List of Titles

Technical Information Report

ANSI/AAMI/ISO TIR15843:2000

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

AAMI Association for the Advancement of Medical Instrumentation

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

Approved 16 October 2000 by
The Association for the Advancement of Medical Instrumentation

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American National Standards Institute

Abstract: Describes methods and rationale for changing the number of product units required for dose setting verification and dose audits as defined in annex B of ANSI/AAMI/ISO 11137.

Keywords: sterilization, radiation, health care products, dose, audits, design verification, procedures

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AAMI Technical Information Report

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Comments on the content of this document should be sent to AAMI, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

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Committee representation

Association for the Advancement of Medical Instrumentation

Sterilization Standards Committee

This technical information report was developed and balloted by the AAMI Radiation Sterilization Working Group under the auspices of the AAMI Sterilization Standards Committee. Approval of this technical information report does not necessarily imply that all working group members voted for its approval.

At the time this document was published, the **AAMI Sterilization Standards Committee** had the following members:

Cochairs: Victoria Hitchins, PhD
William E. Young

Members: Trabue D. Bryans, Viromed Biosafety Laboratories
Virginia C. Chamberlain, PhD, Hendersonville, NC
Anne M. Cofiell, IAHCSMM
Neal E. Danielson, Wichita, KS
Dorothy M. Fogg, Association of periOperative Registered Nurses
Lisa Foster, Ion Beam Applications
James M. Gibson, Jr., Odessa, FL
Barbara J. Goodman, Baltimore, MD
Joel R. Gorski, PhD, North American Science Associates, Inc.
Susan Hadfield, Canadian Standards Association
Victoria Hitchins, PhD, U.S. Food and Drug Administration
Sue Kuhnert, STSduoTEK
Byron J. Lambert, PhD, Guidant Corporation
Paul S. Malchesky, STERIS Corporation
Patrick C. McCormick, PhD, Bausch & Lomb, Inc.
Robert F. Morrissey, PhD, Johnson & Johnson
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Janet K. Schultz, Roswell, GA
Harry L. Shaffer, Titan Corporation–Titan Scan
Robert J. Sharbaugh, PhD, CIC, Association for Professionals in Infection Control and Epidemiology
Frank Sizemore, American Society for Healthcare Central Service Professionals
James L. Whitby, University of Western Ontario
Thelma Wilcott, Becton Dickinson
Stephen C. Yeadon, Alcon Laboratories, Inc.
William E. Young, Baxter Healthcare Corporation

Alternates: Bettye Beebe, Alcon Laboratories, Inc.
Carl Bruch, PhD, Pennsylvania Engineering Company
Louis M. Glasgow, Bausch & Lomb, Inc.
Joyce M. Hansen, Baxter Healthcare Corporation
Lois A. Jones, Becton Dickinson
Susan G. Klacik, IAHCSMM
Sandra A. Lee, STERIS Corporation
Chiu Lin, PhD, U.S. Food and Drug Administration
Janet Prust, 3M Healthcare
Bruce Schullo, Ion Beam Applications
James Whitbourne, STSduoTEK

At the time this document was published, the **AAMI Radiation Sterilization Working Group** had the following members:

Cochairs: Joyce M. Hansen
Byron J. Lambert, PhD

Members: Krisann Anderson, St. Jude Medical, Inc.
Richard H. Bean, Zimmer, Inc.
Bettye Beebe, Alcon Laboratories, Inc.
Leonard S. Berman, PhD, Pall Corporation

Chitra S. Bhambhani, Ethox Corporation
Anne F. Booth, Barrington, IL
John Broad, North American Science Associates, Inc.
Delores Bruce, Northview Biosciences
Trabue D. Bryans, Viromed Biosafety Laboratories
Virginia C. Chamberlain, PhD, Hendersonville, NC
Rod Chu, MDS Nordion
Charles Cogdill, Boston Scientific Corporation
Gary N. Cranston, Taunton, MA
Christine A. Czap, Fresenius Medical Care NA Dialysis Products Division
Douglas D. Davie, Sterilization Validation Services
Brian R. Drumheller, CR Bard
Joyce Elkins, STERIS Corporation
William F. FitzGerald, Hot Springs Village, AR
Lisa Foster, Ion Beam Applications
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Gerry O'Dell, Wesley Chapel, FL
Frank Peacock, Jr., Bausch & Lomb, Inc.
Steven G. Richter, PhD, Microtest Laboratories, Inc.
Susan Edel Satter, Boulder, CO
Zenius V. Seliokas, Stericon, Inc.
Jon Seulean, Gambro, Inc.
Harry L. Shaffer, Titan Corporation–Titan Scan
Steven R. Thompson, Datascope Corporation
William Thompson, TYCO Healthcare
James L. Whitby, University of Western Ontario
Thelma Wilcott, Becton Dickinson
Martell Kress Winters, Nelson Laboratories, Inc.

Alternates:

Ruth Brinston, MDS Nordion
Susan Bullis, Bausch & Lomb, Inc.
Harry F. Bushar, PhD, U.S. Food and Drug Administration
Craig Day, Nelson Laboratories, Inc.
Kristina Dean, Allegiance Healthcare Corporation
Anthony J. DeMarinis, CR Bard
Niki Fidopiastis, Ion Beam Applications
Ruth Garcia, STERIS Corporation
Doug F. Harbrecht, Boston Scientific Corporation
Lisa N. Macdonald, Becton Dickinson
Dave Parente, North American Science Associates, Inc.
Timothy Ramsey, Northview Biosciences
John F. Reger, Johnson & Johnson
Manny Saavedra, Kimberly-Clark Corporation
Mark Seybold, Baxter Healthcare Corporation
Fuh-Wei Tang, PhD, Guidant Corporation
Glen M. Thibault, Titan Corporation–Titan Scan
Robert P. Tomaselli, Zimmer, Inc.
Richard L. Weisman, Fresenius Medical Care NA Dialysis Products Division
Stephen C. Yeadon, Alcon Laboratories, Inc.

NOTE—Participation by federal agency representatives in the development of this technical information report does not constitute endorsement by the federal government or any of its agencies.

Background of AAMI Adoption of ISO/TS 15843:2000

ISO/TS 15843:2000 (Technical Specification) was developed by ISO Technical Committee 198, *Sterilization of health care products*, to fill a need for a technical report for the selection of a sterilization dose for a single production batch.

The United States made a considerable contribution to this report. The AAMI Radiation Sterilization Working Group of the AAMI Sterilization Standards Committee had originally initiated the development of this document in the U.S. When a committee draft had been developed, it was proposed for processing as an ISO Technical Report (type 2) and submitted for a parallel adoption as an AAMI Technical Information Report. ISO/TC 198 and AAMI approved the technical report in 2000. U.S. participation in ISO/TC 198 is organized through the U.S. Technical Advisory Group for ISO/TC 198, administered by the Association for the Advancement of Medical Instrumentation (AAMI).

