
**Sterilization of health care products —
Radiation sterilization — Product families
and sampling plans for verification dose
experiments and sterilization dose audits,
and frequency of sterilization dose audits**

*Stérilisation des produits de santé — Stérilisation par irradiation —
Familles de produits, plans d'échantillonnage pour les expositions à la dose
de vérification et les audits de la dose stérilisante, et fréquence des audits
de la dose stérilisante*



Reference number
ISO/TS 15843:2000(E)

PDF disclaimer

This PDF file may contain embedded typefaces. In accordance with Adobe's licensing policy, this file may be printed or viewed but shall not be edited unless the typefaces which are embedded are licensed to and installed on the computer performing the editing. In downloading this file, parties accept therein the responsibility of not infringing Adobe's licensing policy. The ISO Central Secretariat accepts no liability in this area.

Adobe is a trademark of Adobe Systems Incorporated.

Details of the software products used to create this PDF file can be found in the General Info relative to the file; the PDF-creation parameters were optimized for printing. Every care has been taken to ensure that the file is suitable for use by ISO member bodies. In the unlikely event that a problem relating to it is found, please inform the Central Secretariat at the address given below.

© ISO 2000

All rights reserved. Unless otherwise specified, no part of this publication may be reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying and microfilm, without permission in writing from either ISO at the address below or ISO's member body in the country of the requester.

ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.ch
Web www.iso.ch

Printed in Switzerland

Contents

Page

Foreword.....	iv
Introduction	v
1 Scope	1
2 Normative references	1
3 Terms and definitions	1
4 Establishment and maintenance of product families	2
4.1 General.....	2
4.2 Establishing product families.....	3
4.3 Designation of representative products for performance of verification dose experiment and sterilization dose audit.....	3
4.4 Failure of sterilization dose audit.....	5
4.5 Maintaining product families	5
5 Sample sizes for the verification dose experiment and sterilization dose audit	5
5.1 General.....	5
5.2 Limitations of use	6
5.3 Selection and testing of product.....	6
5.4 Procedures for verification dose experiments and sterilization dose audits	8
6 Frequency of sterilization dose audits	22
6.1 Rationale.....	22
6.2 Conditions for reduction in frequency of sterilization dose audits from a 3-month to a 6-month interval	22
6.3 Conditions for reduction in frequency of sterilization dose audits from a 6-month to a 12-month interval	23
6.4 Sterilization dose audit failure.....	23
Annex A (normative) Sample sizes for implementation of sampling plans and sampling scheme	24
Bibliography	25

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 3.

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.

In other circumstances, particularly when there is an urgent market requirement for such documents, a technical committee may decide to publish other types of normative document:

- an ISO Publicly Available Specification (ISO/PAS) represents an agreement between technical experts in an ISO working group and is accepted for publication if it is approved by more than 50 % of the members of the parent committee casting a vote;
- an ISO Technical Specification (ISO/TS) represents an agreement between the members of a technical committee and is accepted for publication if it is approved by 2/3 of the members of the committee casting a vote.

An ISO/PAS or ISO/TS is reviewed every three years with a view to deciding whether it can be transformed into an International Standard.

Attention is drawn to the possibility that some of the elements of this Technical Specification may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO/TS 15843 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

Annex A forms a normative part of this Technical Specification.

Introduction

This Technical Specification is intended to be used in conjunction with ISO 11137:1995, *Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization*. One of the activities encompassed within ISO 11137 is the selection and routine auditing of the sterilization dose to be applied to health care products.

Informative annex B to ISO 11137:1995 describes two methods of selecting a sterilization dose. Both of these methods require that a relatively large number of product units be drawn from production batches and used in procedures for selection of the sterilization dose. In addition, the two methods require that a relatively large number of product units, drawn from production batches, be tested at least every three months to confirm the continued validity of the selected sterilization dose.

In some circumstances, a primary manufacturer may wish to reduce the number of product units used, provided that this can be accomplished while maintaining assurance that the designated Sterility Assurance Level (SAL) is attained. The guidance contained within this Technical Specification provides strategies by which the primary manufacturer may reduce the total number of product units to be tested for establishing and maintaining the sterilization dose through three separate approaches:

a) Product families

This approach consists of the grouping of products into product families and testing a representative member of that family in the selection of the sterilization dose and in sterilization dose auditing. This Technical Specification provides guidance for establishing product families and for selecting the product to be tested. Such establishment and selection are subjective and require technical judgment in their application to specific health care products.

b) Alternative sampling plans

This approach employs alternative sampling plans that are statistically equivalent to the sample size of 100 product units in ISO 11137, even though a different number of products is tested. However, with this approach, there is no provision for the augmentation of the sterilization dose in the case of audit failure, and the sterilization dose has to be re-established.

c) Audit frequency

This approach consists of the reduction in the frequency of sterilization dose audits based on a documented history of successful sterilization dose audits and information to demonstrate that the manufacturing process is under control. ISO 11137 requires that sterilization dose audits be carried out at three-month intervals because of the potential for seasonal variations in product bioburden. However, the methods described in ISO 11137 presume that the manufacturing process is under control and will yield product with a consistent bioburden.

