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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 14160 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This second edition cancels and replaces the first edition (ISO 14160:1998), which has been technically revised.

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) may, prior to sterilization, have microorganisms on them, 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 may survive regardless of the extent of treatment applied. For a given treatment, the probability of survival is determined by the number and resistance of microorganisms and by the environment in which the organisms exist during treatment. It follows that the sterility of any one 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 International Standard 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 may 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 might 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 International Standard 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 may 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 International Standard 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 International Standard 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 International Standard is not applicable to material of human origin.

This International Standard does not describe methods for the validation of the inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents (see Note 2).

This International Standard 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 International Standard 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 International Standard 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 International Standard does not cover the level of residual sterilizing agent within medical devices (see Note 6).

This International Standard does not describe a quality management system for the control of all stages of manufacture (see Note 7).

NOTE 1 The prior application of risk management principles to medical devices utilizing animal tissues, as described in ISO 22442-1, is important.

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 International Standard 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 defined 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 referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10012, *Measure management systems — Requirements for measurement processes and measuring equipment*

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 medical devices — Microbiological methods — Part 1: Determination of a population of microorganisms on products*

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

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

ISO 22442-2, *Medical devices utilizing animal tissues and their derivatives — Part 2: Controls on sourcing, collection and handling*

3 Terms and definitions

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

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

[ISO/TS 11139:2006, definition 2.1]

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

[ISO/TS 11139:2006, definition 2.2]

3.3
carrier
supporting material on or in which test microorganisms are deposited

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

[ISO/TS 11139:2006, definition 2.11]

3.5
exposure time
period for which the process parameters are maintained within their specified tolerances

[ISO/TS 11139:2006, definition 2.18]

3.6
inactivation
loss of the ability of microorganisms to grow and/or multiply

[ISO/TS 11139:2006, definition 2.21]

3.7
inoculated carrier
supporting material on or in which a defined number of viable test organisms have been deposited

3.8
installation qualification
IQ
process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

[ISO/TS 11139:2006, definition 2.22]

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

3.10
medical device
instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material, or other related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purposes of:

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

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

— investigation, replacement, modification or support of the anatomy or of a physiological process;

— supporting or sustaining life;

— control of conception;

— disinfection of medical devices;

— providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body;

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

[ISO 13485:2003, definition 3.7]

NOTE This definition from ISO 13485:2003 was developed by the Global Harmonization Task Force (GHTF 2002).

3.11
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[ISO/TS 11139:2006, definition 2.27]

3.12
parametric release
declaration that product is sterile, based on records demonstrating that the process parameters were delivered within specified tolerances

[ISO/TS 11139:2006, definition 2.29]

3.13
performance qualification
PQ
process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification

[ISO/TS 11139:2006, definition 2.30]

3.14
product family
group or subgroup of product characterized by similar attributes such as mass, material, construction, shapes, lumens and packaging system, and which presents a similar challenge to the sterilization process

[ISO 17665-1:2006, definition 3.38]

3.15
requalification
repetition of part of validation for the purpose of confirming the continued acceptability of a specified process

[ISO/TS 11139:2006, definition 2.40]

3.16
specify
stipulate in detail within an approved document

[ISO/TS 11139:2006, definition 2.42]

3.17
sterile
free from viable microorganisms

[ISO/TS 11139:2006, definition 2.43]

3.18
sterility
state of being free from viable microorganisms

[ISO/TS 11139:2006, definition 2.45]

NOTE In practice, no such absolute statement regarding the absence of microorganisms can be proven (see 3.19).

3.19
sterilization
validated process used to render a product free from viable microorganisms

NOTE In a sterilization process, the nature of microbiological 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.

