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Technical Information Report

AAMI TIR27:2001

Sterilization of health care products—Radiation sterilization—Substantiation of 25 kGy as a sterilization dose—Method VD_{max}

AAMI
Association for the Advancement of Medical Instrumentation

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AAMI Techical Information Report AAMI TIR27:2001

Sterilization of health care products—Radiation sterilization—Substantiation of 25 kGy as a sterilization dose—Method VD_{max}

Approved 12 March 2001 by
Association for the Advancement of Medical Instrumentation

Abstract: This technical information report describes a method of substantiation of 25 kGy as the sterilization dose for radiation sterilization of health care products with an average bioburden for the entire product unit (SIP = 1) ≤ 1,000 colony-forming units (CFU). Application of the method of substantiation of 25 kGy described in this technical information report may be used to meet the requirements specified under subclause 6.2.2 of ISO 11137, relating to product qualification.

Keywords: sterilization dose, substantiation of 25 kGy, bioburden, dose audit, dose substantiation

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AAMI Technical Information Report

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NOTE—Participation by federal agency representatives in the development of this AAMI Technical Information Report does not constitute endorsement by the federal government or any of its agencies.

Introduction

This document 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*. One of the activities encompassed within the standard is the selection of the sterilization dose to be applied to health care products. ANSI/AAMI/ISO 11137 specifies that one of two approaches is to be used to select the sterilization dose: (1) the establishment of a product-specific sterilization dose; or (2) the application of a minimum dose of 25 kGy following substantiation of the appropriateness of this dose.

Informative annex B to ANSI/AAMI/ISO 11137 describes two methods for establishing a product-specific sterilization dose. These methods are designated Method 1 and Method 2. The basis of these methods owes much to the ideas first propounded by Tallentire (Tallentire, 1973; Tallentire, Dwyer, and Ley, 1971; Tallentire and Khan, 1978). Subsequently, standardized methods were developed (Davis et al., 1981; Davis, Strawderman, and Whitby, 1984; Whitby and Gelda, 1979) that formed the basis of the dose selection procedures put forward in the AAMI recommended practice for sterilization by gamma irradiation, *Guideline for gamma radiation sterilization* (AAMI, 1984).

These methods of selection of a sterilization dose use data derived from the inactivation of the microbial population in its natural state and are based on a probability model for the inactivation of microbial populations. The probability model, as applied to bioburden made up of a mixture of various microbial species, assumes that each species has its own unique "D_{10}" value. In the model, the probability that a particular item will be sterile after exposure to a given dose of radiation is defined in terms of the number of organisms on the item prior to irradiation and their D_{10} values.

Annex B of ANSI/AAMI/ISO 11137 does not provide specific guidance on how 25 kGy may be substantiated. However, two principal approaches to substantiation have generally been followed.

— A dose-setting exercise using either Method 1 or Method 2 has been applied. Provided that the outcome of such an exercise is the establishment of a sterilization dose that is less than 25 kGy, the method is considered to have been substantiated.

— A method of substantiation described in AAMI/ISO TIR13409 has been applied. This method, based on Method 1, is, however, intended for use only with small or infrequent production batches.

The method described in this report is a simple, alternative approach to substantiation of 25 kGy as an appropriate sterilization dose to attain a sterility assurance level (SAL) of 10^{-6}. The application of this method is not limited by batch size or production frequency, and the number of product units irradiated in the verification dose experiment remains constant. The method employs as its basis the standard distribution of resistances (SDR) on which Method 1 is also founded and embodies the following three principles:

— Existence of a direct link between the outcome of the verification dose experiment and the attainment of an SAL of 10^{-6} at a sterilization dose of 25 kGy.

— Possession of a level of conservativeness at least equal to that of the SDR.

— For a given bioburden, use of a maximum verification dose (VD_{max}) commensurate with substantiation of 25 kGy.

This approach to the substantiation of 25 kGy as a sterilization dose was first outlined by Kowalski and Tallentire (1999), and from subsequent evaluations involving computational techniques (Kowalski, Aoshuang, and Tallentire, 2000), it was concluded that the method is safe and yields unambiguous results. An overview of the method is provided in Kowalski and Tallentire (2000).

