INTERNATIONAL STANDARD

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Sterilization of medical devices — Microbiological methods —

Part 1: Determination of a population of microorganisms on products

Stérilisation des dispositifs médicaux — Méthodes microbiologiques — Partie 1: Détermination d'une population de micro-organismes sur des produits

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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 11737-1 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This second edition cancels and replaces the first edition (ISO 11737-1:1995) which has been technically revised and ISO 11737-3:2004 whose contents it now incorporates.

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 validation of a sterilization process*

Introduction

A sterile medical device is one that is free of 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 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. 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 product 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 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.

International Standards specifying procedures for the validation and routine control of the processes used for the sterilization of medical devices have been prepared (see, for example, ISO 11135, ISO 11137 series and ISO 17665). However, it is important to be aware that exposure to a properly validated and accurately controlled sterilization process is not the only factor associated with the provision of assurance that the product is sterile and, in this respect, suitable for its intended use. Furthermore, for the effective validation and routine control of a sterilization process, it is important to be aware of the microbiological challenge that is presented in the process, in terms of number, characteristics and properties of microorganisms.

The term bioburden is used to describe the population of viable microorganisms present on or in product and/or a sterile barrier system. A knowledge of bioburden can be used in a number of situations as part of:

— validation and revalidation of sterilization processes;

— routine monitoring for control of manufacturing processes;

— monitoring of raw materials, components or packaging;

— assessment of the efficiency of cleaning processes;

— an overall environmental monitoring programme.

Bioburden is the sum of the microbial contributions from a number of sources, including raw materials, manufacturing of components, assembly processes, manufacturing environment, assembly/manufacturing aids (e.g., compressed gases, water, lubricants), cleaning processes and packaging of finished product. To control bioburden, attention must be given to the microbiological status of these sources.

It is not possible to enumerate the bioburden exactly and, in practice, a determination of bioburden is made using a defined method. Definition of a single method for use in the determination of bioburden in all situations is not practicable because of the wide variety of designs and materials of construction of medical devices. Nor is it possible to define a single technique to be used in all situations for the removal of microorganisms in preparation for enumeration. Furthermore, the selection of conditions for enumeration of microorganisms will be influenced by the types of microorganism likely to be present on or in medical devices.

This part of ISO 11737 specifies the requirements to be met in the determination of bioburden. The requirements are the normative parts of this part of ISO 11737 with which compliance is claimed. The guidance given in the informative annexes is not normative and is not provided as a checklist for auditors. The guidance provides explanations and methods that are regarded as being a suitable means for complying with the requirements. Methods other than those given in the guidance may be used, if they are effective in achieving compliance with the requirements of this part of ISO 11737.

Sterilization of medical devices — Microbiological methods —

Part 1: Determination of a population of microorganisms on products

1 Scope

This part of ISO 11737 specifies requirements and provides guidance for the enumeration and microbial characterization of the population of viable microorganisms on or in a medical device, component, raw material or package.

NOTE 1 The nature and extent of microbial characterization is dependent on the intended use of the bioburden data.

This part of ISO 11737 does not specify requirements for the enumeration or identification of viral or protozoan contaminants.

NOTE 2 Furthermore, the requirements specified in this part of ISO 11737 are not intended to address the removal and detection of the causative agents of spongiform encephalopathies such as scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob disease.

This part of ISO 11737 does not specify requirements for the microbiological monitoring of the environment in which medical devices are manufactured.

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

[ISO/TS 11139:2006, definition 2.2]

3.2
correction
action to eliminate a detected nonconformity

NOTE A correction can be made in conjunction with a **corrective action** (3.4).

[ISO 9000:2005, definition 3.6.6]

3.3
correction factor
numerical value applied to compensate for incomplete removal from product and/or culture of microorganisms

3.4
corrective action
action to eliminate the cause of a detected nonconformity or other undesirable situation

NOTE 1 There can be more than one cause for a nonconformity.

NOTE 2 Corrective action is taken to prevent recurrence whereas **preventive action** (3.9) is taken to prevent occurrence.

NOTE 3 There is a distinction between **correction** (3.2) and corrective action.

[ISO/TS 11139:2006, definition 2.8]

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 may include the temperature, time and any other conditions specified for incubation.

[ISO/TS 11139:2006, definition 2.10]

3.6
establish
determine by theoretical evaluation and confirm by experimentation

[ISO/TS 11139:2006, definition 2.17]

3.7
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

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

[ISO 13485:2003]

3.8
microbial characterization
process by which microorganisms are grouped into categories

NOTE Categories may be broadly based, for example, on the use of selective media, colony or cellular morphology, staining properties or other characteristics.

[ISO/TS 11139:2006, definition 2.25]

3.9
preventive action
action to eliminate the cause of a potential nonconformity or other undesirable potential situation

NOTE 1 There can be more than one cause for a potential nonconformity.

NOTE 2 Preventive action is taken to prevent occurrence whereas **corrective action** (3.4) is taken to prevent recurrence.

[ISO 9000:2005, definition 3.6.4]

3.10
product
result of a process

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

[ISO 9000:2005, definition 3.4.2]

3.11
recognized culture collection
depository authority under the Budapest Treaty on “The International Recognition of the Deposit of Microorganisms for the Purposes of Patent and Procedure”

[ISO/TS 11139:2006, definition 2.38]

3.12
recovery efficiency
measure of the ability of a specified technique to remove and/or culture microorganisms from product

3.13
sample item portion
SIP
defined part of a medical device that is tested

3.14
specify
stipulate in detail within an approved document

[ISO/TS 11139:2006, definition 2.42]

3.15
validation
documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications

NOTE In the context of determination of bioburden, the “process” is the test methodology and the “product” is the test result. The validation of a technique for the determination of bioburden consists of a series of investigations to assess the effectiveness and reproducibility of the test method.