[ISO/TS 11139:2006, definition 2.47]

3.20
storage solution
liquid in which a medical device in its final form is presented for use

3.21
surrogate product
simulation of the item to be sterilized that presents an equal or greater challenge to the sterilization process

3.22
test for sterility
technical operation defined in an official pharmacopoeia performed on product following exposure to a sterilization process or following an aseptic manufacturing process

[ISO/TS 11139:2006, definition 2.53]

3.23
tissue
organization of cells, cells and extra-cellular constituents, or extra-cellular constituents

3.24
validation
documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications

[ISO/TS 11139:2006, definition 2.55]

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

4 Quality management system elements

4.1 Documentation

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

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

4.2 Management responsibility

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

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

4.3 Product realization

4.3.1 Procedures for purchasing shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.

4.3.2 Procedures for identification and traceability of the product shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.

4.3.3 Controls on the sourcing, collection and handling of animal tissues and their derivatives shall be performed in accordance with ISO 22442-2.

4.3.4 A system complying with the applicable clauses of ISO 13485 or ISO 10012 shall be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this International Standard.

4.4 Measurement, analysis and improvement — Control of non-conforming products

Procedures for control of products designated as non-conforming and for correction, corrective action and preventive action shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.

5 Sterilizing agent characterization

5.1 General

The purpose of this activity is to define the liquid chemical 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 the safety of personnel and protection of the environment.

5.2 Sterilizing agent

5.2.1 The sterilizing agent shall be specified. This specification shall include, if appropriate:

a) the formulation of a sterilizing solution, including concentration of the active agent and pH;

b) an expiration date;

c) a statement that the sterilizing agent shall not be reused;

d) the storage conditions.

The specification for the liquid chemical sterilizing agent should take into account possible contaminants that could affect the suitability of the processed animal material for its intended use.

5.2.2 The means of ensuring that the sterilizing agent is free from viable microorganisms before use shall be specified.

5.3 Microbicidal effectiveness

5.3.1 Microbicidal effectiveness studies shall

a) demonstrate the lethal action of the sterilizing agent against a range of representative microorganisms,

NOTE Guidance on microorganism selection is included in A.6.2 and in Table A.2.

b) identify the process variables that affect the lethal action of the sterilizing agent, e.g. time, temperature, liquid chemical sterilizing agent concentration and pH (potential interactions of process variables should be considered),

c) assess those factors that can adversely affect the delivery, or distribution, or both, of the sterilizing agent, and those that can influence its effectiveness [i.e. the sterilizing agent(s) should be able to reach all areas since microorganisms could be inside cell/tissue structures], and

d) assess the microbicidal effectiveness of the sterilizing agent at the tolerance limits for the combination of process variables that results in the lowest microbicidal activity.

5.3.2 The microbicidal effectiveness studies shall include a screening test to identify microorganisms with a high resistance to the process. This shall include organisms from the product bioburden and the environment, as well as a reference organism(s) known to be innately resistant to the sterilizing agent.

5.4 Effects on materials

5.4.1 The effects of exposure to the sterilizing agent on the physical, chemical, or physical and chemical properties of component materials of the medical devices, and on their suitability for use, shall be assessed. The materials used in the assessment should be selected on the basis of their likely use in products to be treated with the sterilizing agent.

5.4.2 If the product is to be exposed repeatedly to the sterilizing agent, the effects of such multiple exposures on properties of component materials using the combination of process parameters likely to maximize material effects shall be evaluated.

5.4.3 The materials tested and the outcomes of all tests shall be recorded (see 4.1.2), together with the criteria against which the properties of materials were assessed before and after exposure to the sterilizing agent.

5.5 Safety and the environment

5.5.1 Either a material safety data sheet (MSDS) or analogous safety information shall be specified for the sterilizing agent. This MSDS may be provided by a supplier for a chemical agent or be prepared as a prelude to experimental studies on the sterilizing agent.

5.5.2 The potential impact on the environment of any substance which could be released, either deliberately or accidentally, during or following use of the sterilizing agent, shall be assessed and measures established for the control of the substance(s). This assessment, including the potential impact (if any) and the measures for control (if identified), shall be recorded (see 4.1.2).

6 Process and equipment characterization

6.1 General

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