The method described here and given the designate VD_{max} procedurally comprises elements that closely parallel those of dose-setting Method 1. One key area of difference is the number of product units used in the verification dose experiment. In the computer evaluations referred to above, changing the verification SAL value had little effect on the substantiation outcome, and this finding led to a sample size of 10 product units being chosen for subsequent field evaluations and, ultimately, as the basis of the sampling plan described in this document. Manufacturers of health care products who intend to use the protocols contained in this technical information report are reminded that the requirements for all users of radiation sterilization contained in ANSI/AAMI/ISO 11137 apply to the manufacture and control of production batches for which a sterilization dose of 25 kGy is substantiated by this method. In particular, one requirement states that products be manufactured in circumstances such that the bioburden is controlled. Compliance with the requirements for proper control of the quality of raw materials, for the manufacturing environment, and for the establishment of the basic properties of the packaging material are all essential.

List of Titles

Sterilization of health care products—Radiation sterilization—Substantiation of 25 kGy as a sterilization dose—Method VD_{max}

1 Scope

1.1 Inclusions

This technical information report describes a method of substantiation of 25 kGy as the sterilization dose for an SAL of 10^{-6} for radiation sterilization of health care products with an average bioburden estimate for the entire product unit of between 1 and 1,000 colony-forming units (CFU).

NOTE 1—Application of the method of substantiation of 25 kGy described in this technical information report may be used to meet the product qualification requirements specified in ANSI/AAMI/ISO 11137:1994, *Sterilization of health care products—Requirements for validation and routine control—Radiation sterilization*.

NOTE 2—This technical information report is considered "informative," and use of the terms "shall," "should," etc. should be considered only within the context of this TIR. That is, if the decision is made to use this method of substantiation of 25 kGy, then this method should be followed in adherence with the requirements ("shall") and recommendations ("should") as set forth in this technical information report.

1.2 Exclusions

This method, as described, is for the substantiation of 25 kGy only and cannot be used to substantiate other sterilization doses. The method cannot be used when the average bioburden estimate of the entire product unit is greater than 1,000 CFU.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this technical information report. For dated references, subsequent amendments to or revisions of any of these publications do not apply. However, parties to agreements based on this technical information report 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. The Association for the Advancement of Medical Instrumentation maintains a register of currently valid international standards.

ANSI/AAMI/ISO 11137:1994, *Sterilization of health care products—Requirements for validation and routine control—Radiation sterilization.*

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

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

3 Terms and definitions

For the purposes of this technical information report, the following terms and definitions apply.

3.1 batch: Defined quantity of bulk, intermediate, or finished product that is intended or purported to be uniform in character and quality and which has been produced during a defined cycle of manufacture.

3.2 bioburden: Population of viable microorganisms on a product.

NOTE—In the context of radiation sterilization, bioburden is determined immediately before sterilization.

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

3.4 D_{10}: Radiation dose required to kill 90 % of a homogenous microbial population where it is assumed that the death of microbes follows first order kinetics.

NOTE—In this context, the unit of D_{10} is kGy.

3.5 false positive: Result of a test of sterility in which a true negative is interpreted as a positive.

3.6 positive test of sterility: Test of sterility that exhibits detectable microbial growth after incubation.

3.7 presterilization count: Viable count obtained prior to sterilization.

3.8 product unit: Health care product, collection of products, or components within a primary package.

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

3.10 sterility assurance level (SAL): Probability of a viable microorganism being present on a product unit after sterilization.

NOTE 1—SAL is normally expressed as 10^{-n}.

NOTE 2—In the context of validation, SAL may take a value of probability other than that specified for sterilization.

3.11 sterilization dose: Minimum absorbed dose required to achieve the specified sterility assurance level.

3.12 sterilization dose audit: Action taken to detect whether a change in sterilization dose is needed.

3.13 test of sterility: Test performed to establish the presence or absence of viable microorganisms on product units or portions thereof when subjected to defined culture conditions.

3.14 verification dose: Dose of radiation estimated to produce a higher SAL (lower assurance of sterility) than that specified for sterilization and used to establish or confirm the sterilization dose.

3.15 VD_{max}: Maximum acceptable verification dose for a given bioburden and verification dose sample size.

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

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

4 Selection and testing of product

4.1 Selection of product units

Substantiation of the sterilization dose of 25 kGy is performed for a given product unit. A *product unit* is defined as a "health care product, collection of products, or components within a primary package." This definition, therefore, covers four situations:

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

b) a set of components presented in a primary package that 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 situations, the objective is to substantiate that the sterilization dose of 25 kGy is appropriate for the product unit.

The experimentation carried out for the substantiation of 25 kGy is the determination of the average bioburden estimate and the performance of a verification dose experiment. The outcome of this experiment ultimately allows the substantiation of 25 kGy. For the above situations (a) through (d), the nature of the item or items used in the dose substantiation exercise will influence the design and outcome of the substantiation exercise, and these, in turn, will affect the decision as to the appropriateness of 25 kGy. Thus, a rationalized selection of the item or items has to be made. Because the product unit undergoes sterilization treatment to produce 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 to decide the nature of the item to be used in the substantiation exercise. Guidance for this consideration is given in Table 1.

