INTERNATIONAL STANDARD

ISO 11737-2

First edition
1998-07-01

Sterilization of medical devices — Microbiological methods —

Part 2:
Tests of sterility performed in the validation of a sterilization process

Stérilisation des dispositifs médicaux — Méthodes microbiologiques

Partie 2: Essais de stérilité pratiqués en cours de validation d'un procédé de stérilisation

International Organization for Standardization
Case postale 56 • CH-1211 Genève 20 • Switzerland
Internet iso@iso.ch
Printed in Switzerland

Contents

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 3.

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.

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

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

— *Part 1: Estimation of the population of microorganisms on product*

— *Part 2: Tests of sterility performed in the validation of a sterilization process*

Annex A of this International Standard is for information only.

Foreword

A sterile product item is one which is free of viable microorganisms. The International Standards for sterilization of medical devices require, when it is necessary to supply a sterile product item, that adventitious microbiological contamination of a medical device from all sources be minimized by all practical means. Even so, product items produced under standard manufacturing conditions in accordance with the requirements for quality systems for medical devices may, prior to sterilization, have microorganisms on them, albeit in low numbers. Such product items are non-sterile. The purpose of sterilization processing is to inactivate the microbiological contaminants and thereby transform the non-sterile items into sterile ones.

The inactivation of a pure culture of microorganisms by physical and/or chemical agents used to sterilize medical devices often approximates an exponential relationship; 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 of items subjected to sterilization processing cannot be guaranteed, and the sterility of the processed population of items has to be defined in terms of the probability of the existence of a non-sterile item in that population.

Requirements for the quality system for the design/development, production, installation and servicing of medical devices are given in ISO 9001 and ISO 9002 in conjunction with ISO 13485 and ISO 13488, respectively.

The ISO 9000 series of standards designates certain processes used in manufacture as 'special' if the results cannot be fully verified by subsequent inspection and testing of the product. Sterilization is an example of a special process because process efficacy cannot be verified by inspection and testing of the product. For this reason, sterilization processes have to be validated before use, the performance of the process monitored routinely and the equipment maintained.

International Standards specifying procedures for the validation and routine control of the processes used for sterilization of medical devices have been prepared (see ISO 11134, 11135 and 11137). An element of this validation may consist of exposing medical devices to the sterilizing agent when the extent of treatment has been reduced relative to that which will be used in routine 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. An example of the use of such a test is in establishing a sterilizing dose for sterilization by radiation and for demonstrating the continued validity of this sterilization dose (see ISO 11137, Annex B).

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 validation of a sterilization process

1 Scope

1.1 This part of ISO 11737 specifies the general criteria for tests of sterility on medical devices which have been exposed to a treatment with the sterilizing agent that is a fraction of the specified sterilization process. These tests are intended to be performed when validating 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) performance of a pharmacopoeial test for sterility; or

NOTE 1 The performance of a) or b) above is not a requirement of ISO 11134, 11135 or 11137.

c) culturing of biological indicators, including inoculated products.

NOTE 2 Methods of culturing biological indicators are described in ISO 11138.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 11737. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 11737 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 9001:1994, *Quality Systems — Model for quality assurance in design, development, production, installation and servicing.*

ISO 9002:1994, *Quality systems — Model for quality assurance in production, installation and servicing*.

3 Terms and definitions

For the purposes of this part of ISO 11737, the following terms and definitions apply.

3.1
aerobic organism
microorganisms that utilize oxygen as the final electron acceptor during metabolism and which will only grow in the presence of oxygen

3.2
anaerobic organism
microorganisms that do not utilize oxygen as the final electron acceptor during metabolism and which will only grow in the absence of oxygen

3.3
bacteriostasis/fungistasis test
test performed with selected microorganisms to demonstrate the presence of substances that inhibit the multiplication of these microorganisms

3.4
culture conditions
stated combination of conditions, including the growth medium with the period and temperature of incubation, used to promote growth and multiplication of microorganisms

3.5
facultative organism
microorganism capable of both aerobic and anaerobic metabolism

3.6
false negative
result of a test of sterility in which a true positive is interpreted as negative

3.7
false positive
result of a test of sterility in which a true negative is interpreted as a positive

3.8
growth promotion test
test performed to demonstrate that a given medium will support microbial growth

3.9
product
generic term used to describe raw materials, intermediate products, subassemblies and finished medical devices

3.10
product unit
medical device, collection of products or components within a primary package

3.11
sample item portion
SIP
defined portion of a product unit that is tested

3.12
test of sterility
test performed to establish the presence or absence of viable microorganisms on product units (or portions thereof) when subjected to defined culture conditions

4 General

4.1 Documentation

4.1.1 Documented instructions detailing the testing technique to be employed and the use and operation of relevant equipment shall be available. These documented instructions shall be approved and controlled as specified in ISO 9001 or ISO 9002.

4.1.2 The documented instructions required by this part of ISO 11737 shall be implemented effectively.

4.1.3 Records of original observations, derived data and final reports shall be retained in accordance with ISO 9001 or ISO 9002. The records shall include the identity of personnel involved in sampling, preparation and testing.