TIR15843 is intended to be used in conjunction with ANSI/AAMI/ISO 11137, *Sterilization of health care products—Requirements for validation and routine control—Radiation sterilization*. AAMI has produced other TIRs that are intended as companion documents to ANSI/AAMI/ISO 11137. These are:

- AAMI/ISO TIR13409:1996, Sterilization of health care products—Radiation sterilization—Substantiation of 25 kGy as a sterilization dose for small or infrequent production batches
- AAMI TIR17:1997, Radiation sterilization—Material qualification
- AAMI/ISO TIR15884:1998, Sterilization of health care products—Radiation sterilization—Selection of a sterilization dose for a single production batch

Procedures require that AAMI consult with the technical committee about 5 years after the publication date (and periodically thereafter) for guidance on whether the document is still useful and whether the information is relevant or of historical value. In the event that the information is not useful, the TIR is removed from circulation.

Suggestions for improving this report are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

NOTE—Beginning with the ISO foreword on page x, this AAMI Technical Information Report is identical to ISO/TS 15843:2000.

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 documents:

— 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 two-thirds of the members of the committee casting a vote.

An ISO/PAS or ISO/TS is reviewed every 3 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, S*terilization 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 3 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 reestablished.

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 3-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 described in this Technical Specification. In the ISO 11137 sampling plan, the results derived from each sample are evaluated independently. It should be noted that the sterilization dose audit sampling plan in ISO 11137 is not typical for a statistical double-sampling plan. In a typical double-sampling plan, the results are summed when a second sample is obtained. All of the alternative sampling plans described here utilize the sum of the results when a second sample is obtained.

5.2 Limitations of use

In the performance of an ISO 11137 verification dose experiment or sterilization dose audit, a sample size of 100 product units is utilized together with acceptance criterion of, on average, one positive test of sterility in 100 units tested (i.e., 1 %). In the design of the alternative sampling plans contained in this Technical Specification, an acceptance criterion of an average of 1 positive test of sterility in every 200 units tested (i.e., 0.5 %) was used for the simulations. This acceptance criterion is close to an industry experience which was reported in a review of the use of

dose-setting Methods 1 and 2 [2]. It follows that the alternative sampling plans for sterilization dose audit should only be used for products or product families which have a history of audit results with less than 1 positive in 200 units. In the absence of this history, there is an increased risk of failure using these alternative sampling plans.

In the performance of a sterilization dose audit in accordance with Method 1 or 2 of ISO 11137, augmentation of the sterilization dose as an interim measure is permitted. However, the procedures for augmentation of the sterilization dose when using these alternative sampling plans have not yet been developed. In the event of failure of the sterilization dose audit when using the alternative sampling plans, the sterilization dose shall be reestablished.

5.3 Selection and testing of product

5.3.1 Selection

5.3.1.1 Method of selection

The method of selecting product units for testing shall be in accordance with ISO 11137:1995, B.3.1.

5.3.1.2 Sample item portion (SIP)

5.3.1.2.1 Whenever practicable, an entire product unit should be used for testing, but it is recognized that this is not always possible. In such situations, a selected portion of a product unit (sample item portion, SIP), which is convenient to handle during testing, may be substituted. The SIP should be as large a portion of the product unit as is possible to manipulate readily in the laboratory. SIP can be calculated on the basis of length, mass, volume, or surface area of the product unit to be tested, as appropriate.

5.3.1.2.2 The SIP shall represent validly the microbial challenge presented to the sterilization process and the diverse elements of complex product units. The distribution of viable microorganisms on the product unit shall be considered and, if it can be demonstrated that these microorganisms are evenly distributed, the SIP may 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.

5.3.1.2.3 Twenty SIPs should be prepared and a test of sterility performed in accordance with ISO 11737-2. At least 17 of these tests shall be positive. If this criteria is not achieved, a larger SIP is required.

NOTE—The occurrence of 17 positives out of 20 tests of sterility indicates that there is an average of 2 cfu/SIP.

If the entire product unit is tested, no minimum number of positives is specified for non-irradiated samples.

5.3.1.2.4 If a product unit or SIP cannot be tested in available laboratory glassware, it may be divided into two or more containers and these containers scored together as one unit. If in the performance of a test of sterility one container yields a positive result, the entire unit is considered positive.

5.3.1.2.5 If the product unit has a label claim of sterility of the fluid path only, testing of the fluid path should be considered as the entire product unit (i.e., SIP = 1.0).

5.3.1.2.6 The preparation and packaging of an SIP shall be conducted under conditions chosen to minimize alterations in the bioburden.

Environmentally controlled conditions should be used for preparation of SIPs.

Packaging materials and conditions should be equivalent to those used for the finished product.

5.3.1.2.7 Packaging shall be capable of withstanding the radiation doses to be delivered. Packaging for products, or portions thereof, for irradiation shall be chosen in order to minimize contamination during post-irradiation handling.

5.3.1.3 Selection of items for dose-setting

5.3.1.3.1 A sterilization dose is established for a given product unit. The definition of product unit (see 3.6) covers four situations:

a) an individual health care product within its primary package;

b) a set of components presented in a primary package which are assembled at the point of use to form the health care product, together with accessories required to use the assembled product;

c) a number of identical health care products within a primary package; and

d) a kit comprising a variety of procedure-related health care products.

In all these situations, the objective is to establish the sterilization dose appropriate for the product unit.

5.3.1.3.2 The experimentation to be carried out in performance of a dose-setting exercise in Method 1 or Method 2 is described in ISO 11137:1995, B.3.4. It is the outcome of this experimentation that ultimately determines the choice of the sterilization dose. For the situations described in 5.3.1.3.1 a) through d), the nature of the item(s) employed in the dose-setting exercise will also influence the choice of sterilization dose; thus, a rationalized selection of the item has to be made. As it is the product unit which undergoes sterilization treatment in order to provide an item that is sterile for use in patient care, it follows that each situation requires consideration of the manner of use of the health care product in clinical practice in order to decide the nature of the item to be employed in a dose-setting exercise. Guidance in this regard is given in Table 1.

5.3.2 Microbiological testing

Bioburden determinations and tests of sterility undertaken as part of the performance of the verification dose experiment or the sterilization dose audit shall be conducted using acceptable laboratory practices and in accordance with ISO 11737-1 and ISO 11737-2, respectively.

