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Sterilization of medical devices — Microbiological methods —

Part 1: Estimation of population of microorganisms on products

Stérilisation des dispositifs médicaux — Méthodes microbiologiques —

Partie 1: Estimation de la population de micro-organismes sur les produits

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Contents

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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.

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 11737-1 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*, and is based on three European Standard drafts prepared by Working Group 5 of CEN Technical Committee 204, *Sterilization of medical devices*.

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

— *Part 1: Estimation of population of microorganisms on products*

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

Additional parts will be published later.

Annexes A, B and C of this part of ISO 11737 are for information only.

Introduction

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

The inactivation of a pure culture of microorganisms by physical and/or chemical agents used to sterilize health care products often approximates to 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 nonsterile item in that population.

Requirements for the quality system for the design/development, production, installation and servicing of health care products are given in ISO 9001 and ISO 9002. The ISO 9000 series of International 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 efficiency cannot be verified by inspection and testing of the product. For this reason, sterilization processes have to be validated before use, the performance of each process monitored routinely and the equipment properly 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 ISO 11134, ISO 11135 and ISO 11137). 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. Indeed for the effective validation and routine control of a sterilization process, it is also important to be aware of the microbiological challenge which is presented to that process, in terms of number, identities and properties of microorganisms.

The presterilization microbiological contamination is the sum of contributions from a number of sources; therefore attention also has to be given to factors including the microbiological status of incoming raw materials and/or components and their subsequent storage, and to the control of the environment in which the product is manufactured, assembled and packaged.

The term "bioburden" is commonly used to describe the population of viable microorganisms present on a material or product. It is not possible to determine the exact bioburden and therefore, in practice, a viable count is determined using a defined technique. Validation exercises are performed to relate this viable count to a bioburden estimate on a material or product by the application of a correction factor.

The knowledge of the bioburden results from the investigation of microbiological contamination levels. Bioburden estimations are performed in a number of separate situations as part of the:

a) validation and revalidation of a sterilization process for which the extent of exposure to sterilizing conditions is to be directly related to the bioburden estimate;

b) validation and revalidation of a sterilization process for which the extent of exposure to sterilizing conditions is not to be directly related to the bioburden estimate, but for which a general knowledge of bioburden is required;

c) routine control of the manufacturing process for a sterile product for which sterilization validation was as stated in a) above;

d) routine control of the manufacturing process for a sterile product for which sterilization validation was as stated in b) above.

Bioburden estimations may also be employed as part of the quality system for the manufacture of health care products as an element of:

e) an overall environmental monitoring programme;

f) the assessment of the efficiency of a cleaning process in removing microorganisms;

g) the process monitoring for products which are supplied nonsterile but for which the microbiological cleanliness is specified;

h) the monitoring of raw materials, components or packaging.

The bioburden estimation of a medical device generally consists of four distinct stages:

— removal of microorganisms from the medical device;

— transfer of these isolated microorganisms to culture conditions;

— enumeration of the microorganisms with subsequent characterization;

— application of the correction factor(s) determined during bioburden recovery studies in order to calculate the bioburden estimate from the presterilization count.

It is not possible to define a single technique to be used for the removal of microorganisms in all situations because of the wide variety of materials for construction and design of health care products. Furthermore, the selection of conditions for enumeration will be influenced by the types of contaminant which may be anticipated.

This part of ISO 11737 therefore specifies the general criteria to be applied to the estimation of bioburden. The annexes of this part of ISO 11737 provide additional guidance (annex A) and methods which may be used for validating the technique (annex B).

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Sterilization of medical devices — Microbiological methods —

Part 1:
Estimation of population of microorganisms on products

1 Scope

1.1 This part of ISO 11737 specifies general criteria to be applied in the estimation of the population of viable microorganisms on a medical device or component, raw material or package thereof. This estimation consists of both enumeration and characterization of the population.

NOTES

1 Prior to routine use, a technique for estimating the population of microorganisms on product is validated. The level to which identification is necessary during characterization depends on the use to be made of the data generated.

2 Annexes to this part of ISO 11737 provide guidance on selection of a technique and outline method(s) which may be used to validate the technique selected.

1.2 This part of ISO 11737 is not applicable to the enumeration or identification of viral contamination.

This part of ISO 11737 is not applicable to the microbiological monitoring of the environment in which medical devices are manufactured.

NOTE 3 Attention is drawn to the International Standards for quality systems (see ISO 9001 and ISO 9002) which control all stages of manufacture including the sterilization process. It is not a requirement of this part of ISO 11737 to have a complete quality system during manufacture, but certain elements of such a system are required and these are normatively referenced at appropriate places in the text.