[ISO/TS 11139:2006, definition 2.55]

4 Quality management system elements

4.1 Documentation

4.1.1 Procedures for determination of bioburden 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.

4.1.3 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.

4.1.4 Calculations and data transfers shall be subject to appropriate checks.

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 responsibilities and authority of each party shall be specified.

4.2.3 All items of 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 Methods shall be specified for the preparation and sterilization of materials used in the determination of bioburden, including appropriate quality tests.

4.4 Measurement, analysis and improvement — Control of nonconforming product

Procedures for investigation of 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 determination of bioburden shall ensure that selected product is representative of routine production including packaging materials and processes.

5.1.2 If product(s) are grouped for the purpose of determination of bioburden, 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 bioburden determined for a product selected from the group is representative of the whole group.

5.1.3 Consideration shall be given to the timing of the performance of determination of the bioburden relative to taking samples, because bioburden determination can be subject to change with the passage of time.

5.2 Sample item portion (SIP)

If the bioburden is demonstrated as being evenly distributed on and/or in the product item, the SIP may be selected from any portion of the item. Otherwise, the SIP shall consist of portion(s) of product, selected at random, which proportionally represent each of the materials from which product is made. If the bioburden distribution is known, the SIP may be selected from the portion of the product that is considered to be the most severe challenge to the sterilization process. The SIP can be calculated on the basis of length, mass, volume or surface area (see Table 1 for examples).

Table 1 — Examples of SIP calculation

Basis for SIP	Product
Surface area	Implants (non-absorbable)
Mass	Powders Gowns Implants (absorbable)
Length	Tubing (consistent diameter)
Volume	Fluid in water cup

NOTE If appropriate, the standard specifying requirements for validation and routine control of the sterilization process stipulates criteria for the adequacy of SIP.

6 Methods of determination and microbial characterization of bioburden

6.1 Determination of bioburden

6.1.1 Selection of an appropriate method

An appropriate method shall be selected for determination of bioburden. The method shall comprise techniques for:

a) removal of microorganisms, if appropriate;

b) culturing of microorganisms;

c) enumeration of microorganisms.

The precision shall be determined and shall be appropriate to the purpose for which the data are to be used.

6.1.2 Removal of microorganisms

6.1.2.1 For an identified product where removal of viable microorganisms is part of the method, the efficiency of removal shall be considered and the outcomes of this consideration recorded (see 4.1.3). Consideration shall, at least, be given to:

a) ability of the technique to remove microorganisms;

b) possible type(s) of microorganism and their location(s) on product;

c) effect(s) of the removal technique on the viability of microorganisms;

d) the physical or chemical nature of product under test.

6.1.2.2 For an identified product for which removal of viable microorganisms is not part of the method, the efficiency of enumeration of microorganisms shall be considered and the outcomes of this consideration recorded (see 4.1.3). Consideration shall, at least, be given to:

a) possible type(s) of microorganism and their location(s) on product;

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

c) aggregates of cells forming single colonies due to *in-situ* culturing.

6.1.2.3 If the physical or chemical nature of product is such that substances can be released that adversely affect either the number or the types of microorganism found, then a system shall be used to neutralize, remove or, if this is not possible, minimize the effect of any such released substance. The effectiveness of such a system shall be demonstrated.

NOTE Annex B describes techniques that may be used to assess the release of microbicidal or microbiostatic substances.

6.1.3 Culturing of microorganisms

Culture conditions shall be selected after consideration of the types of microorganism likely to be present. The results of this consideration and the rationale for the decisions reached shall be recorded (see 4.1.2).

6.1.4 Enumeration of microorganisms

The technique for enumeration shall be selected after consideration of the types of microorganism likely to be present. The results of this consideration and the rationale for the decisions reached shall be recorded (see 4.1.2).

6.2 Microbial characterization of bioburden

6.2.1 Appropriate techniques for microbial characterization of bioburden shall be selected.

NOTE Microbial characterization is necessary to detect a change to product microflora that might affect some aspect of the use of the bioburden data (e.g. establishing a sterilization process).

6.2.2 Microbial characterization shall be accomplished using one or more of the following:

a) staining properties;

b) cell morphology;

c) colony morphology;

d) use of selective culturing;

e) biochemical properties;

f) genetic sequence data for which there is an adequate data base.

7 Validation of method for determining bioburden

7.1 The method for determining of bioburden shall be validated and documented.

7.2 Validation shall consist of the following:

a) assessment of the adequacy of the technique for removal of microorganisms from product, if removal is part of the method;

b) determination of the recovery efficiency in order that a correction factor be derived;

c) assessment of the adequacy of the enumeration of microorganisms, including culture conditions and microbiological counting techniques;

d) assessment of the suitability of the technique(s) of microbial characterization.

8 Routine determination of bioburden and interpretation of data

8.1 Routine determination of bioburden shall be performed employing documented sampling plan(s) defining sample size and sampling frequency.

8.2 Determination of bioburden shall be performed using a method specified for a product or group of products (see 5.1.2).

8.3 Microbial characterization of bioburden shall be performed to a degree dependent on the purpose for which the data derived from the determination of bioburden are to be used (see 6.2).

If, on microbial characterization, isolates are recovered that are not part of the normal microflora, consideration should be given to assessing the properties of these isolates.