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Sterilization of health care products — Microbiological methods —

Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process

Stérilisation des produits de santé — Méthodes microbiologiques —

Partie 2: Contrôles de stérilité pratiqués au moment de la définition, de la validation et de la maintenance d'un procédé de stérilisation

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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 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 third edition cancels and replaces the second edition (ISO 11737-2:2009), which has been technically revised.

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

— addition of a requirement concerning the test samples and the interval of time between the manufacture of product and the exposure to the sterilizing agent being as short as possible;

— addition of a requirement about the samples staying immersed in the culture media and providing a rationale where this is not possible;

— provision of additional guidance regarding performing tests of sterility on packaging, clarifying that package testing is not typically done except when it is an integral part of the product;

— provision of additional guidance regarding what is meant by “controlled environment” for performing tests of sterility;

— provision of additional guidance to discuss circumstances where the method suitability test does not give acceptable results, stating that after multiple attempts to eliminate inhibitory substances, it is appropriate to accept a reduction of inhibitory substances, with an accompanying rationale and risk assessment;

— provision of guidance regarding identification of microbial growth in a test of sterility, saying generally for positive growth the microorganism(s) should be identified;

— provision of guidance regarding method suitability, saying that consideration should be given to periodically demonstrating ongoing method suitability in order to ensure that an accumulation of minor changes over time has not occurred;

— addition of a table to clarify where typical responsibilities reside for the manufacturer or the laboratory.

A list of all parts in the ISO 11737 series can be found on the ISO website.

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 from 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 from all sources 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) can, prior to sterilization, have microorganisms on them. Such products are non-sterile. The purpose of sterilization is to inactivate the microbiological contaminants and thereby transform the non-sterile products into sterile ones.

The kinetics of inactivation of a pure culture of microorganisms by physical and/or chemical agents used to sterilize medical devices can generally best be described by an exponential relationship between the numbers of microorganisms surviving and the extent of treatment with the sterilizing agent; inevitably this means that there is always a finite probability that a microorganism might 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 item 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 product item.

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.

International Standards specifying procedures for the development, validation and routine control of the processes used for sterilization of medical devices have been prepared [see ISO 11135, ISO 11137 (all parts), ISO 14937, ISO 14160, ISO 17665-1 and ISO 20857]. An element of validation might consist of exposing medical devices to the sterilizing agent with the extent of treatment being reduced relative to that which will be used in routine sterilization processing, in order to provide a knowledge of the resistance to the agent of the microbial contamination as it occurs naturally on medical devices. The reduced exposures applied in these instances are often called fractional exposures or verification doses. Subsequent to this reduced exposure, medical devices are subjected individually to tests of sterility as described in this document. Examples of the use of such tests are in:

a) establishing a dose for sterilization by radiation,

b) demonstrating the continued validity of an established sterilization dose, and

c) establishing a cycle for sterilization by evaluating the product's naturally occurring bioburden.

Product that has been exposed to a terminal sterilization process in its final packaged form has a very low probability of the presence of a viable microorganism; such as one in one million or 10^{-6}. As such, performing a test of sterility on product that has been exposed to the complete sterilization process provides no scientifically usable data and is not recommended.

Annex A of this document gives guidance on the techniques used and on practical aspects of the requirements.

Sterilization of health care products — Microbiological methods —

Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process

1 Scope

1.1 This document specifies the general criteria for tests of sterility on medical devices that have been exposed to a treatment with the sterilizing agent which has been reduced relative to that anticipated to be used in routine sterilization processing. These tests are intended to be performed when defining, validating or maintaining a sterilization process.

1.2 This document is not applicable to:

a) sterility testing for routine release of product that has been subjected to a sterilization process,

b) performing a test for sterility (see 3.12),

NOTE 1 The performance of a) or b) is not a requirement of ISO 11135, ISO 11137-1, ISO 11137-2, ISO 14160, ISO 14937, ISO 17665-1 or ISO 20857.

c) test of sterility or test for sterility for demonstration of product shelf life, stability and/or package integrity, and

d) culturing of biological indicators or inoculated products.