Sterilization of health care products — Radiation sterilization — Product families and sampling plans for verification dose experiments and sterilization dose audits, and frequency of sterilization dose audits

1 Scope

This Technical Specification describes approaches to the selection and auditing of a sterilization dose that economize in relation to the number of product units required while maintaining assurance of attaining the desired sterility assurance level (SAL). These approaches address

- a) establishing and maintaining product families for the selection and auditing of a sterilization dose,
- b) sampling plans for verification dose experiments and sterilization dose audits, and
- c) frequency of sterilization dose audits.

NOTE Notification of the method of dose selection described in this Technical Specification may be used to meet the requirements specified under 6.2.2 relating to product qualification or 6.6.3 relating to sterilization dose auditing in ISO 11137.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this Technical Specification. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this Technical Specification 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 ISO and IEC maintain registers of currently valid International Standards.

ISO 11137:1995, *Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization*.

ISO 11737-1:1995, *Sterilization of medical devices — Microbiological methods — Part 1: Estimation of population of microorganisms on products*.

ISO 11737-2:1998, *Sterilization of medical devices — Microbiological methods — Part 2: Tests of sterility performed in the validation of a sterilization process*.

ISO 13485:1996, *Quality systems — Medical devices — Particular requirements for the application of ISO 9001*.

ISO 13488:1996, *Quality systems — Medical devices — Particular requirements for the application of ISO 9002*.

3 Terms and definitions

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

3.1
augmentation

action taken to increase the sterilization dose based upon the results obtained from a sterilization dose audit

3.2
bioburden

population of viable microorganisms on a product

NOTE In the context of radiation sterilization, bioburden is determined immediately prior to sterilization.

3.3
characterization

general process in which microorganisms are grouped into broad categories

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

3.4
false positive

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

3.5
health care product

product group encompassing medical devices, medical products (pharmaceuticals and biologics) and *in vitro* diagnostics

3.6
product unit

health care product, collection of products or components within a primary package

3.7
revision

action taken to increase the verification dose based upon the results obtained from a sterilization dose audit

3.8
sampling plan

sample size(s) to be used, and associated acceptance criteria

3.9
sampling scheme

series of sampling plans with rules for switching between them

3.10
sterilization dose audit

activity taken to detect whether or not a change in sterilization dose is needed

3.11
verification dose

dose of radiation to which product units, or a portion thereof, are nominally exposed in the verification dose experiment with the intention of achieving a predetermined sterility assurance level

4 Establishment and maintenance of product families

4.1 General

Selecting a sterilization dose and carrying out sterilization dose audits are activities that are part of validation and routine control of radiation sterilization. Products may be grouped into families for these activities, based on the number and types of microorganisms present on product items (the bioburden). Processing variables, such as

density and product configuration within its packaging, are not considered in the establishment of these product families, as they are not factors that influence bioburden.

The principles for establishing product families described here are unique to radiation sterilization and are not necessarily appropriate for use with other sterilization methods (for example ethylene oxide or moist heat sterilization).

It is important to be aware of the risks associated with using product families for establishing the sterilization dose and for sterilization dose auditing. One such risk results from a reduction in the ability to detect an inadvertent change within the manufacturing process. Furthermore, the use of a single product to represent the family may not detect changes that occur in other members of the product family. The risk associated with a reduction in ability to detect changes in other members of the product family should be evaluated, and a plan for maintaining product families (4.5) should be developed and implemented before proceeding.

4.2 Establishing product families

4.2.1 The criteria for establishing a product family shall be documented. Individual products shall be assessed against these criteria, and the similarities between potential family members considered. Consideration shall include all variables that impact on bioburden, such as

- a) raw materials,
- b) components,
- c) product design and size,
- d) manufacturing process,
- e) manufacturing equipment,
- f) manufacturing environment, and
- g) manufacturing location.

The outcome of the assessment and considerations shall be documented.

4.2.2 Products manufactured in different locations shall only be included in a product family if it is demonstrated that the product-related variables are under control. In order to include such products into a product family, it shall be demonstrated that the product bioburden, determined in accordance with ISO 11737-1, comprises similar numbers and types of microorganisms. In particular, consideration shall be given to the impact on bioburden of

- a) geographic and/or climatic differences between locations;
- b) any differences in control of the manufacturing processes or environment;
- c) sources of raw materials and processing adjuvants (e.g. water).