The method described hereafter uses a single culture medium for the performance of the test of sterility. The use of a single medium assumes that the medium is optimal for the culture of aerobic and facultative organisms that could survive. When this assumption is not valid, this method shall be conducted using other appropriate media and incubation conditions.

NOTE—Soybean Casein Digest Broth, with an incubation temperature of (30 ± 2) °C and an incubation period of 14 days, is generally recommended when a single medium is used.

Table 1—Selections of items for dose-setting

Product unit	Item for bioburden estimation or incremental dose experiment	Item for verification experiment	Basis for the choice of sterilization dose	Rationale
a) Individual health care product in its primary package	Individual health care product	Individual health care product	Individual health care product	Each health care product is used independently in clinical practice
b) Set of components in primary package	Combination of components	Combination of components	Combination of components	Components are assembled as a product and used together in clinical practice
c) Number of identical health care products in primary package	Single health care product taken from the primary package	Single health care product taken from the primary package	Single health care product taken from the primary package	Each health care product is used independently in clinical practice
d) Kit of procedure-related health care products	Each type of health care product	Each type of health care product	Health care product requiring the highest sterilization dose	Each health care product is used independently in clinical practice

5.3.3 Product irradiation

The irradiation of product, or SIPs, shall be in accordance with ISO 11137:1995, C.1.5.4.

It is preferred that the product be irradiated in its original form and package. However, to minimize and/or simplify the manipulations during testing and to reduce the possibility of false positives in the performance of tests of sterility, the product may be disassembled and repackaged prior to irradiation.

NOTE—Manipulations prior to irradiation are not always acceptable. In certain instances, such manipulations can change the response of the microorganisms to irradiation. For example, manipulations can alter the chemical environment (typically oxygen tension) in the vicinity of the microorganisms.

5.4 Procedures for verification dose experiments and sterilization dose audits

5.4.1 General

5.4.1.1 The procedures for the verification dose experiment and sterilization dose audits described in ISO 11137, together with alternative procedures, are presented in the following subclauses under the headings:

a) Method 1: ISO 11137 sampling plan (5.4.2.2) for verification dose experiment (Table 2);

b) Method 1: Alternative sampling plan (5.4.2.3) for verification dose experiment (Table 3);

c) Method 1 or 2: ISO 11137 sampling plan (5.4.3.2) for sterilization dose audit (Table 4);

d) Method 1 or 2: Alternative 1 sampling plan (5.4.3.3) for sterilization dose audit (Table 5);

e) Method 1 or 2: Alternative 2 sampling plan (5.4.3.4) for sterilization dose audit (Table 6);

f) Method 1 or 2: Alternative 3 sampling plan (5.4.3.5) for sterilization dose audit (Table 7);

g) Method 1: Alternative sampling scheme (5.4.4) for verification dose experiment and sterilization dose audit (Tables 8 and 9).

A summary of all of these sampling plans and the alternative sampling scheme is provided in annex A, Table A.1.

5.4.1.2 The selection of the sampling plan procedure to be utilized for verification dose and sterilization dose audits shall be documented. The selection of the sampling plan procedure should include the following considerations:

a) historical data from previous sterilization dose audits,

b) cost of the product units,

c) availability of the product units, and

d) cost of testing.

Guidance for selecting the appropriate sampling plan or sampling scheme for a specific product can be found in [1]. Additional guidance for sampling plans can also be found in [8].

5.4.1.3 Once the performance of a sampling plan procedure has been initiated, the manufacturer shall complete the procedure with the sampling plan selected. If the manufacturer decides to switch from one sampling plan procedure to another, the new selection shall be documented prior to the performance of the procedure.

5.4.2 Method 1: Verification dose experiment

5.4.2.1 General

The performance of the verification dose experiment is Stage 4 of the procedure for Method 1 (refer to ISO 11137:1995, B.3.4.1.2.4). The following subclauses detail both the ISO 11137 sampling plan for Stage 4 and an alternative sampling plan for Stage 4. In addition, summaries of the ISO 11137 sampling plan and alternative sampling plan are presented in Tables 2 and 3.

5.4.2.2 Method 1: ISO 11137 sampling plan for the verification dose experiment

5.4.2.2.1 To perform the experiment, select 100 product units, or portions thereof, from a single batch of product.

5.4.2.2.2 The 100 product units for the performance of Stage 4 shall be selected from any one of the three batches from which a bioburden estimation was obtained in Stage 2, or a fourth batch manufactured under conditions which are representative of normal production. The product units selected shall be typical in regards to bioburden of those to be routinely presented for sterilization.

Bioburden may change over time. The selection of the batch for the verification dose experiment should take this into account.

5.4.2.2.3 Irradiate the product units, or portions thereof, at the verification dose derived from ISO 11137:1995, Table B.1 in Stage 3.

Use of the verification dose experiment without bioburden estimation is not valid.

5.4.2.2.4 The actual dose should vary from the calculated verification dose by not more than +10 %. If the delivered dose is less than 90 % of the calculated verification dose, the test may be repeated.

NOTE 1—In this context the “actual dose” refers to the maximum dose received by the group of product units.

NOTE 2—In this context the “delivered dose” refers to the arithmetic mean of the maximum and minimum doses. If, on the other hand, the positive results can be ascribed to incorrect performance of the estimation of bioburden, the test of sterility, or delivery of the verification dose, a retest is permitted.

5.4.2.2.5 Subject each of the irradiated product units, or portions thereof, to a test of sterility. Tests of sterility should be performed using Soybean Casein Digest Broth, incubated at (30 ± 2) °C for 14 days (in accordance with ISO 11737-2). Record the number of positive tests of sterility.

NOTE—Other media and incubation conditions may be employed as appropriate (see 5.3.2).

5.4.2.2.6 If there are no more than two positive tests of sterility from the 100 tests carried out, accept statistical verification and proceed to Stage 5 (ISO 11137:1995, B.3.4.1.2.5) to establish the sterilization dose.

NOTE—The rationale for allowing up to two positives is based upon the statistical probability that, when the average bioburden is used to predict the dose at which one of 100 samples is expected to be non-sterile, there is a 0.92 probability that zero, one, or two positives may occur (refer to ISO 11137:1995, Table B.25).

5.4.2.2.7 If there are more than two positive tests of sterility and their occurrence cannot be ascribed to incorrect performance of the estimation of bioburden, the test of sterility, or the delivery of the verification dose (e.g., the delivered dose was less than 90 % of the calculated verification dose), this method of dose-setting is not valid; a retest is not permitted and an alternative method involving measurement of the resistance to radiation of contaminating microorganisms as they occur naturally should be used (e.g., Method 2).