Table 1—Selection of items for substantiation of 25 kGy

Product unit	Item for bioburden estimation	Item for verification experiment	Rationale
a) Individual health care product in its primary package	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	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	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	Each health care product is used independently in clinical practice

4.1.1 Method of selection

The method of selecting product units for testing can influence the test result. Selected product units shall be representative of the batch and be selected at random. Product units for testing may be selected from items rejected during the manufacturing process, provided that they have been subjected to the same processing conditions as the remainder of the batch.

4.1.2 Sample item portion (SIP)

An entire product unit should be used for testing, but it is recognized that this condition is not always practicable. In these situations, a selected portion of a product unit that 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. The SIP may be calculated on the basis of length, weight, volume, surface area, or bioburden distribution of the product unit to be tested.

The SIP has to validly represent 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 portion of the product unit. In the absence of this demonstration, the SIP shall be constituted from several portions of a product unit selected at random.

The adequacy of a selected SIP shall be demonstrated in either of two ways:

a) bioburden techniques described in ANSI/AAMI/ISO 11737-1 shall show a viable count for at least 85 % of the SIPs; or

b) sterility testing of 20 non-irradiated SIPs shall yield at least 17 positive tests of sterility (85 %).

If this criterion is not achieved, a larger SIP is required.

If the entire product unit is tested, the test of SIP adequacy is not required.

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

If the product unit has a label claim of sterility for only a portion of the product unit, testing that portion should be considered the entire product unit (i.e., SIP = 1.0). For instance, if the product unit has a label claim of sterility of the fluid path only, testing the fluid path should be considered the entire product unit.

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

NOTE 1—Environmentally controlled conditions should be used for preparation of SIPs.

NOTE 2—Packaging materials should be equivalent to those used for the finished product. Packaging shall be capable of withstanding the radiation doses to be delivered. Packaging for products or portions thereof for irradiation shall be chosen to minimize contamination during post-irradiation handling.

4.2 Microbiological testing

Bioburden estimates and tests of sterility conducted as part of this method shall be conducted using acceptable laboratory practices and in accordance with ANSI/AAMI/ISO 11737-1 and ANSI/AAMI/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 will be optimal for the culture of aerobic and facultative organisms that may 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 growth medium is used.

4.3 Product irradiation

The irradiation of products or portions thereof shall be in compliance with ANSI/AAMI/ISO 11137, annex C.1.5.4.

The preferred process is that the product is irradiated in its original form and package. However, to minimize or simplify the manipulations during testing and reduce the possibility of false positives in the performance of tests of sterility, testers may decide to disassemble the product and repackage it prior to exposure to the verification dose.

NOTE—Manipulations prior to irradiation may not always be acceptable. In certain instances, these manipulations may change the response of the microorganisms to radiation. For example, manipulations may alter the chemical environment in the vicinity of the microorganisms, typically, oxygen tension.

Materials used for repackaging products or portions thereof for irradiation shall be capable of withstanding the radiation doses to be delivered. Packaging for products or portions thereof for irradiation shall be chosen to minimize contamination during post-irradiation handling.

5 Method VD_{max}

5.1 Rationale

Operationally, this method for substantiation of 25 kGy is similar to dose-setting Method 1 described in ANSI/AAMI/ISO 11137; it, too, requires a determination of bioburden and the performance of a verification dose experiment. The key difference is that verification is conducted at an SAL of 10^{-1}, with 10 product units irradiated in the performance of the verification dose experiment.

In substantiating 25 kGy, the method verifies that bioburden present on product before sterilization is less resistant to gamma, electron, or X-ray radiation than a microbial population of maximal resistance consistent with the attainment of an SAL of 10^{-6} at 25 kGy. Verification is conducted at an SAL of 10^{-1}. Clearly, the dose corresponding to this SAL (verification dose, VD_{max}) is characteristic of both the bioburden level and the associated maximal resistance. In establishing the maximal resistance for a particular bioburden level, due account has been taken of the various resistance components of the SDR. Components of the SDR of high resistance that have significant effect on the attainment of an SAL of 10^{-6} at 25 kGy have been used to define the maximal resistances on which this substantiation method is based. In this way, the level of conservativeness of the SDR and, thus, of Method 1 is preserved.

