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Sterilization of health care products — Microbiological methods —

Part 1: Determination of a population of microorganisms on products

Stérilisation des produits de santé — Méthodes microbiologiques —

Partie 1: Détermination d'une population de microorganismes sur des produits

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Foreword

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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 on 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 11737-1:2006), which has been technically revised. It also incorporates the Technical Corrigendum ISO 11737-1:2006/Cor.1:2007.

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

— the term “bioburden spikes” has been introduced as a normal and consistent part of the bioburden, and examples of data have been provided;

— clarification has been added that package testing is not typically done except when it is an integral part of the product;

— more information has been provided on the most probable number (MPN) technique and its applications;

— details have been provided on ways to improve limit of detection (LOD) and correct use of the data;

— some discussion has been deleted of statistical methods for the evaluation of bioburden data where information was not typical or not required;

— a table has been added with criteria for selection of a bioburden recovery efficiency approach, the use of the correction factor (CF) has been explained, and the bioburden recovery efficiency value of < 50 % mentioned for technique modifications has been eliminated;

— more information has been provided on the application and performance of a bioburden method suitability test;

— a section has been added to detail rules for direct plate counts, estimated counts and counts beyond the ideal range;

— a table has been added to clarify where typical responsibilities reside for the manufacturer or the laboratory;

— the focus on a risk-based approach has been increased, including the purpose for which bioburden data will be used.

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

Introduction

A sterile health care product is one that is free of viable microorganisms. International Standards that specify requirements for the validation and routine control of sterilization processes require, when it is necessary to supply a sterile health care product, that adventitious microbiological contamination of a health care product prior to sterilization be minimized. 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 health care products 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 there is always a finite probability that a microorganism can 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 microorganisms 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 health care products have been prepared (see, for example, ISO 14937, ISO 11135, the ISO 11137 series, the ISO 17665 series and ISO 14160). 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 a product and/or a sterile barrier system. A knowledge of bioburden can be used in a number of situations as part of the following:

— validation and requalification 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 products. To control bioburden, attention should be given to the microbiological status of these sources.

It is not possible to enumerate bioburden exactly and, in practice, a determination of bioburden is made using a defined method. Definition of a single method for use in determining bioburden in all situations is not practicable because of the wide variety of designs and materials of construction of health care products. 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 culture conditions for enumeration of microorganisms will be influenced by the types of microorganism likely to be present on or in health care products.

This document specifies the requirements to be met for the determination of bioburden. In addition, it gives guidance in the annexes to provide explanations and methods that are deemed suitable to conform with the requirements. Methods other than those given in the guidance may be used, if they are effective in achieving conformity with the requirements of this document.

Sterilization of health care products — Microbiological methods —

Part 1: Determination of a population of microorganisms on products

1 Scope

This document specifies requirements and provides guidance on the enumeration and microbial characterization of the population of viable microorganisms on or in a health care product, component, raw material or package.

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

NOTE 2 See Annex A for guidance on Clauses 1 to 9.

This document does not apply to the enumeration or identification of viral, prion or protozoan contaminants. This includes the removal and detection of the causative agents of spongiform encephalopathies, such as scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob disease.

NOTE 3 Guidance on inactivating viruses and prions can be found in ISO 22442-3, ICH Q5A(R1) and ISO 13022.

This document does not apply to the microbiological monitoring of the environment in which health care products are manufactured.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 15189, *Medical laboratories — Requirements for quality and competence*

ISO/IEC 17025, *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.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

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

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

3.1
batch
defined quantity of a *product* (3.16) intended or purported to be uniform in character and quality, which has been produced during a defined cycle of manufacture

[SOURCE: ISO 11139:—[1)], 3.21]

3.2
bioburden
population of viable microorganisms on or in a *product* (3.16) and/or *sterile barrier system* (3.22)

[SOURCE: ISO 11139:—, 3.23]

3.3
bioburden correction factor
numerical value applied to a viable count to compensate for incomplete removal of microorganisms from a *product* (3.16) and/or failure to culture microorganisms

[SOURCE: ISO 11139:—, 3.24]

3.4
bioburden estimate
value *established* (3.10) by applying a *bioburden correction factor* (3.3) to a *bioburden* (3.2) count

[SOURCE: ISO 11139:—, 3.25]

3.5
bioburden method suitability
assessment of the test method to demonstrate its ability to allow microbial growth

[SOURCE: ISO 11139:—, 3.168, modified — "bioburden" has been added to the term.]

3.6
bioburden spike
individual *bioburden* (3.2) value that is significantly greater than other bioburden values in a set
[SOURCE: ISO 11139:—, 3.26]

3.7
correction
action to eliminate a detected nonconformity

Note 1 to entry: A correction can be made in conjunction with a *corrective action* (3.8).

[SOURCE: ISO 9000:2015, 3.12.3, modified — The Note 1 to entry has been revised and the Note 2 to entry has been deleted.]

3.8
corrective action
situation action to eliminate the cause of a nonconformity and to prevent recurrence

Note 1 to entry: There can be more than one cause for a nonconformity.

Note 2 to entry: Corrective action is taken to prevent recurrence whereas *preventive action* (3.15) is taken to prevent occurrence.

Note 3 to entry: There is a distinction between *correction* (3.7) and corrective action.

[SOURCE: ISO 9000:2015, 3.12.2, modified — "situation" has been added to the definition and the Note 3 to entry has been replaced.]

1) Under preparation. Stage at the time of publication: ISO/DIS 11139:2017.