NOTE 2 Guidance on culturing biological indicators is included in ISO 11138-7.

2 Normative references

There are no normative references in this document.

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:

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

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

3.1
aseptic technique
conditions and procedures used to minimize the risk of the introduction of microbial contamination

[SOURCE: ISO 11139:2018, 3.16]

3.2
bacteriostasis/fungistasis test
technical operation performed to detect the presence of substances that inhibit microbial multiplication

[SOURCE: ISO 11139:2018, 3.20]

3.3
bioburden
population of viable microorganisms on or in a product and/or sterile barrier system

[SOURCE: ISO 11139:2018, 3.23]

3.4
culture condition
combination of growth media and manner of incubation used to promote germination, growth and/or multiplication of microorganisms

Note 1 to entry: The manner of incubation can include the temperature, time, and any other conditions specified for incubation.

[SOURCE: ISO 11139:2018, 3.70]

3.5
facultative organism
microorganism capable of both aerobic and anaerobic metabolism

[SOURCE: ISO 11139:2018, 3.114]

3.6
health care product
medical device (3.7), including in vitro diagnostic medical device, or medicinal product, including biopharmaceutical

[SOURCE: ISO 11139:2018, 3.132]

3.7
medical device
instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, or software material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific 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 or sterilization 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 the Note 1 to entry have been added.]

3.8
method suitability
<microbiological> assessment of the test method to demonstrate its ability to allow microbial growth

[SOURCE: ISO 11139:2018, 3.168]

3.9
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]

3.10
sample item portion
SIP
specified part of a health care product that is tested

[SOURCE: ISO 11139:2018, 3.240, modified — Acronym SIP has been added.]

3.11
sterile
free from viable microorganisms

[SOURCE: ISO 11139:2018, 3.271]

3.12
test for sterility
technical operation specified in a pharmacopoeia performed on product following an aseptic process or exposure to a sterilization process

[SOURCE: ISO 11139:2018, 3.298]

3.13
test of sterility
technical operation performed as part of development, validation or requalification to determine the presence or absence of viable microorganisms on product or portions thereof

Note 1 to entry: This is performed after exposure to the sterilizing agent at a level which is reduced compared to the complete sterilization process.

[SOURCE: ISO 11139:2018, 3.299, modified — Note 1 to entry 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 products. To ensure the consistent implementation of the requirements specified in this document, the necessary processes need to be established, implemented

and maintained (see Annex B). 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 products 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.

5 Selection of product

5.1 General

5.1.1 The procedures for selection and handling of product for performing tests of sterility shall ensure that the selected product is representative of routine production, including packaging materials and processes (see also 5.3).

5.1.2 If product(s) is grouped in a product family for the purposes of development, validation and routine control of the sterilization process in which tests of sterility are performed, the rationale for inclusion of a product within a product family shall be recorded. The rationale shall include criteria to ensure that a product selected from a product family for testing is representative of the whole product family.

5.1.3 The rationale for the number of product items that are selected and the number of batches from which this selection is made shall be documented.

NOTE This could be described in the relevant International Standard specifying the requirements for validation and routine control of the sterilization process.

5.2 Sample item portion (SIP)

5.2.1 Whenever practicable the test of sterility is performed on the entire product. A selected portion of the product [sample item portion (SIP)] may be substituted for the entire product in the test of sterility when permitted in the applicable sterilization standard.

5.2.2 The determination of portions selected for tests of sterility shall be based on whether the bioburden is known to be evenly distributed (see 5.2.2.1) or not (see 5.2.2.2).

5.2.2.1 When the bioburden distribution is known:

a) if the bioburden is evenly distributed on and/or in the item, the SIP for tests of sterility may be selected from any portion of the item;