2 Normative reference

The following standard contains provisions which, through reference in this text, constitute provisions of this part of ISO 11737. At the time of publication, the edition indicated was valid. All standards are subject to revision, and parties to agreements based on this part of ISO 11737 are encouraged to investigate the possibility of applying the most recent edition of the standard indicated below.

Members of the 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.*

3 Definitions

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

3.1 bioburden: Population of viable microorganisms on a product and/or a package.

3.2 bioburden estimate: Value established for the number of microorganisms comprising the bioburden by applying to a viable count or presterilization count a factor compensating for the recovery efficiency.

3.3 characterization: General process in which microorganisms are grouped into broad categories.

NOTE 4 Categories may be based, for example, on colony or cellular morphology, staining properties or other characteristics.

3.4 correction factor: Numerical value applied to a viable count or presterilization count to compensate for the incomplete removal of microorganisms from product and thus produce a bioburden estimate.

3.5 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.

3.6 medical device: Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purposes of

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;

— investigation, replacement or modification of the anatomy or of a physiological process;

— control of conception;

and which does not achieve its principal 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.

3.7 presterilization count: Viable count obtained prior to sterilization.

3.8 product: Generic term used to describe raw materials, intermediate products, subassemblies and finished medical devices.

3.9 recovery efficiency: Measure of the ability of a specified technique to remove microorganisms from product.

3.10 revalidation: Set of documented procedures to confirm an established validation.

3.11 sample item portion (SIP): Defined portion of a health care product unit that is tested.

3.12 validation: Documented procedure for obtaining, recording and interpreting the results needed to show that a process will consistently yield a product complying with predetermined specifications.

NOTE 5 In the context of estimating the bioburden, the "process" is the test methodology and the "product" is the test result. The validation of a technique for bioburden estimation consists of a series of investigations to determine the effectiveness and reproducibility of the test method.

3.13 viable count: Number of microorganisms estimated by growth of discrete colonies under the stated culture conditions.

NOTE 6 A discrete colony may not necessarily originate from a single viable microorganism.

4 General

4.1 Documentation

4.1.1 Documented procedures and instructions on the testing techniques to be employed and the use and operation of all relevant equipment shall be available. These procedures and instructions shall be approved on issue and shall be controlled as specified in ISO 9001.

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

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

NOTE 7 If calculations are performed by electronic data-processing techniques, the software should be validated prior to use and records of this validation should be retained.

4.1.4 Records of all original observations, calculations, derived data and final reports shall be retained as specified in ISO 9001. The records shall include the identity of all personnel involved in sampling, preparation and testing.

4.2 Personnel

4.2.1 Responsibility for bioburden estimation shall be assigned to specific personnel as specified in ISO 9001.

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

4.3 Equipment

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 having measurement or control functions. This calibration system shall comply with ISO 9001.

4.4 Media and materials

Methods shall be established and documented for the preparation and sterilization of materials used in bioburden estimation, including appropriate quality tests.

NOTE 8 Appropriate quality tests should include growth promotion tests on batches of media/each batch of medium.

5 Selection of product units

5.1 Product unit selection

The procedures for selection and procurement of product for testing shall be established to ensure that the product is representative of routine production.

5.2 Sample item portion (SIP)

If a sample item portion (SIP) of less than one whole product unit is to be used, it shall be selected to possess microorganisms representative of the whole product. If it has been demonstrated that the microorganisms are evenly distributed on the product, the portion shall be selected from any single location. In the absence of such a demonstration, the portion shall be made up of pieces of product from several locations.

NOTE 9 The standards specifying the requirement for validation and routine control of the sterilization process should stipulate the criteria for the adequacy of SIP.

6 Selection of technique

6.1 For an identified product, factors relevant to the efficiency of removal of viable microorganisms from product shall be considered and recorded, if such removal is part of the technique. Factors shall include:

a) ability to remove microbiological contamination;

b) possible type(s) of contaminating microorganisms and their locations on product;

c) effect(s) of the removal method on the viability of microbiological contamination;

d) the physical or chemical nature of product to be tested.

6.2 If the physical or chemical nature of product to be tested [see item d) of 6.1] is such that substances may be released which would adversely affect either the number or the types of microorganisms detected, then a system to neutralize, remove or, if this is not possible, minimize the effect of any such released substance shall be used. The effectiveness of each system shall be demonstrated.

NOTE 10 Annex B describes methods which may be used to assess the release of microbicidal or microbiostatic substances.

6.3 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.

