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Sterilization of medical devices — Microbiological methods —

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

Stérilisation des dispositifs médicaux — Méthodes microbiologiques — Partie 2: Essais 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.

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 11737-2 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This second edition cancels and replaces the first edition (ISO 11737-2:1998) which has been technically revised.

ISO 11737 consists of the following parts, under the general title *Sterilization of medical devices — Microbiological methods*:

— *Part 1: Determination of a population of microorganisms on products*

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

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) may, prior to sterilization, have microorganisms on them, albeit in low numbers. 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 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 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[16] 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 11135-1[1], ISO 11137-1[3], ISO 14937[12], ISO 14160[7], ISO 17665-1[13] and ISO 20857[14]). 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. Subsequent to this exposure, medical devices are subjected individually to tests of sterility as described in this part of ISO 11737. Examples of the use of such tests are in a) establishing a dose for sterilization by radiation, and b) demonstrating the continued validity of an established sterilization dose.

Annex A of this part of ISO 11737 gives guidance on the techniques used and on practical aspects of the requirements.

Sterilization of medical devices — Microbiological methods —

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

1 Scope

1.1 This part of ISO 11737 specifies the general criteria for tests of sterility on medical devices that have been exposed to a treatment with the sterilizing agent 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 part of ISO 11737 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 11135-1, ISO 11137-1, ISO 14160, ISO 14937 or ISO 17665-1.

c) culturing of biological indicators or inoculated products.

NOTE 2 Guidance on culturing biological indicators is included in ISO 14161[8].

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, *Measurement management systems — Requirements for measurement processes and measuring equipment*

ISO 11737-1:2006, *Sterilization of medical devices — Microbiological methods — Part 1: Determination of a population of microorganisms on products*

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

ISO/IEC 17025:2005, *General requirements for the competence of testing and calibration laboratories*

3 Terms and definitions

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

3.1
aerobic organism
microorganism that requires oxygen for metabolism

3.2
anaerobic organism
microorganism that does not require oxygen for metabolism

3.3
bacteriostasis/fungistasis test
technical operation performed with selected microorganisms to detect the presence of substances that inhibit the multiplication of these microorganisms in a test of sterility

3.4
bioburden
population of viable microorganisms on a product and/or a package

NOTE Adapted from ISO/TS 11139:2006, definition 2.2.

3.5
culture conditions
combination of growth media and manner of incubation used to promote germination, growth and/or multiplication of microorganisms

NOTE The manner of incubation can include the temperature, time and any other conditions specified for incubation.

[ISO/TS 11139:2006, definition 2.10]

3.6
facultative organism
microorganism capable of both aerobic and anaerobic metabolism

3.7
growth promotion test
technical operation performed to demonstrate that a growth medium will support microbial multiplication

3.8
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 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 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 has been developed by the Global Harmonization Task Force (GHTF 2002).

3.9
product
result of a process

NOTE 1 For the purposes of sterilization standards, product is tangible and can be raw material(s), intermediate(s), sub-assembly(ies) and health care product(s).

NOTE 2 Adapted from ISO 9000:2005, definition 3.4.2.

3.10
sample item portion
SIP
defined part of a medical device that is tested

3.11
sterile
free from viable microorganisms

[ISO/TS 11139:2006, definition 2.43]

3.12
test for sterility
technical operation defined in a Pharmacopoeia, performed on product following exposure to a sterilization process

[ISO/TS 11139:2006, definition 2.53]

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

[ISO/TS 11139:2006, definition 2.54]

4 Quality management system elements

4.1 Documentation

4.1.1 Procedures for the performance of tests of sterility shall be specified.

4.1.2 Documents and records required by this part of ISO 11737 shall be reviewed and approved by designated personnel (see 4.2.1). Documents and records shall be controlled in accordance with ISO 13485 or ISO/IEC 17025. Records retained shall include all original observations, calculations, derived data and final reports. The records shall include the identity of all personnel involved in sampling, preparation and testing.

4.1.3 Calculations and data transfers shall be subjected to appropriate verification.

4.2 Management responsibility

4.2.1 The responsibility and authority for implementing and performing the procedures described in this part of ISO 11737 shall be specified. Responsibility shall be assigned to competent personnel in accordance with ISO 13485 or ISO/IEC 17025.