Table 2—ISO 11137 sampling plan for Method 1 verification dose experiment

No. of positive tests of sterility	Sampling plan
	Procedure
	Irradiate 100 product units, or portions thereof, at the verification dose and subject each to a test of sterility.
	Acceptance criteria
≤ 2	Statistical verification is accepted.
≥ 3	This method of dose-setting is not valid. An alternative method involving measurement of the resistance to radiation of contaminating microorganisms as they occur naturally should be used (e.g., Method 2).

5.4.2.3 Method 1: Alternative sampling plan for the verification dose experiment

5.4.2.3.1 To perform the experiment, select 52 product units, or portions thereof, from a single batch of product.

5.4.2.3.2 The 52 product units for the performance of Stage 4 shall be selected from any one of the batches from which a bioburden estimation was obtained in Stage 2, or a fourth batch manufactured under conditions which are representative of normal production. The product units selected shall be typical in regards to bioburden of those to be routinely presented for sterilization.

Bioburden may change over time. The selection of the batch for the verification dose experiment should take this into account.

5.4.2.3.3 Irradiate the product units, or portions thereof, at the verification dose derived from ISO 11137:1995, Table B.1 in Stage 3.

Use of the verification dose experiment without bioburden estimation is not valid.

5.4.2.3.4 The actual dose may vary from the calculated verification dose by not more than +10 %. If the delivered dose is less than 90 % of the calculated verification dose, the test may be repeated.

NOTE 1—In this context the “actual dose” refers to the maximum dose received by the group of product units.

NOTE 2—In this context the “delivered dose” refers to the arithmetic mean of the maximum and minimum doses. If, on the other hand, the positive results can be ascribed to incorrect performance of the estimation of bioburden, test of sterility, or delivery of the verification dose, a retest is permitted.

5.4.2.3.5 Subject each of the irradiated product units, or portions thereof, to a test of sterility. Tests of sterility should be performed using Soybean Casein Digest Broth, incubated at (30 ± 2) °C for 14 days (in accordance with ISO 11737-2). Record the number of positive tests of sterility.

NOTE—Other media and incubation conditions may be employed as appropriate (see 5.3.2).

5.4.2.3.6 Interpret the results as follows:

a) If there are no positive tests of sterility from the 52 tests carried out, accept statistical verification and proceed to Stage 5 (ISO 11137:1995, B.3.4.1.2.5) to establish the sterilization dose.

b) If one or two positive tests of sterility are obtained, select 52 additional product units, or portions thereof, either from the same batch as tested previously or from a subsequent batch of product. Irradiate the product units, or portions thereof, at the verification dose derived from ISO 11137:1995, Table B.1, in Stage 3. Subject each of the irradiated product units to a test of sterility and record the number of positive tests of sterility. Sum the number of positive tests of sterility from the 104 tests carried out on the first and second sets of product units. If a total of not more than two positive tests of sterility are obtained from the 104 tests, statistical verification is accepted. If there are more than a total of two positive tests of sterility from the 104 tests, and their occurrence cannot be ascribed to incorrect performance of the estimation of bioburden and/or the test of sterility, or the delivery of the verification dose (e.g., the delivered dose was less than 90 % of the calculated verification dose), this method of dose-setting is not valid and an alternative method involving measurement of the resistance to radiation of contaminating microorganisms as they occur naturally should be used (e.g., Method 2).

c) If there are more than two positive tests of sterility from the 52 tests, and their occurrence cannot be ascribed to incorrect performance of the estimation of bioburden and/or the test of sterility, or the delivery of the verification dose (e.g., the delivered dose was less than 90 % of the calculated verification dose), this method of dose-setting is not valid; a retest is not permitted and an alternative method involving measurement of the resistance to radiation of contaminating microorganisms as they occur naturally should be used (e.g., Method 2).

5.4.3 Method 1 or 2: Sterilization dose audits

5.4.3.1 General

Sterilization dose audits are performed on a periodic basis to reaffirm the sterilization dose (refer to ISO 11137:1995, B.3.5). The following subclauses detail both the ISO 11137 sterilization dose audit procedure (5.4.3.2) and three alternative sterilization dose audit procedures (5.4.3.3, 5.4.3.4, and 5.4.3.5). Summaries of the ISO and alternative sampling plans are presented in Tables 4, 5, 6, and 7.

Table 3—Method 1: Alternative sampling plan for the verification dose experiment

No. of positive tests of sterility	Sampling plan
	Procedure
	Irradiate 52 product units, or portions thereof, at the verification dose and subject each to a test of sterility.
	Acceptance criteria
0	Statistical verification is accepted.
1 to 2	Additional testing is required; perform as described below.
≥ 3	This method of dose-setting is not valid. An alternative method involving measurement of the resistance to radiation of contaminating microorganisms as they occur naturally should be used (e.g., Method 2).
	Additional testing
	Irradiate a further 52 product units, or portions thereof, at the same verification dose and subject each to a test of sterility. These product units may be selected either from the same batch as tested previously or from a subsequent batch. The total product units tested is thus 104.
	Acceptance criteria
	Sum the positive tests of sterility derived from the initial 52 and the additional 52 tests of sterility.
≤ 2	Statistical verification is accepted.
≥ 3	This method of dose-setting is not valid. An alternative method involving measurement of the resistance to radiation of contaminating microorganisms as they occur naturally should be used (e.g., Method 2).

5.4.3.2 ISO 11137 sampling plan for the sterilization dose audit

5.4.3.2.1 To perform the sterilization dose audit, select 110 product units, or portions thereof, from a single batch of product.

5.4.3.2.2 Utilizing the same SIP and bioburden test methods as used in the original dose-setting exercise, determine the bioburden on each of 10 product units or portions of product unit.

5.4.3.2.3 Again utilizing the same SIP, irradiate the remaining 100 product units, or portions thereof, at the verification dose (for Method 2, D** kGy) found in the original dose-setting exercise.

5.4.3.2.4 If the verification dose has been revised during a previous sterilization dose audit, the revised verification dose should be used.

5.4.3.2.5 The actual dose may vary from the calculated verification dose (for Method 2, D** kGy) by not more than +10 %. If the delivered dose is less than 90 % of the calculated verification dose, the test may be repeated.

NOTE 1—In this context the “actual dose” refers to the maximum dose received by the group of product units.

NOTE 2—In this context the “delivered dose” refers to the arithmetic mean of the maximum and minimum doses. If, on the other hand, the positive results can be ascribed to incorrect performance of the estimation of bioburden, test of sterility, or delivery of the verification dose, a retest is permitted.

5.4.3.2.6 Subject each of the irradiated product units, or portions thereof, to a test of sterility. Tests of sterility should be performed using the medium and incubation conditions employed in the original dose-setting exercise. Record the number of positive tests of sterility.