In practice, an estimate is made of the average bioburden. The dose that gives an SAL of 10^{-1} for product units having this average value is read from Table 2. This dose is designated VD_{max}; it is the dose at which the verification dose experiment is carried out. A sample of 10 product units or portions thereof is then exposed to the selected VD_{max} dose, and each product unit is subjected individually to a test of sterility. If there is no more than one positive test in the 10 tests of sterility, a sterilization dose of 25 kGy is substantiated.

Inspection of the values of VD_{max} for the various bioburden levels given in Table 2 reveals an unexpected change in the relationship between the bioburden levels and the values of VD_{max}. With increasing bioburden up to a level of 80 CFU, VD_{max} doses progressively increase, as might be expected. However, at a bioburden of 80 CFU, VD_{max} takes a maximum value, and for higher bioburden levels, the corresponding VD_{max} values decline. This trend is not an error in either the table or the calculations of the VD_{max} values.

The reason that the values reach a maximum and then decline can be explained by the following:

The VD_{max} approach to substantiation of 25 kGy as the sterilization dose rigorously preserves the conservative aspects of the resistance characteristics of the SDR. The SDR serves as the basis for determining the verification doses used in Method 1 of ANSI/AAMI/ISO 11137. At bioburden levels below 80 CFU, the maximal resistance that

product bioburden can take while preserving the conservativeness of the SDR is best modeled by a simple linear inactivation plot linking a particular bioburden level prior to irradiation and an SAL of 10^{-6} at 25 kGy. Using this model, as bioburden level increases, the slope of the inactivation plot increases, with a consequent increase in the value of VD_{max} at a fixed SAL of 10^{-1}. So that the conservativeness of the SDR at bioburden levels above 80 CFU is preserved, a nonlinear model for the inactivation plot should be used to derive the maximal allowable resistance. This plot is convex with respect to the dose axis, the concavity of the plot decreasing with increasing bioburden level. The consequence of deriving maximal resistances and, in turn, VD_{max} doses from the nonlinear model is that doses decline progressively from the maximum seen at a bioburden of 80 CFU with increasing bioburden above this level. More detail on the derivation of VD_{max} verification doses and discussion of this phenomenon may be found in Kowalski and Tallentire (1999).

5.2 Technical requirements

Basic technical requirements to substantiate 25 kGy as the sterilization dose shall be the following:

a) access to competent microbiological laboratory services;

b) microbiological testing performed in accordance with ANSI/AAMI/ISO 11737-1 and ANSI/AAMI/ISO 11737-2; and

c) access to a radiation source capable of delivering accurate and precise doses with either:

   1) for gamma sterilization, a Co 60 or Cs 137 radiation source; or

   2) for electron beam or X-ray sterilization, an electron beam or X-ray irradiator operated at an energy level and dose rate similar to those used in routine processing.

In conducting dose substantiation in accordance with this technical information report, the requirements of ANSI/AAMI/ISO 11137:1995 concerning the manufacture and control of products intended for radiation sterilization shall apply.

5.3 Procedure

The following five procedural stages shall be carried out.

5.3.1 Stage 1: Obtain product units

Select at random at least 10 product units from each of a minimum of three production batches immediately before the sterilization phase of production. The number of product units that is sampled shall be sufficient to represent validly the bioburden on the product to be sterilized.

NOTE—A sample may be the whole product unit or an SIP.

5.3.2 Stage 2: Determine average bioburden estimate

Using methods such as those contained in ANSI/AAMI/ISO 11737-1, determine:

a) the average bioburden estimate per product unit, or SIP, for each of the three batches; and

b) the average bioburden estimate per product unit, or SIP, for all product units sampled (overall average bioburden estimate).

Compare the three batch averages to the overall average bioburden estimate. Determine whether any one of the batch averages is two or more times greater than the overall average bioburden estimate.

5.3.3 Stage 3: Establish verification dose

To establish the verification dose, use one of the following (as determined in stage 2 above):

a) highest batch average, if one or more batch averages is equal to or greater than two times the overall average bioburden estimate; or

b) overall average bioburden estimate, if each of the batch averages is less than two times the overall average bioburden estimate.

Using Table 2, find the verification dose as follows:

a) For an SIP = 1, find the closest bioburden estimate value greater than or equal to the average bioburden estimate value determined above. The VD_{max} dose is listed in the adjacent column; or

b) For an SIP < 1, calculate the bioburden estimate of an SIP = 1 by dividing the SIP bioburden estimate by the SIP decimal value. Using the closest bioburden estimate value equal to or greater than the SIP = 1 bioburden estimate value, locate the SIP dose reduction factor and use it in the following equation to find the SIP verification dose:

$$\text{SIP verification dose} = (\text{SIP} = 1 \text{ verification dose}) + (\log \text{SIP} \times \text{SIP dose reduction factor})$$

5.3.4 Stage 4: Perform verification dose experiment

Select at random 10 product units from a single batch.