4.2.2 If the requirements of this part of ISO 11737 are undertaken by organizations with separate quality management systems, the responsibility and authority of each party shall be specified.

4.2.3 All equipment required for correct performance of the specified tests and measurements shall be available.

4.3 Product realization

4.3.1 Procedures for purchasing shall be specified. These procedures shall comply with ISO 13485 or ISO/IEC 17025.

4.3.2 A documented system complying with ISO 13485, ISO/IEC 17025 or ISO 10012 shall be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this part of ISO 11737.

4.3.3 Equipment or parts thereof that come into contact with product, eluent or media during testing shall be sterile.

4.3.4 Methods shall be specified for the preparation and sterilization of materials used in the tests of sterility, including appropriate quality tests.

4.4 Measurement, analysis and improvement

Procedures for investigation of unusual, unexpected or out-of-specification results and for correction, corrective action and preventive action shall be specified. These procedures shall comply with ISO 13485 or ISO/IEC 17025.

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 product is representative of routine production, including packaging materials and processes. (See also 5.3.)

5.1.2 If product is grouped 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 group shall be recorded (see 4.1.2). The rationale shall include criteria to ensure that product selected for testing is representative of the whole group.

5.2 Sample item portion (SIP)

5.2.1 If allowed in an applicable standard, for the development, validation and routine control of the sterilization process, and when the use of an entire product is not practicable, a selected portion of product [sample item portion (SIP)] may be substituted if allowed by the sterilization method.

5.2.2 If the bioburden distribution on/in product, is not known, the SIP shall consist of portions of product selected at random, which proportionally represent each of the materials from which product is made.

If the bioburden distribution is known and bioburden is evenly distributed on/in product, the SIP may be selected from any portion of the product.

If the bioburden distribution is known and bioburden is not evenly distributed on/in product, the SIP shall either be selected from the portion of product that is considered to be the most severe challenge to the sterilization process or consist of portions of product, selected at random, which proportionally represent each of the materials from which product is made.

5.2.3 The adequacy of a selected SIP shall be demonstrated.

NOTE The standard specifying requirements for development, validation and routine control of the sterilization process might stipulate the criteria for the adequacy of the SIP.

5.3 Packaging of product and sample item portions

If packaging materials and/or methods for product or SIPs to be used in tests of sterility are different from those used in routine production, selection of packaging material and the method of packaging shall ensure that:

a) product or SIP receives the intended treatment with the sterilizing agent;

b) microbiological status of product or SIP is maintained;

c) access of the sterilizing agent to product or SIP is similar to that achieved with packaging used in routine production.

6 Methods for performing tests of sterility

6.1 There are two general methods for performing tests of sterility. These are:

a) direct immersion of product in growth medium or addition of growth medium in product, followed by incubation;

b) removal of microorganisms from product and transfer of removed microorganisms to growth medium followed by incubation.

6.2 For an identified product, factors that influence the design of the method for performing tests of sterility shall be considered and recorded (see 4.1.2). Factors to be considered include, at least:

a) the part(s) of product for which sterility is claimed on the label;

b) the physical and/or chemical nature of product to be tested (see also 6.6);

c) possible type(s) of contaminating microorganisms and their locations on/in product.

6.3 In performing tests of sterility, aseptic technique shall be applied in carrying out manipulations that might affect the result of the test.

6.4 If microorganisms are to be removed from product by elution before transfer to growth medium, factors to be considered shall include:

a) selection of an appropriate eluent;

b) ability of the elution technique to remove contaminating microorganisms effectively (see, for example, 7.2 of ISO 11737-1);

c) effect(s) of the elution technique on the viability of contaminating microorganisms.

6.5 If microorganisms are to be removed from an eluent or a fluid product by filtration before transfer to growth medium, factors to be considered shall also include:

a) selection of an effective filtration system;

b) selection of an appropriate fluid for rinsing the container, the filter and associated equipment (if needed).

6.6 If the physical or chemical nature of product to be tested [see 6.2 b)] is such that substances might be present or released which could adversely affect the multiplication of microorganisms, a system to neutralize, remove, or, if this is not possible, minimize the effect of any such substances shall be used. The effectiveness of such a system shall be demonstrated.