5.4.3.2.7 Interpret the results as follows:

a) If no more than two positive tests of sterility are obtained, the original sterilization dose is acceptable. No action is required.

b) If three or four positive tests of sterility are obtained, the original sterilization dose might not be acceptable and, therefore, the sterilization dose shall be augmented immediately (refer to ISO 11137:1995, B.3.5.4.1 or B.3.5.4.2, as appropriate).

Thereafter, a repeat of the sterilization dose audit to determine if augmentation of the sterilization dose has to continue is permitted.

1) If, on retest, two or fewer positives are obtained and the review of environmental and manufacturing controls and product unit bioburden indicates no values outside established specifications, use of the original sterilization dose may be resumed.

2) If, on retest, three to four positives are obtained, follow the actions prescribed for five to six positives.

3) If, on retest, five or more positives are obtained, follow the actions prescribed for seven or more positives.

If augmentation of the sterilization dose was continued, the next quarterly sterilization dose audit shall be conducted using a revised verification dose. If augmentation of the sterilization dose was not continued, the next quarterly sterilization dose audit shall be conducted using the original verification dose.

A repeat of the sterilization dose audit is not permitted unless the occurrence of positives can be ascribed to incorrect performance of the estimation of bioburden and/or the test of sterility, or to the delivery of the verification dose (e.g., the delivered dose was less than 90 % of the calculated verification dose).

c) If five or six positive tests of sterility are obtained, the original sterilization dose is not adequate and, therefore, the sterilization dose shall be augmented immediately (refer to ISO 11137:1995, B.3.5.4.1, or B.3.5.4.2, as appropriate). A repeat of the sterilization dose audit is not allowed. The sterilization dose shall be reestablished.

The next quarterly sterilization dose audit shall be performed utilizing the revised verification dose or, when the sterilization dose has been reestablished, the new verification dose.

A repeat of the sterilization dose audit is not permitted unless the occurrence of positives can be ascribed to incorrect performance of the estimation of bioburden and/or the test of sterility, or the delivery of the verification dose (e.g., the delivered dose was less than 90 % of the calculated verification dose).

d) If seven or more positive tests of sterility are obtained, the radiation resistance of the bioburden has probably changed by an amount which invalidates the use of the assumed resistance. In these circumstances, the sterilization dose cannot be augmented and it shall be reestablished.

A repeat of the sterilization dose audit is not permitted unless the occurrence of positives can be ascribed to incorrect performance of the estimation of bioburden and/or the test of sterility, or the delivery of the verification dose (e.g., the delivered dose was less than 90 % of the calculated verification dose).

Table 4—ISO 11137 sampling plan for Method 1 or 2: Sterilization dose audit

No. of positive tests of sterility	Sampling plan
	Procedure
	Irradiate 100 product units, or portions thereof, at the verification dose and subject to a test of sterility.
	Acceptance criteria
≤ 2	The sterilization dose is acceptable. No action required.
3 to 4	Augment the sterilization dose in accordance with the guidance provided in ISO 11137. Additional testing as described below may be performed to reestablish original sterilization dose.
5 to 6	Augment the sterilization dose and sterilization dose audit dose in accordance with the guidance provided in ISO 11137, while the sterilization dose is reestablished.
≥ 7	The sterilization dose shall be reestablished.
	Additional testing
	Irradiate a further 100 product units, or portions thereof, at the verification dose used for the initial 100 product units and subject each to a test of sterility. These product units may be selected either from the same batch as tested previously or from a subsequent batch.
	Acceptance criteria
	Determine the positive tests of sterility derived from the additional 100 tests of sterility.
≤ 2	The sterilization dose audit is acceptable. Use of the original sterilization dose may be resumed.
3 to 4	Augment sterilization dose and revise verification dose in accordance with the guidance provided in ISO 11137, while the sterilization dose is reestablished.
≥ 5	The sterilization dose shall be reestablished.

5.4.3.3 Alternative 1 sampling plan for the sterilization dose audit

5.4.3.3.1 To perform the sterilization dose audit, select 60 product units, or portions thereof, from a single batch of product.

5.4.3.3.2 Utilizing the same SIP and bioburden test methods as used in the original dose-setting exercise, determine the bioburden on each of 10 product units or portions of product unit.

5.4.3.3.3 Again utilizing the same SIP, irradiate the remaining 50 product units, or portions thereof, at the verification dose (for Method 2, D** kGy) found in the original dose-setting exercise.

5.4.3.3.4 If the verification dose has been augmented during a previous sterilization dose audit, the augmented verification dose should be used.

5.4.3.3.5 The actual dose may vary from the calculated verification dose (for Method 2, D** kGy) by not more than +10 %. If the delivered dose is less than 90 % of the calculated verification dose, the test may be repeated.

NOTE 1—In this context the “actual dose” refers to the maximum dose received by the group of product units.

NOTE 2—In this context the “delivered dose” refers to the arithmetic mean of the maximum and minimum doses.

5.4.3.3.6 Subject each of the irradiated product units, or portions thereof, to a test of sterility. Tests of sterility should be performed using the medium and incubation conditions employed in the original dose-setting exercise. Record the number of positive tests of sterility.

5.4.3.3.7 Interpret the results as follows:

a) If no positives are obtained, the sterilization dose is acceptable. No action is required.

b) If one, two, or three positive tests of sterility are obtained, the sterilization dose might not be acceptable and additional testing shall be performed. Select 100 additional products, or portions thereof, either from the same batch as tested previously or from a subsequent batch of product. Irradiate the product units, or portions thereof, at the dose used to irradiate the initial 50 product units. Subject each of the irradiated product units to a test of sterility and record the number of positive tests of sterility. Sum the number of positive tests of sterility from the 150 tests carried out on the first and second sets of product units. If a total of not more than four positive tests of sterility are obtained from the 150 tests, the sterilization dose is acceptable and no further action is required. If there are more than four positive tests of sterility from the 150 tests, the sterilization dose is not acceptable and shall be reestablished.

c) If four or more positive tests of sterility are obtained from the initial 50 tests, the radiation resistance of the bioburden has probably changed by an amount that invalidates the use of the assumed resistance. In these circumstances, the sterilization dose cannot be augmented and shall be reestablished.