The 10 product units may be selected from any one of the batches for which a bioburden estimate was obtained in stage 2 or from a new batch manufactured under conditions that are representative of normal production. The ability of the health care product to support microbial growth should be taken into account in selecting the batch to be used.

Irradiate the product units or portions thereof at the verification dose derived in stage 3 above.

The actual dose may vary from the tabulated VD_{max} dose obtained from Table 2 by not more than +10 %. If the delivered dose is less than 90 % of the verification dose, the verification dose experiment 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.

NOTE 3—Use of the verification dose experiment without bioburden estimation is not valid.

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

NOTE—Other media and incubation conditions may be used as appropriate (see 4.2).

5.3.5 Stage 5: Interpretation and action

If no more than one positive test of sterility is obtained in the 10 tests, a sterilization dose of 25 kGy is substantiated and the confirmatory verification dose experiment described in 5.4 is not required.

If two positive tests of sterility are obtained in the 10 tests, the confirmatory verification dose experiment described in 5.4 shall be conducted.

If three or more positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy is not substantiated. An alternative method (e.g., a dose-setting method) shall be used.

This dose substantiation experiment shall not be repeated unless the results can be ascribed to incorrect performance of the estimation of bioburden, the sterility testing, or the delivery of the verification dose (e.g., the delivered dose was less than 90 % of the verification dose obtained from Table 2).

5.4 Confirmatory verification dose experiment

5.4.1 Obtain product units

Select at random 10 product units from a single batch. The 10 product units may be from one of the batches sampled previously (5.3.1 or 5.3.4) or from a new batch manufactured under conditions that are representative of normal production.

5.4.2 Confirmatory verification dose

Use the same verification dose as determined in 5.3.3.

5.4.3 Perform confirmatory verification dose experiment

Irradiate the 10 product units or portions thereof at the confirmatory verification dose.

The same tolerances for the actual and delivered doses as described in 5.3.4 apply.

The 10 irradiated product units or portions thereof are each subjected to a test of sterility as described in 5.3.4.

5.4.4 Interpretation and action

If no positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy is substantiated. This substantiation represents a total of two positive tests of sterility obtained from the initial and confirmatory verification dose experiments.

If one or more positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy has not been substantiated. This finding represents a total of three or more positive tests of sterility from the initial and confirmatory verification dose experiments. An alternative method (e.g., a dose-setting method) shall be used.

This dose substantiation experiment shall not be repeated unless the results can be ascribed to incorrect performance of the estimation of bioburden, the sterility testing, or the delivery of the verification dose (e.g., the delivered dose was less than 90 % of the verification dose obtained from Table 2).

5.5 Sterilization dose audit

Once the sterilization dose has been established, periodic audits are required to reaffirm the sterilization dose. For products in regular production, audits shall be performed once per calendar quarter to detect changes in the bioburden that could require an increase in the sterilization dose. Audits shall be conducted as follows:

5.5.1 Obtain product units

Select at random at least 20 product units from a single production batch immediately before the sterilization phase of production.

5.5.2 Determine bioburden estimate

Using the same SIP as used in the original dose substantiation experiment and a validated bioburden estimate test method, determine the bioburden estimate on each of 10 product units or portions thereof. Calculate the average bioburden estimate.

5.5.3 Perform dose audit experiment

Using the same SIP, irradiate the remaining 10 product units or portions thereof at the verification dose determined in the original dose substantiation experiment (5.3.3).

The same tolerances for the actual and delivered doses as described in 5.3.4 apply.

Subject each of the irradiated product units or portions thereof to a test of sterility using the media and incubation conditions used in the original dose substantiation experiment.

5.5.4 Interpretation and action

If no more than one positive test of sterility is obtained in the 10 tests, a sterilization dose of 25 kGy is reaffirmed. The confirmatory verification dose experiment described in 5.6 is not required.

If two positive tests of sterility are obtained in the 10 tests, the confirmatory verification dose experiment described in 5.6 shall be conducted.

If three, four, five, or six positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy is not reaffirmed. The 25 kGy sterilization dose shall be immediately augmented (5.7), and an alternative method (e.g., a dose-setting method) shall be used.

If seven or more positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy is not reaffirmed. The 25 kGy sterilization dose cannot be augmented using the equation in 5.7. An alternative method (e.g., a dose-setting method) shall be used.