NOTE Software used for data capture and transfer should be validated prior to use.

4.2 Personnel

4.2.1 Responsibility for performing tests of sterility shall be assigned to specific personnel as specified in ISO 9001 or ISO 9002.

4.2.2 Training shall be performed in accordance with documented procedures, and records of the relevant qualifications, training and experience of technical personnel shall be maintained.

4.3 Equipment and materials

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

4.3.2 All equipment requiring planned maintenance shall be maintained in accordance with documented procedures. Records of maintenance shall be retained.

4.3.3 An effective system shall be established, documented and maintained for the calibration of all equipment with measurement or control functions. This calibration system shall comply with ISO 9001 or ISO 9002.

4.3.4 Methods shall be established and documented for the preparation and sterilization of materials such as glassware, growth media and eluents used in performing tests of sterility, including appropriate quality tests.

4.3.5 Quality tests for each batch of growth medium shall include a growth promotion test.

5 Selection and preparation of product units for testing

5.1 Selection

5.1.1 Product unit selection

The procedures for selection and procurement of product units for testing shall be established to ensure that these product units are representative of routine production.

5.1.2 Sample item portion (SIP)

If an SIP is used in testing, it shall be selected to possess microorganisms representative of those on the product unit.

If it has been demonstrated that the microorganisms are evenly distributed on the product unit, the SIP shall be selected from any single location on the product unit. In the absence of such a demonstration, the SIP shall be constituted from several portions of a product unit selected at random.

NOTE The standards specifying the requirement for validation and routine control of the sterilization process should stipulate the criteria for the adequacy of the SIP.

5.2 Packaging of product units and SIPs

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

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

b) the microbiological status of the product unit or the SIP is maintained;

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

6 Tests of sterility

There are two general approaches in the performance of tests of sterility. These are:

a) direct immersion of the product in growth medium or growth medium into the product, followed by incubation; and

b) removal of microorganisms from the product by elution, and transfer of the removed microorganisms to culture conditions.

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

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

b) the physical and/or chemical nature of the product to be tested;

c) possible type(s) of contaminating microorganisms and their locations on or within the product.

6.3 If microorganisms are to be removed from product before transfer to culture conditions, the factors to be considered shall also include:

a) selection of an appropriate eluent;

b) ability of the elution technique to remove contaminating microorganisms;

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

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

6.5 Culture conditions shall be selected after consideration of the types of microorganisms expected to be present. The results of this consideration and the rationale for the decisions reached shall be documented.

7 Assessment of method for test of sterility

7.1 The appropriateness of the methods selected for the test of sterility shall be assessed and the results of the assessment shall be documented (see 4.1.3).

NOTE 1 Actions taken under 6.4 and 6.5 should minimize the occurrence of false negatives.

NOTE 2 The correct application of the method by qualified and trained personnel should minimize the occurrence of false positives.

7.2 Modifications to the product and/or manufacturing process shall be reviewed formally to determine whether they are likely to require a change in the method for the tests of sterility. If the review indicates that a change is required, the procedures given in clause 6 shall be repeated.

6.1

Annex A
(informative)

Guidance on tests of sterility performed in validation of a sterilization process

A.1 Introduction

This annex provides guidance on the implementation of the specified requirements. The guidance given is not intended to be exhaustive, but to highlight important aspects that should be given attention.

This annex is not intended as a checklist for assessing compliance with the requirements.

A.2 General

A.2.1 Laboratory quality systems

In order that the data obtained from performing tests of sterility will be reliable and reproducible, it is important that the tests be performed under controlled conditions. The laboratory facilities used for the tests, whether on the site of the medical device manufacturer or at a remote location, should therefore be managed and operated in accordance with a documented quality system.

If tests of sterility are performed in a laboratory under the direct management of the medical device manufacturer, the operation of the laboratory should be within the manufacturer's quality system. If an external laboratory is used, it is recommended that such a laboratory be formally certified against an appropriate International Standard (e.g. ISO/IEC Guide 25).

Any laboratory should be committed to providing a quality service, and this commitment should be documented as a quality policy. The lines of authority and responsibility within the laboratory organization should be formally established and documented. An individual should be nominated to be responsible for the establishment of the laboratory quality system and have sufficient authority to ensure that the system is implemented.

The operation of the laboratory should be subject to regular internal audits. The results of the audit should be documented and reviewed by the laboratory management.

Further information on quality management is available in ISO 9004. ISO/IEC Guide 25 outlines requirements for laboratory quality systems. Particular requirements for quality systems for the manufacture of medical devices are available in ISO 13485 and ISO 13488.

A.3 Apparatus and materials

A.3.1 Electronic data processing

A.3.1.1 Computers may be used in laboratories for both direct and indirect collection, processing and/or storage of data. Both the hardware and software used for such applications should be controlled.

A.3.1.2 The computer system in use should be identified, both in terms of hardware and software, and any changes in either of these aspects should be documented and subject to appropriate approval.