Table 5—Alternative 1 sampling plan for the sterilization dose audit

No. of positive tests of sterility	Sampling plan
	Procedure
	Irradiate 50 product units, or portions thereof, at the verification dose and subject each to a test of sterility.
	Acceptance criteria
0	The sterilization dose is acceptable. No action required.
1 to 3	The sterilization dose might not be acceptable. Additional testing is required; perform as described below.
≥ 4	The sterilization dose is not acceptable and shall be reestablished. Augmentation of the sterilization dose cannot be carried out.
	Additional testing
	Irradiate a further 100 product units, or portions thereof, at the same dose used for the initial 50 product units and subject each to a test of sterility. These product units may be selected either from the same batch as tested previously or from a subsequent batch. The combined total products tested is thus 150.
	Acceptance criteria
	Sum the positive tests of sterility derived from the initial 50 and the additional 100 tests of sterility.
≤ 4	The sterilization dose is acceptable. No action required
≥ 5	The sterilization dose is not acceptable and shall be reestablished. Augmentation of the sterilization dose cannot be carried out.

5.4.3.4 Alternative 2 sampling plan for the sterilization dose audit

5.4.3.4.1 To perform the sterilization dose audit, select 80 product units, or portions thereof, from a single batch of product.

5.4.3.4.2 Utilizing the same SIP and bioburden test methods as used in the original dose-setting exercise, determine the bioburden on each of 10 product units or portions of product unit.

5.4.3.4.3 Again utilizing the same SIP, irradiate the remaining 70 product units, or portions thereof, at the verification dose (for Method 2, D** kGy) found in the original dose-setting exercise.

5.4.3.4.4 If the verification dose has been augmented during a previous sterilization dose audit, the augmented verification dose should be used.

5.4.3.4.5 The actual dose may vary from the calculated verification dose (for Method 2, D** kGy) by not more than +10 %. If the delivered dose is less than 90 % of the calculated verification dose, the test may be repeated.

NOTE 1—In this context the “actual dose” refers to the maximum dose received by the group of product units.

NOTE 2—In this context, the “delivered dose” refers to the arithmetic mean of the maximum and minimum doses. If, on the other hand, the positive results can be ascribed to incorrect performance of the estimation of bioburden, test of sterility, or delivery of the verification dose, a retest is permitted.

5.4.3.4.6 Subject each of the irradiated product units, or portions thereof, to a test of sterility. Tests of sterility should be performed using the medium and incubation conditions employed in the original dose-setting exercise. Record the number of positive tests of sterility.

5.4.3.4.7 Interpret the results as follows:

a) If no more than one positive test of sterility is obtained, the sterilization dose is acceptable. No action is required.

b) If two, three, four, or five positive tests of sterility are obtained, the sterilization dose might not be acceptable and additional testing shall be performed. Select 130 additional products, or portions thereof, either from the same batch as tested previously or from a subsequent batch of product. Irradiate the product units, or portions thereof, [at the dose used to irradiate the original][1)] 70 units. Subject each of the irradiated product units to a test of sterility and record the number of positive tests of sterility. Sum the number of positive tests of sterility from the 200 tests carried out on the first and second sets of product units. If a total of not more than five positive tests of sterility are obtained from the 200 tests, the sterilization dose is acceptable and no further action is required. If there are more than five positive tests of sterility from the 200 tests, the sterilization dose is not acceptable and shall be reestablished.

c) If six or more positive tests of sterility are obtained from the initial 70 tests, the radiation resistance of the bioburden has probably changed by an amount that invalidates the use of the assumed resistance. In these circumstances, the sterilization dose cannot be augmented and shall be reestablished.

Table 6—Alternative 2 sampling plan for the sterilization dose audit

No. of positive tests of sterility	Sampling plan
	Procedures
	Irradiate 70 product units, or portions thereof, at the verification dose and subject each to a test of sterility.
	Acceptance criteria
≤ 1	The sterilization dose is acceptable. No action required.
2 to 5	The sterilization dose might not be acceptable. Additional testing is required; perform as described below.
≥ 6	The sterilization dose is not acceptable and shall be reestablished. Augmentation of the sterilization dose cannot be carried out.
	Additional testing
	Irradiate a further 130 product units, or portions thereof, at the same dose used for the initial 70 products and subject each to a test of sterility. These product units may be selected either from the same batch as tested previously or from a subsequent batch. The combined total products tested is thus 200.
	Acceptance criteria
	Sum the positive tests of sterility derived from the initial 70 and the additional 130 tests of sterility
≤ 5	The sterilization dose is acceptable. No action required.
≥ 6	The sterilization dose is not acceptable and shall be reestablished. Augmentation of the sterilization dose cannot be carried out.

[1)] The text contained in brackets was inadvertently omitted from ISO/TS 15843:2000.

5.4.3.5 Alternative 3 sampling plan for the sterilization dose audit

5.4.3.5.1 To perform the sterilization dose audit, select 150 product units, or portions thereof, from a single batch of product.

5.4.3.5.2 Utilizing the same SIP and bioburden test methods as used in the original dose-setting exercise, determine the bioburden on each of 10 product units or portions of product unit.

5.4.3.5.3 Again utilizing the same SIP, irradiate the remaining 140 product units, or portions thereof, at the verification dose (for Method 2, D** kGy) found in the original dose-setting exercise.

5.4.3.5.4 If the verification dose has been augmented during a previous sterilization dose audit, the augmented verification dose should be used.

5.4.3.5.5 The actual dose may vary from the calculated verification dose (for Method 2, D** kGy) by not more than +10 %. If the delivered dose is less than 90 % of the calculated verification dose, the test may be repeated.

NOTE 1—In this context the "actual dose" refers to the maximum dose received by the group of product units.

NOTE 2—In this context the "delivered dose" refers to the arithmetic mean of the maximum and minimum doses. If, on the other hand, the positive results can be ascribed to incorrect performance of the estimation of bioburden, test of sterility, or delivery of the verification dose, a retest is permitted.

5.4.3.5.6 Subject each of the irradiated product units, or portions thereof, to a test of sterility. Tests of sterility should be performed using the medium and incubation conditions employed in the original dose-setting exercise. Record the number of positive tests of sterility.

5.4.3.5.7 Interpret the results as follows:

a) If no more than four positive tests of sterility are obtained, the sterilization dose is acceptable. No action is required.

b) If five or more positive tests of sterility are obtained from the 140 tests, the radiation resistance of the bioburden has probably changed by an amount that invalidates the use of the assumed resistance. In these circumstances, the sterilization dose cannot be augmented and shall be reestablished.

Table 7—Alternative 3 sampling plan for the sterilization dose audit

No. of positive tests of sterility	Sampling plan
	Procedures
	Irradiate 140 product units, or portions thereof, at the verification dose and subject each to a test of sterility.
	Acceptance criteria
≤ 4	The sterilization dose is acceptable. No action is required.
≥ 5	The sterilization dose is not acceptable and shall be reestablished. Augmentation of the sterilization dose cannot be carried out.

