ISO 11139:2018, 3.21]

3.2
bioburden
population of viable microorganisms on or in product and/or sterile barrier system

[SOURCE: ISO 11139:2018, 3.23]

3.3
carrier
<biological indicator> supporting material on or in which test microorganisms are deposited

[SOURCE: ISO 11139:2018, 3.33]

3.4
***D* value**
D_{10} value
time or dose required under stated conditions to achieve inactivation of 90 % of a population of the test microorganisms

[SOURCE: ISO 11139:2018, 3.75]

3.5
holding time
period during which process parameters are maintained, within their specified tolerances

[SOURCE: ISO 11139:2018, 3.133]

3.6
inactivation curve
graphical representation of decrease in viability of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions

[SOURCE: ISO 11139:2018, 3.137]

3.7
inoculated carrier
supporting material on or in which a specified number of viable test microorganisms has been deposited

[SOURCE: ISO 11139:2018, 3.144]

3.8
installation qualification
IQ
process of establishing 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]

3.9
liquid chemical sterilizing agent
liquid chemical entity, or combination of entities, having sufficient microbicidal activity to achieve *sterility* (3.21) under defined conditions

[SOURCE: ISO 11139:2018, 3.288, modified — "liquid chemical" added to term and in definition "physical or chemical entity is "replaced by "liquid chemical entity "]

3.10
medical device
instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, or 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 may be considered to be medical devices in some jurisdictions but not in others include:

— items specifically intended for cleaning, packaging, or sterilization of medical devices

— 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 11139:2018, 3.166]

3.11
microbial inactivation
inactivation
loss of ability of microorganisms to grow and/or multiply

[SOURCE: ISO 11139:2018, 3.172, modified — "inactivation" added as admitted term]

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

[SOURCE: ISO 11139:2018, 3.220.3]

3.13
parametric release
declaration that product is *sterile* (3.23), based on records demonstrating that the sterilization process variables were delivered within specified tolerances

[SOURCE: ISO 11139:2018, 3.193]

3.14
performance qualification
PQ
process of establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements

[SOURCE: ISO 11139:2018, 3.220.4]

3.15
product family
group or subgroup of product characterized by similar attributes determined to be equivalent for evaluation and processing purposes

[SOURCE: ISO 11139:2018, 3.218]

3.16
reference microorganism
microbial strain obtained from a recognized culture collection

[SOURCE: ISO 11139:2018, 3.228]

3.17
requalification
repetition of part or all of validation for the purpose of confirming the continued acceptability of a specified process

[SOURCE: ISO 11139:2018, 3.220.5]

3.18
specify
stipulate in detail within an approved document

[SOURCE: ISO 11139:2018, 3.259]

3.19
sterile
free from viable microorganisms

[SOURCE: ISO 11139:2018, 3.271]

3.20
sterile barrier system
SBS
minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the *sterile* (3.19) contents at the point of use

[SOURCE: ISO 11139:2018, 3.272]

3.21
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]

3.22
sterility assurance level
SAL
probability of a single viable microorganism occurring on an item after *sterilization* (3.23)

Note 1 to entry: It is expressed as the negative exponent to the base 10.

[SOURCE: ISO 11139:2018, 3.275]

3.23
sterilization
validated process used to render a product free from viable microorganisms

Note 1 to entry: In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

[SOURCE: ISO 11139:2018, 3.277]

3.24
storage solution
liquid in which a medical device in its final form is presented for use

[SOURCE: ISO 11139:2018, 3.290]

3.25
surrogate product
item designed to represent product in process simulations and which is comparable with the actual product

[SOURCE: ISO 11139:2018, 3.291]

3.26
test for sterility
technical operation specified in a pharmacopoeia performed on product following an aseptic process or exposure to a *sterilization* (3.23) process

[SOURCE: ISO 11139:2018, 3.298]

3.27
tissue
organization of cells, cells and extra-cellular constituents, or extra-cellular constituents

[SOURCE: ISO 11139:2018, 3.303]

3.28
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.

Note 4 to entry: For sterilization by liquid chemical sterilizing agents, validation is considered as a total programme, which consists of installation qualification, operational qualification and performance qualification.

[SOURCE: ISO 11139:2018, 3.313, modified — Note 4 to entry has been added]

4 General

4.1 The development, validation and routine control of a sterilization process is a critical element in product realization of health care product. To ensure the consistent implementation of the requirements specified in this document, the necessary processes need to be established, implemented and maintained. Processes of particular importance in relation to the development, validation and routine control of a sterilization process include but are not limited to:

— control of documentation, including records,

— assignment of management responsibility,

— provision of adequate resources, including competent human resources and infrastructure,

— control of product provided by external parties,

— identification and traceability of product throughout the process, and

— control of non-conforming product.

NOTE ISO 13485 covers all stages of the lifecycle of medical devices in the context of quality management systems for regulatory purposes. National and/or regional regulatory requirements for the provision of health care product can require the implementation of a full quality management system and the assessment of that system by a recognized conformity assessment body.

4.2 A process shall be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this document.