This dose audit experiment shall not be repeated unless the results can be ascribed to incorrect performance of the estimation of bioburden, the sterility testing, or the delivery of the verification dose (e.g., the delivered dose was less than 90 % of the verification dose obtained from Table 2).

5.6 Confirmatory dose audit experiment

5.6.1 Obtain product units

Select at random 10 product units from a single batch. The 10 product units may be from the batch sampled previously for audit (5.5.1) or from a new batch manufactured under conditions that are representative of normal production.

5.6.2 Confirmatory audit dose

Use the same verification dose as determined in 5.3.3.

5.6.3 Perform confirmatory dose audit experiment

Irradiate the 10 product units or portions thereof at the confirmatory audit dose identified in 5.6.2.

The same tolerances for the actual and delivered doses as described in 5.3.4 apply.

Subject each of the product units or portions thereof to a test of sterility using the media and incubation conditions used in the original dose substantiation experiment.

5.6.4 Interpretation and action

If no positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy is reaffirmed. This finding represents a total of two positive tests of sterility obtained from the initial and confirmatory dose audit experiments.

If one, two, three, or four positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy has not been reaffirmed. This finding represents a total of three, four, five, or six positive tests of sterility from the initial and confirmatory dose audit experiments. The 25 kGy sterilization dose shall immediately be augmented, and an alternative method (e.g., a dose-setting method) shall be used.

If five or more positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy is not reaffirmed. This finding represents a total of seven or more positive tests of sterility from the initial and confirmatory dose audit experiments. The 25 kGy sterilization dose cannot be augmented using the equation in 5.7. An alternative method (e.g., a dose-setting method) shall be used.

The dose audit shall not be repeated unless the results can be ascribed to incorrect performance of the estimation of bioburden, the sterility testing, or the delivery of the verification dose (e.g., the delivered dose was less than 90 % of the confirmatory verification dose obtained from Table 2).

5.7 Dose augmentation

When a total of three, four, five, or six positive tests of sterility are obtained in the combined initial and confirmatory audit dose experiments (5.5.4 or 5.6.4), the 25 kGy sterilization dose shall immediately be augmented until an alternative method (e.g., a dose-setting method) can be completed.

Using the average bioburden estimate calculated in 5.5.2 (SIP = 1) and Table 2, find the closest bioburden estimate value equal to or greater than the average bioburden estimate value, and read across the table to the augmentation value column. Use this value in the following equation to calculate the augmented sterilization dose:

augmented sterilization dose (kGy) = 25 kGy + dose augmentation value

When a total of seven or more positive tests of sterility are obtained in the combined initial and confirmatory dose audit experiments (5.5.4 or 5.6.4), the dose augmentation equation shall not be used, and an alternative method (e.g., a dose-setting method) shall be used to establish the sterilization dose.

6 Worked examples

6.1 Verification dose experiment (SIP < 1) example

Term	Value	Comment
Stage 1		
SAL	10^{-6}	This method substantiates only a 10^{-6} SAL at 25 kGy.
SIP	0.5	The product was too large to be sterility tested easily. A one-half portion was selected for testing.
Stage 2		
SIP bioburden estimate	59	SIP bioburden estimate results of 50, 62, and 65 were observed from the three batches tested for an average SIP bioburden estimate of 59.

Term	Value	Comment
Average bioburden estimate	118	The bioburden for the entire product unit was calculated as follows: 50/0.5 = 100 62/0.5 = 124 65/0.5 = 130 The average bioburden estimate is 118. None of the individual batch bioburden estimates was twice the average bioburden estimate of 118; therefore, the average bioburden estimate will be used to calculate the verification dose.
Stage 3		
Verification dose	8.1 kGy	Use the average bioburden estimate and Table 2 to determine the verification dose. A bioburden estimate of 118 is not listed in the table, so the next higher bioburden of 120 is used. The verification dose for an SIP of 0.5 is calculated using the following equation: SIP Verification Dose = (SIP = 1 verification dose) + (log SIP * SIP dose reduction factor) SIP verification dose = 9.0 + (log 0.5 * 2.91) = 8.1
Stage 4		
Test of sterility results	0 positives at 7.9 kGy	The verification dose was within the specified dose range.
Stage 5		
Sterilization dose	25 kGy	The sterility test results were acceptable (≤ 1 positive). Therefore, 25 kGy has been substantiated to achieve at least a 10^{-6} SAL.