NOTE—This alternative corresponds to a single sampling plan. It would be appropriate in situations where individual product units are relatively inexpensive to obtain a test. The increased sample size allows for more positives without failing the sterilization dose audit.

5.4.4 Method 1: Alternative sampling scheme for the verification dose experiment and the sterilization dose audit

5.4.4.1 General

Subclause 5.4.2.2 describes the ISO 11137 procedure for the performance of the Method 1 verification dose experiment and 5.4.3.2 describes the ISO 11137 procedure for the performance of the sterilization dose audit. The two procedures together can be considered as a sampling scheme. The following subclauses detail an alternative sampling scheme: an alternative sampling plan for the verification dose experiment (5.4.4.2) and alternative sampling plan for the sterilization dose audit (5.4.4.3). Summaries of the alternative sampling scheme are presented in Tables 8 and 9.

This alternative sampling scheme utilizes a statistical technique that is referred to as a quick switching system (QSS) [7]. A QSS first employs a tightened inspection level (i.e., verification dose experiment). If the tightened inspection is passed, a reduced inspection level (i.e., sterilization dose audit) can be utilized. If the reduced inspection level is failed, the tightened inspection level is reinstated.

5.4.4.2 Alternative sampling scheme for Method 1: Sampling plan for the verification dose experiment (tightened inspection level)

5.4.4.2.1 To perform the experiment, select 60 product units, or portions thereof, from a single batch of product.

5.4.4.2.2 The 60 product units for the performance of Stage 4 may be selected either from one of the batches for which a bioburden estimation was obtained in Stage 2 or from a fourth batch manufactured under conditions which are representative of normal production. The product units selected shall be typical in regards to bioburden of those to be routinely presented for sterilization.

Bioburden may change over time. The selection of the batch for the verification dose experiment should take this into account.

5.4.4.2.3 Irradiate the product units, or portions thereof, at the verification dose derived from ISO 11137:1995, Table B.1 in Stage 3.

Use of the verification dose experiment without bioburden estimation is not valid.

5.4.4.2.4 The actual dose may vary from the calculated verification dose by not more than +10 %. If the delivered dose is less than 90 % of the calculated verification dose, the test may be repeated.

NOTE 1—In this context the “actual dose” refers to the maximum dose received by the group of product units.

NOTE 2—In this context the “delivered dose” refers to the arithmetic mean of the maximum and minimum doses. If, on the other hand, the positive results can be ascribed to incorrect performance of the estimation of bioburden, test of sterility, or delivery of the verification dose, a retest is permitted.

5.4.4.2.5 Subject each of the irradiated product units, or portions thereof, to a test of sterility. Tests of sterility should be performed using Soybean Casein Digest Broth, incubated at (30 ± 2) °C for 14 days (in accordance with ISO 11737-2). Record the number of positive tests of sterility.

NOTE—Other media and incubation conditions may be employed as appropriate (see 5.3.2).

5.4.4.2.6 Interpret the results as follows:

a) If there are no positive tests of sterility from the 60 tests carried out, accept statistical verification. Also, switching to the reduced inspection level for the sterilization dose audit is allowed.

b) If one or two positive tests of sterility are obtained, this dose-setting method might not be appropriate and additional testing shall be performed. Select an additional 60 product units, or portions thereof, either from the same batch as tested previously or from a subsequent batch of product. Irradiate the product units, or portions thereof, at the verification dose specified for the initial set of product units. Subject each of the irradiated product units to a test of sterility and record the number of positive tests of sterility. Sum the number of positive tests of sterility from 120 tests carried out on the first and second sets of product units. If a total of not more than two positive tests of sterility are obtained from the 120 tests, statistical verification is accepted and switching to the reduced inspection level (i.e., the sterilization dose audit) is allowed. If there are more than two positive tests of sterility from the 120 tests, and their occurrence cannot be ascribed to incorrect performance of the estimation of bioburden and/or the test of sterility, or the delivery of the verification dose (e.g., the delivered dose was less than 90 % of the calculated verification dose), this method of dose-setting is not valid and an alternative method involving measurement of the resistance to radiation of contaminating microorganisms as they occur naturally should be used (e.g., Method 2).

c) If three or more positive tests of sterility are obtained from the initial 60 product units, and their occurrence cannot be ascribed to incorrect performance of the estimation of bioburden and/or the test of sterility, or the delivery of the verification dose (e.g., the delivered dose was less than 90 % of the calculated verification dose), this method of dose-setting is not valid; a retest is not permitted and an alternative method involving measurement of the resistance to radiation of contaminating microorganisms as they occur naturally should be used (e.g., Method 2).

Table 8—Alternative sampling scheme for Method 1: Sampling plan for the verification dose experiment (tightened inspection level)

No. of positive tests of sterility	Sampling plan
	Procedures
	Irradiate 60 product units, or portions thereof, at the verification dose and subject each to a test of sterility.
	Acceptance criteria
0	The sterilization dose is acceptable and switching to the reduced inspection level for the sterilization dose audit is allowed.
1 to 2	The sterilization dose might not be acceptable. Additional testing is required; perform as described below.
≥ 3	This method of dose-setting is not valid. An alternative method involving measurement of the resistance to radiation of contaminating microorganisms as they occur naturally should be used (e.g., Method 2).
	Additional testing
	Irradiate a further 60 product units, or portions thereof, at the same verification dose and subject each to a test of sterility. These product units may be selected either from the same batch as tested previously or from a subsequent batch. The combined total product units tested is thus 120.
	Acceptance criteria
	Sum the positive tests of sterility derived from the initial 60 and the additional 60 tests of sterility.
≤ 2	The sterilization dose is acceptable and switching to a reduced inspection level (i.e. the sterilization dose audit) is allowed.
≥ 3	This method of dose-setting is not valid. An alternative method involving measurement of the resistance to radiation of contaminating microorganisms as they occur naturally should be used (e.g., Method 2).

5.4.4.3 Alternative sampling scheme for Method 1: Sampling plan for the sterilization dose audit (reduced inspection level)

5.4.4.3.1 To perform the sterilization dose audit, select 45 product units, or portions thereof, from a single batch of product.

5.4.4.3.2 Utilizing the same SIP and bioburden test methods as used in the original dose-setting exercise, determine the bioburden on each of 10 product units or portions of product unit.

5.4.4.3.3 Again utilizing the same SIP, irradiate the remaining 35 product units, or portions thereof, at the verification dose found in the original dose-setting exercise.

5.4.4.3.4 If the verification dose has been revised during a previous sterilization dose audit, the revised verification dose should be used.

5.4.4.3.5 The actual dose may vary from the calculated verification dose by not more than +10 %. If the delivered dose is less than 90 % of the calculated verification dose, the test may be repeated.