3.9
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:—, 3.71]

3.10
establish
determine by theoretical evaluation and confirm by experimentation

[SOURCE: ISO 11139:—, 3.107]

3.11
facultative microorganism
microorganism capable of both aerobic and anaerobic metabolism

[SOURCE: ISO 11139:—, 3.114]

3.12
health care product
medical device, including *in vitro* diagnostic medical device, or medicinal *product* (3.16), including biopharmaceutical

[SOURCE: ISO 11139:—, 3.132]

3.13
microbial characterization
process by which microorganisms are grouped into categories

Note 1 to entry: Categories can be broadly based, for example, on the use of selective media, colony or cellular morphology, staining properties or other characteristics.

[SOURCE: ISO 11139:—, 3.170]

3.14
obligate anaerobe
organism that lives and grows in the absence of molecular oxygen

[SOURCE: ISO 11139:—, 3.186]

3.15
preventive action
action to eliminate the cause of a potential nonconformity or other potential undesirable situation

Note 1 to entry: There can be more than one cause for a potential nonconformity.

Note 2 to entry: Preventive action is taken to prevent occurrence whereas *corrective action* (3.8) is taken to prevent recurrence.

[SOURCE: ISO 9000:2015, 3.12.1]

3.16
product
tangible result of a process

EXAMPLE Raw material(s), intermediate(s), sub-assembly(ies), *health care product(s)* (3.12).

[SOURCE: ISO 11139:—, 3.219]

3.17
recovery efficiency
measure of the ability of a specified technique to remove, collect and/or culture microorganisms from a *product* (3.16)

[SOURCE: ISO 11139:—, 3.228]

3.18
requalification
repetition of part or all of *validation* (3.23) for the purpose of confirming the continued acceptability of a specified process

[SOURCE: ISO 11139:—, 3.235]

3.19
sample item portion
SIP
defined part of a *health care product* (3.12) that is tested

[SOURCE: ISO 11139:—, 3.244]

3.20
specify
stipulate in detail within an approved document

[SOURCE: ISO 11139:—, 3.263]

3.21
sterile
free from viable microorganisms

[SOURCE: ISO 11139:—, 3.275]

3.22
sterile barrier system
minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the *sterile* (3.21) *product* (3.16) at the point of use

[SOURCE: ISO 11139:—, 3.276]

3.23
validation
confirmation process, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The objective evidence needed for a validation is the result of a test or other form of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The word "validated" is used to designate the corresponding status.

Note 3 to entry: The use conditions for validation can be real or simulated.

[SOURCE: ISO 9000:2015, 3.8.13, modified — "process" has been added to the definition.]

4 General requirements

4.1 Documentation

4.1.1 Procedures for the determination of bioburden shall be specified.

4.1.2 Documents and records required by this document shall be reviewed and approved by designated personnel (see 4.2.1). Documents and records shall be controlled in accordance with ISO 13485, ISO 15189 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 document shall be specified. Responsibility shall be assigned to competent personnel in accordance with ISO 13485, ISO 15189 or ISO/IEC 17025.

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

NOTE See Annex D for additional information.

4.2.3 All items of equipment required for the 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 conform with ISO 13485, ISO 15189 or ISO/IEC 17025.

4.3.2 A documented system conforming with ISO 13485, ISO 15189, 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 document.

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

4.4.1 For the purpose of bioburden test methods and results, measurement uncertainty, precision and bias typically do not apply and therefore this type of data analysis may not be necessary, except in evaluating the overall competency of the laboratory.

4.4.2 For control of nonconforming products, procedures for the investigation of out-of-specification results and for correction, corrective action and preventive action shall be specified. These procedures shall conform with ISO 13485, ISO 15189 or ISO/IEC 17025.

5 Selection of products

5.1 General

5.1.1 The procedures for the selection and handling of products for the determination of bioburden shall ensure that the selected product is representative of routine production, including packaging materials and processes.

5.1.2 If product(s) are grouped in a product family for the purpose of the determination of bioburden, the rationale for inclusion of a product within a product family shall be recorded. The rationale shall include criteria to ensure that bioburden determined for a product selected from the product family is representative for the whole product family.

5.1.3 Consideration shall be given to the timing of the determination of bioburden relative to manufacturing because bioburden can change with the passage of time.

5.2 Sample item portion (SIP)

5.2.1 Either the entire product (SIP = 1,0) or a portion of the product (SIP < 1,0) may be used for the determination of bioburden.

5.2.2 If an SIP < 1,0 is used, the SIP shall be of sufficient size to adequately represent the bioburden of the entire product. The determination of portions selected shall be based on whether the bioburden is evenly distributed or not, as described in 5.2.3 to 5.2.5.

5.2.3 When the bioburden distribution is known, the following applies:

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

b) if the bioburden is not evenly distributed, the SIP shall include either

   1) portions of the product selected that proportionally represent each of the materials from which the product is made, or

   2) the portion of the product that contains the most severe microbial challenge (numbers and/or types) to the sterilization process.

When selecting the portion that contains the most severe microbial challenge, the relationship of the bioburden of the SIP tested to the entire product bioburden should be established.

5.2.4 If the bioburden distribution is not known, the SIP shall consist of portions of the product selected that proportionally represent each of the materials from which the product is made.

5.2.5 The SIP can be calculated on the basis of dimensional characteristics, such as length, mass, volume or surface area (see Table A.1 for examples).

NOTE Some standards specifying requirements for validation and routine control of the sterilization process stipulate criteria for the adequacy of the SIP, e.g. the ISO 11137 series.

6 Methods of determination and microbial characterization of bioburden

6.1 Determination of bioburden

6.1.1 Selection of an appropriate method

The method shall be appropriate to the purpose for which the data are to be used. The method/s shall comprise techniques for the following:

a) neutralization of inhibitory substances, if needed;

b) removal of microorganisms, if appropriate;

c) culturing of microorganisms;