6.2 Quarterly dose audit with audit failure and dose augmentation example

Term	Value	Comment
Product units	20	Twenty product units were obtained from a single production batch.
SIP	0.5	The original substantiation of 25 kGy was conducted using an SIP of 0.5.
SIP bioburden estimate	354	The average bioburden estimate for the 10 samples tested was 354.
Average bioburden estimate	708	The average bioburden estimate for the entire product unit was calculated as follows: 354/0.5 = 708.
Audit dose	8.1 kGy	The original substantiation of 25 kGy was conducted at a verification dose of 8.1 kGy. Ten product units were irradiated at this target dose.
Sterility results	2 positives at 8.3 kGy	The audit dose was delivered within the specified dose range. The occurrence of two positive tests of sterility requires that a confirmatory dose audit be conducted.
Product units	10	Ten additional product units were obtained from a single production batch.
Audit dose	8.1 kGy	The confirmatory audit dose is the same as the audit dose. Ten product units were irradiated at this target dose.

Term	Value	Comment
Sterility results	1 positive at 7.9 kGy	The confirmatory audit dose was delivered within the specified dose range. The occurrence of one positive test of sterility in the confirmatory test yields a total of three positive tests of sterility for the audit and constitutes a dose audit failure. The 25 kGy sterilization dose must be augmented immediately and an alternative method (e.g., a dose-setting method) shall be used.
Average bioburden estimate	708	Use the average bioburden estimate for the entire device that was calculated from the audit samples to determine the augmented sterilization dose.
Augmenta-tion value	3.4 kGy	Use the average bioburden estimate and Table 2 to determine the augmentation value. A bioburden estimate of 708 is not listed in the table, so the next higher bioburden estimate of 750 is used.
Augmented sterilization dose	28.4 kGy	The augmented sterilization dose is calculated using the following equation: augmented sterilization dose (kGy) = 25 kGy + augmentation value (kGy) augmented sterilization dose (kGy) = 25 kGy + 3.4 kGy = 28.4 kGy

Table 2—Verification doses, SIP factors, and dose augmentation values

Bioburden	Verification dose (kGy)	SIP dose reduction factor	Augmentation value (kGy)
1	4.2	4.17	4.2
2	5.2	3.97	4.0
3	5.7	3.86	3.9
4	6.1	3.79	3.8
5	6.3	3.73	3.7
6	6.6	3.69	3.7
7	6.7	3.65	3.7
8	6.9	3.62	3.6
9	7.0	3.59	3.6
10	7.1	3.57	3.6
11	7.2	3.55	3.6
12	7.3	3.53	3.5
13	7.4	3.51	3.5
14	7.5	3.50	3.5
15	7.6	3.48	3.5
16	7.6	3.47	3.5
17	7.7	3.46	3.5
18	7.8	3.45	3.4
19	7.8	3.43	3.4
20	7.9	3.42	3.4
22	8.0	3.40	3.4
24	8.1	3.39	3.4
26	8.1	3.37	3.4
28	8.2	3.36	3.4
30	8.3	3.34	3.3
35	8.4	3.31	3.3
40	8.6	3.29	3.3
45	8.7	3.27	3.3
50	8.8	3.25	3.2
55	8.9	3.23	3.2

Bioburden	Verification dose (kGy)	SIP dose reduction factor	Augmentation value (kGy)
60	8.9	3.21	3.2
65	9.0	3.20	3.2
70	9.1	3.19	3.2
75	9.1	3.17	3.2
80	9.2	3.15	3.2
85	9.1	3.11	3.2
90	9.1	3.08	3.2
95	9.1	3.05	3.2
100	9.0	3.01	3.2
110	9.0	2.96	3.2
120	9.0	2.91	3.2
130	8.9	2.86	3.2
140	8.9	2.83	3.2
150	8.9	2.79	3.2
160	8.8	2.76	3.2
170	8.8	2.72	3.2
180	8.8	2.69	3.2
190	8.7	2.67	3.3
200	8.7	2.64	3.3
220	8.7	2.60	3.3
240	8.6	2.56	3.3
260	8.6	2.52	3.3
280	8.6	2.49	3.3
300	8.6	2.46	3.3
325	8.5	2.43	3.3
350	8.5	2.40	3.3
375	8.5	2.37	3.3
400	8.4	2.34	3.3
425	8.4	2.32	3.3
450	8.4	2.30	3.3
475	8.4	2.28	3.3
500	8.4	2.26	3.3
525	8.3	2.24	3.3
550	8.3	2.22	3.3
575	8.3	2.21	3.3
600	8.3	2.19	3.3
650	8.3	2.16	3.4
700	8.2	2.14	3.4
750	8.2	2.12	3.4
800	8.2	2.09	3.4
850	8.2	2.07	3.4
900	8.1	2.05	3.4
950	8.1	2.04	3.4
1000	8.1	2.02	3.4

NOTE—Inspection of the values of VD_{max} for the various bioburden levels given in Table 2 reveals an unexpected change in the relationship between the bioburden levels and the values of VD_{max}. With increasing bioburden up to a level of 80, VD_{max} doses progressively increase, as might be expected. However, at a bioburden of 80, VD_{max} takes a maximum value, and for higher bioburden levels, the corresponding VD_{max} values decline. This finding is not an error in either the table or the calculations of the VD_{max} values.