6.4 The selected technique shall be validated as specified in clause 7.

7 Validation of technique

7.1 Each procedure for the validation of bioburden estimations shall be documented.

7.2 The validation procedures shall consist of the following steps:

a) assessment of the adequacy of the technique used to remove microorganisms from the product, if such removal is part of the technique;

b) assessment of the adequacy of the technique used to enumerate removed microorganisms, including microbiological counting techniques and culture conditions; and

c) establishment of the recovery efficiency of the method used in order that the correction factor can be calculated.

NOTE 11 Annex B describes methods which may be used in the validation of techniques for bioburden estimation.

7.3 Any change in a routine method shall be assessed. This assessment shall include:

a) evaluation of the change;

b) establishment of the recovery efficiency of the revised method.

NOTE 12 The assessment of the change may indicate that the previous validation and recovery efficiency are still applicable.

7.4 The validation and any subsequent revalidation data shall be reviewed periodically and the extent of revalidation determined and documented. Procedures for the review of validation and revalidation shall be documented and records of the revalidation shall be retained.

The revalidation report shall be signed by the same functions/organizations that prepared, reviewed and accepted the original validation report.

8 Use of technique

8.1 Presterilization counts shall be performed in accordance with documented sampling plan(s) with defined sampling frequency and sample size.

8.2 If contaminants that are not normally encountered are isolated while performing presterilization counts, they shall be characterized. The influence of such contaminants on the manufacturing process, including the effectiveness of the sterilization process, shall be considered and documented.

8.3 Acceptable limits for either presterilization counts or bioburden estimates shall be established on the basis of previous data and documented. If these limits are exceeded, corrective action shall be undertaken as specified in ISO 9001. Established limits shall

be reviewed formally at defined intervals and revised if necessary.

8.4 If statistical methods are used to define sample size, sampling frequency and/or acceptance limits, they shall conform with ISO 9001.

8.5 When presterilization counts are to be used to determine the extent of treatment of a sterilization process (unless a requirement in a standard for the validation of the particular sterilization process specifies otherwise), then:

a) a correction factor, based on the recovery efficiency, as determined during validation (see 7.2), shall be applied to the presterilization count to calculate the bioburden estimate before the extent of treatment is determined; and

b) the resistance of the microorganisms comprising the population present on product shall be considered in determining the extent of treatment.

NOTE 13 In applying microbiological data to establishing a sterilizing dose for sterilization by irradiation (see annex B of ISO 11137:1995 and see ISO 13409), a presterilization count may be used to select the verification and sterilizing doses.

8.6 If bioburden estimates have been used to determine the extent of treatment of the sterilization process:

a) consideration shall be given to the effect on the assurance of sterility if the acceptable limits are exceeded; and

b) the characterization of contaminants that are not normally encountered shall include an estimation of the resistance of those contaminants to the sterilization process. The consequences of the presence on product of contaminants with high resistance to the sterilization process on the assurance of sterility shall be considered.

All these considerations shall be documented and included in the determination of corrective action. This corrective action shall be conducted in accordance with ISO 9001.

8.7 Changes to product and/or processes shall be reviewed formally to determine whether they are likely to result in a change in the bioburden (see also 8.3). The results of the review shall be documented. If a change in bioburden is envisaged, specific bioburden estimations shall be performed to evaluate the effects of the change.

Annex A
(informative)

Guidance on estimating population of microorganisms on products

A.1 Introduction

This annex contains guidance on the implementation of the requirements specified in this part of ISO 11737, and is aimed at providing better understanding of the requirements. The guidance given is not intended to be exhaustive, but to highlight important aspects to which attention should be given.

Methods other than those given in this annex may be used, but these alternative methods should be demonstrated effective in achieving compliance with the requirements of this part of ISO 11737.

This annex is not intended as a checklist for assessing compliance with the requirements of this part of ISO 11737.

A.2 General

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

If bioburden estimations are performed in a laboratory under the direct management of the manufacturer of the medical device, 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 ISO document (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 a laboratory quality system. Particular requirements for quality systems for manufacture of medical devices are given in ISO 13485 and 13488.

A.3 Equipment and materials

A.3.1 Electronic data-processing equipment

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.

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.

For software, there should be documentation describing:

— applications software run on the computer system;

— operations software;

— data packages in use.

All software should be acceptance-tested before being put into service (see, for example ISO 9000-3).

If commercial software packages are purchased, these packages should have been prepared under a quality system as described in ISO 9000-3.

If computer software is developed in-house, suitable procedures should be developed to ensure that:

— documentation on development, including the source code, is retained;

— records of acceptance testing are retained;

— modifications to programs are documented;