NOTE 1—In this context the “actual dose” refers to the maximum dose received by the group of product units.

NOTE 2—In this context the “delivered dose” refers to the arithmetic mean of the maximum and minimum doses. If, on the other hand, the positive results can be ascribed to incorrect performance of the estimation of bioburden, test of sterility, or delivery of the verification dose, a retest is permitted.

5.4.4.3.6 Subject each of the irradiated product units, or portions thereof, to a test of sterility. Tests of sterility should be performed using the medium and incubation conditions employed in the original dose-setting exercise. Record the number of positive tests of sterility.

5.4.4.3.7 Interpret the results as follows:

a) If no positive tests of sterility are obtained, the sterilization dose is acceptable. No action is required.

b) If one, two, or three positive tests of sterility are obtained, the sterilization dose might not be acceptable and additional testing shall be performed. Select 110 additional products, or portions thereof, either from the same batch as previously tested or from a subsequent batch of product. Irradiate the product units, or portions thereof, at the verification dose specified for the initial set of 35 product units. Subject each of the irradiated product units to a test of sterility and record the number of positive tests of sterility. Sum the number of positive tests of sterility from the 145 tests carried out on the first and second sets of product units. If a total of not more than four positive tests of sterility are observed from the 145 tests, then the sterilization dose is acceptable and no further action is required. If there are more than four positive tests of sterility from the 145 tests, the sterilization dose is not acceptable and shall be reestablished.

c) If four or more positive tests of sterility are obtained from the initial 35 units, the radiation resistance of the bioburden has probably changed by an amount that invalidates the use of the assumed resistance. In these circumstances, the sterilization dose cannot be augmented and shall be reestablished.

Table 9—Alternative sampling scheme for Method 1:
Sampling plan for the sterilization dose audit (reduced inspection level)

No. of positive tests of sterility	Sampling plan
	Procedures
	Irradiate 35 product units, or portions thereof, at the verification dose and subject each to a test of sterility.
	Acceptance criteria
0	The sterilization dose is acceptable. No action is required.
1 to 3	The sterilization dose might not be acceptable. Additional testing is required; perform as described below.
≤ 4	The sterilization dose is not acceptable and shall be reestablished (tightened inspection level). Augmentation of the sterilization dose cannot be carried out.
	Additional testing
	Irradiate a further 110 product units, or portions thereof, at the same dose used for the first 35 product units and subject each to a test of sterility. These product units may be selected from either the same batch as tested previously or from a subsequent batch. The combined total product units tested is thus 145.
	Acceptance criteria
	Sum the positive tests of sterility derived from the initial 35 and the additional 110 tests of sterility.
≤ 4	The sterilization dose is acceptable. No action is required.
≥ 5	The sterilization dose is not acceptable and shall be reestablished (tightened inspection level). Augmentation of the sterilization dose cannot be carried out.

6 Frequency of sterilization dose audits

6.1 Rationale

For the chosen sterilization dose to continue to be valid, product shall be manufactured under controlled conditions that yield stable bioburden in terms of numbers and types of microorganisms. To demonstrate this continued validity, sterilization dose audits are required to be carried out at a predefined frequency. ISO 11137 specifies a frequency of

performance of sterilization dose audits of not less than once every 3 months. This frequency was based on the potential for seasonal variation in bioburden.

Product manufactured under controlled conditions may not exhibit seasonal variation in bioburden. If it can be demonstrated over time that the bioburden is stable in terms of numbers and types of microorganisms and does not exhibit seasonal variation, a reduction in the frequency of dose audits can be considered.

It should be recognized that a reduction in the frequency of performance of the sterilization dose audit results in a reduction in the ability to detect a change within the manufacturing process over time. Consequently, the risk associated with such a reduction in frequency should be evaluated before proceeding.

6.2 Conditions for reduction in frequency of sterilization dose audits from a 3-month to a 6-month interval

6.2.1 A reduction in the frequency of sterilization dose audits shall only be permitted if:

a) successful, consecutive sterilization dose audits (i.e., no dose augmentation) have been carried out, at intervals of no more than 3 months, over a period of 12 months, and

b) data are available that demonstrate stability of bioburden over at least a period of 12 months; these include

4) a minimum of quarterly bioburden determinations, and

5) characterization of bioburden (for example, use of selective media, Gram stain of isolates, an examination of cellular morphology, etc.), and

c) the manufacture of the product in relation to bioburden is controlled and the effectiveness of this control is demonstrated through the implementation of the elements of a quality system identified for sterile medical devices in ISO 13485 or ISO 13488.

6.2.2 If the criteria are met and it is decided to reduce the audit frequency, the initial reduction in frequency shall be from a 3-month to a 6-month interval.

6.3 Conditions for reduction in frequency of sterilization dose audits from a 6-month to a 12-month interval

6.3.1 A reduction in the frequency of sterilization dose audits shall only be permitted if:

a) successful, consecutive sterilization dose audits (i.e., no dose augmentation) have been carried out, at intervals of no more than 6 months, over a period of 24 months, and

b) data are available that demonstrate stability of bioburden over at least a period of 24 months; these include

1) a minimum of quarterly bioburden determinations, and

2) characterization of bioburden (for example, use of selective media, Gram stain of isolates, an examination of cellular morphology, etc.), and

c) the manufacture of the product in relation to bioburden is controlled and the effectiveness of this control is demonstrated through the implementation of the elements of a quality system identified for sterile medical devices in ISO 13485 or ISO 13488.

6.3.2 If the criteria are met and it is decided to reduce the audit frequency, the reduction in frequency shall be from a 6-month to a 12-month interval.

6.3.3 The interval between sterilization dose audits shall not be more than 12 months.

6.4 Sterilization dose audit failure

If a sterilization dose audit is failed:

a) the sterilization dose shall be augmented or reestablished as specified in ISO 11137, and

b) the frequency of sterilization dose audits shall revert to at least every 3 months.

Annex A
(normative)

Sample sizes for implementation of sampling plans and sampling scheme

Table A.1

Application	**Subclause No.**	**Initial test** Product units	**Second test** Product units
Method 1 Verification dose experiment	5.4.2.2 (Table 2)	100	N/A
	5.4.2.3 (Table 3)	52	52
Methods 1 and 2 Sterilization dose audit	5.4.3.2 (Table 4)	100	100
	5.4.3.3 (Table 5)	50	100
	5.4.3.4 (Table 6)	70	130
	5.4.3.5 (Table 7)	140	N/A
Method 1 Alternative sampling scheme, Verification dose experiment, and Sterilization dose audit	5.4.4.2 (Table 8)	60	60
	5.4.4.3 (Table 9)	35	110

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