Inclusion of products from multiple manufacturing locations in a product family shall be justified and documented.

4.3 Designation of representative products for performance of verification dose experiment and sterilization dose audit

4.3.1 Product to represent a product family

4.3.1.1 The establishment and the continued validity of the sterilization dose are related to both the numbers and resistances of microorganisms on or in product. Therefore, these characteristics shall be used as the basis for selecting a product to represent a product family.

4.3.1.2 A family of products shall be represented by

- a) the master product, or
- b) an equivalent product, or
- c) a simulated product.

4.3.1.3 A formal, documented assessment shall be undertaken to decide which of the three potential representative products outlined in 4.3.1.2 is appropriate. In this assessment, consideration should be given to the following:

- a) numbers of microorganisms,
- b) types of microorganisms,
- c) size of product,
- d) number of components,
- e) complexity of product,
- f) degree of automation during manufacture, and
- g) manufacturing environment.

4.3.2 Master product

A master product shall only represent the product family if assessment (see 4.3.1.3) indicates that one member of the product family presents a challenge to the sterilization process that is greater than that of all other family members. In some situations there may be several products within the family that could be considered as the master product. In such circumstances, any one of these products may be selected as the master product to represent the family in accordance with 4.3.3.

4.3.3 Equivalent product

A group of products shall only be considered equivalent in representing the product family if assessment (see 4.3.1.3) indicates that the group represents an equal challenge to the sterilization process. Selection of the equivalent product shall either be a) random or b) in accordance with a planned schedule to include the equivalent family members. The manufacturing volume and availability of product should be considered in the selection of the product to represent the family.

4.3.4 Simulated product

A simulated product shall only represent a product family if it constitutes an equivalent or greater challenge to the sterilization process than that of the products in the family. A simulated product is not intended for clinical use; it is fabricated solely for use in establishment or maintenance of the sterilization dose. A simulated product may be:

- a) one which is similar to the actual product in terms of materials and size, and is subjected to similar manufacturing processes; for example, a piece of the material used for implants which goes through the entire process, or
- b) a combination of components from products within the family that would not typically be combined for use; for example, a tubing set containing multiple filters, clamps and stopcocks that are components of other products within the product family.

The simulated product should be packaged in the same manner and using the same materials as the actual product.

4.4 Failure of sterilization dose audit

In the event of a failure in the sterilization dose audit, all members of that product family shall be considered to be affected. Related decisions (e.g. augmentation of the sterilization dose or cessation of sterilization until re-establishment of the sterilization dose is completed) shall be applied to all products within that family.

4.5 Maintaining product families

4.5.1 General

The individual with responsibility for sterilization shall participate in periodic reviews of product families and in the assessment of the impact of modifications to product/processes. The outcome of such assessments and review shall be documented.

4.5.2 Modifications to product and/or manufacturing processes

Modifications to products, such as raw materials (nature and source), components or product design (including size), and/or modifications to the manufacturing process, such as equipment, environment or location, shall be evaluated through a formal, documented change control system. Such modifications may alter the basis on which the product family was established or the basis on which the selection of product to represent the product family was made. Significant changes may require establishment of a new product family or the selection of different representative product.

4.5.3 Review of product families

A formal review shall be performed at a specified frequency to assure that all product families and product(s) used to represent each family remain valid.

Such a review should be conducted at least annually.

4.5.4 Records of product families

A record of product families shall be established and maintained.

5 Sample sizes for the verification dose experiment and sterilization dose audit

5.1 General

This clause provides guidance on the sample sizes that may be used in place of those employed for:

- a) the performance of the verification dose experiment of Method 1 of ISO 11137, annex B, and

NOTE Where appropriate, these sample sizes may also apply to the verification dose experiment of ISO 15844.

- b) the sterilization dose audit activities that form part of dose-setting Methods 1 and 2 of ISO 11137, annex B.

In ISO 11137, a sample size of 100 product units is specified for conducting the verification dose experiment and sterilization dose audits in order to provide an SAL of 10^{-2} . Generally, this number of product units can be tested consistently in most laboratories with a minimal occurrence of false positives. The use of a sample size of 100 product units continues to be appropriate for the performance of the verification dose experiment and sterilization dose audits.

There are sampling plans other than that described in ISO 11137, which provide equivalent ability to detect increases in the numbers and/or resistance of the microbial population. These sampling plans have a sample size and acceptance criteria different than those described in ISO 11137. Statistical analysis of alternative sampling plans was performed, and the outcome of the analysis has been published [1]. This forms the basis for the methods