The reason that the values reach a maximum and then decline is as follows:

The VD_{max} approach to substantiation of 25 kGy as the sterilization dose rigorously preserves the conservative aspects of the resistance characteristics of the SDR. The SDR serves as the basis for determining the verification doses used in Method 1 of ANSI/AAMI/ISO 11137. At bioburden levels below 80, the maximal resistance that product bioburden can take while preserving the conservativeness of the SDR is best modeled by a simple linear inactivation plot linking a particular bioburden level prior to irradiation and an SAL of 10^{-6} at 25 kGy. Under this model, as the bioburden level increases, the slope of the inactivation plot increases, with a consequent increase in the value of VD_{max} at a fixed SAL of 10^{-1}. So that the conservativeness of the SDR at bioburden levels above 80 is preserved, a nonlinear model for the inactivation plot should be used to derive the maximal allowable resistance. This plot is convex with respect to the dose axis, the concavity of the plot decreasing with increasing bioburden level. The consequence of deriving maximal resistances and, in turn, VD_{max} doses from the nonlinear model is that doses decline progressively from the maximum seen at a bioburden of 80 CFU with increasing bioburden above this level. More detail on the derivation of VD_{max} verification doses and discussion of this phenomenon may be found in Kowalski and Tallentire (1999).

Annex A
(informative)

Substantiation of 25 kGy as the sterilization dose for a single production batch—Method VD_{max}

A.1 Scope

This annex describes a method for substantiating 25 kGy as the sterilization dose for a single production batch of health care products with an average bioburden estimate for the entire product unit (SIP = 1) of ≤ 1000 CFU. The sterilization dose established through the use of this method for a particular batch cannot automatically be used for other batches.

A.2 Terms and definitions

See section 3 in the body of this document.

A.3 Selection and testing of product

See section 4 in the body of this document for the selection and testing of product units from the single production batch.

A.4 Method VD_{max}—Single production batch

See section 5 in the body of this document for the procedure for substantiation of 25 kGy as the sterilization dose for the single production batch. Use the following as replacements to 5.3.1 through 5.3.4:

— *5.3.1 Stage 1: Obtain product units*

Select at random at least 20 product units from the single production batch immediately prior to the sterilization phase of production. The number of product units that is sampled shall be sufficient to represent validly the bioburden on the product to be sterilized.

Note—A sample may be the whole product or a portion thereof.

— *5.3.2 Stage 2: Determine average bioburden estimate*

Using methods such as those contained in ANSI/AAMI/ISO 11737-1, determine the bioburden estimate on each of 10 of the product units or portions thereof. Calculate the average bioburden estimate.

— *5.3.3 Stage 3: Establish the verification dose*

Using Table 2, find the verification dose for the average bioburden estimate using whichever of the following methods is appropriate:

a) For an SIP = 1, find the closest bioburden estimate value greater than or equal to the average bioburden estimate value determined above. The VD_{max} dose is listed in the adjacent column.

or

b) For an SIP < 1, calculate the bioburden estimate for an SIP = 1 by dividing the SIP bioburden estimate by the SIP decimal value. Using the closest bioburden estimate value equal to or greater than the SIP = 1 bioburden estimate value, locate the SIP dose reduction factor, and use it in the following equation to find the SIP VD_{max} dose:

$$\text{SIP } VD_{max} \text{ dose} = (\text{SIP} = 1\ VD_{max} \text{ dose}) + (\log \text{SIP} * \text{SIP dose reduction factor})$$

— *5.3.4 Stage 4: Perform verification dose experiment*

Irradiate the 10 remaining product units, or portions thereof, and subject each to a test of sterility as described in 5.3.4.

The same tolerances for the actual and delivered doses as described in 5.3.4 apply.

Interpret the sterility test results according to 5.3.5. If a confirmatory verification dose experiment is required, follow the procedure in 5.4, taking the product units from the single production batch.

A.5 Audits and augmentation

This method is limited to a single production batch only, and no provisions are given for audits or augmentation.

Annex B
(informative)

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