Technical Information Report

AAMI TIR33:2005

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

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

Approved 21 December 2005 by
Association for the Advancement of Medical Instrumentation

Abstract: This technical information report is intended to prepare the industry for extending application of the VD_{max} method contained in ANSI/AAMI/ISO 11137-2:2006, which is for use with selected doses of 15 kGy and 25 kGy, to the following additional doses: 17.5, 20, 22.5, 27.5, 30, 32.5, and 35 kGy.

Keywords: radiation, VD_{max}, substantiation

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Other normatively referenced International Standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

International designation	U.S. designation	Equivalency
IEC 60601-1:2005	ANSI/AAMI ES60601-1:2005	Major technical variations
IEC 60601-1-2:2001 and Amendment 1:2004	ANSI/AAMI/IEC 60601-1-2:2001 and Amendment 1:2004	Identical
IEC 60601-2-04:2002	ANSI/AAMI DF80:2003	Major technical variations
IEC 60601-2-19:1990 and Amendment 1:1996	ANSI/AAMI II36:2004	Major technical variations
IEC 60601-2-20:1990 and Amendment 1:1996	ANSI/AAMI II51:2004	Major technical variations
IEC 60601-2-21:1994 and Amendment 1:1996	ANSI/AAMI/IEC 60601-2-21 and Amendment 1:2000 (consolidated texts)	Identical
IEC 60601-2-24:1998	ANSI/AAMI ID26:2004	Major technical variations
IEC/TR 60878:2003	ANSI/AAMI/IEC TIR60878:2003	Identical
IEC/TR 62296:2003	ANSI/AAMI/IEC TIR62296:2003	Identical
IEC 62304:2006	ANSI/AAMI/IEC 62304:2006	Identical
IEC/TR 62348:2006	ANSI/AAMI/IEC TIR62348:2006	Identical
ISO 5840:2005	ANSI/AAMI/ISO 5840:2005	Identical
ISO 7198:1998	ANSI/AAMI/ISO 7198:1998/2001/(R)2004	Identical
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996/(R)2002	Identical
ISO 10993-1:2003	ANSI/AAMI/ISO 10993-1:2003	Identical
ISO 10993-2:2006	ANSI/AAMI/ISO 10993-2:2006	Identical
ISO 10993-3:2003	ANSI/AAMI/ISO 10993-3:2003	Identical
ISO 10993-4:2002 and Amendment 1:2006	ANSI/AAMI/ISO 10993-4:2002 and Amendment 1:2006	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
ISO 10993-6:1994	ANSI/AAMI/ISO 10993-6:1995/(R)2001	Identical
ISO 10993-7:1995	ANSI/AAMI/ISO 10993-7:1995/(R)2001	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999/(R)2005	Identical
ISO 10993-10:2002 and Amendment 1:2006	ANSI/AAMI BE78:2002 ANSI/AAMI BE78:2002/A1:2006	Minor technical variations Identical
ISO 10993-11:2006	ANSI/AAMI/ISO 10993-11:2006	Identical
ISO 10993-12:2002	ANSI/AAMI/ISO 10993-12:2002	Identical
ISO 10993-13:1998	ANSI/AAMI/ISO 10993-13:1999/(R)2004	Identical
ISO 10993-14:2001	ANSI/AAMI/ISO 10993-14:2001	Identical
ISO 10993-15:2000	ANSI/AAMI/ISO 10993-15:2000	Identical
ISO 10993-16:1997	ANSI/AAMI/ISO 10993-16:1997/(R)2003	Identical
ISO 10993-17:2002	ANSI/AAMI/ISO 10993-17:2002	Identical
ISO 10993-18:2005	ANSI/AAMI BE83:2006	Major technical variations
ISO/TS 10993-19:2006	ANSI/AAMI/ISO TIR10993-19:2006	Identical

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ISO/TS 10993-20:2006	ANSI/AAMI/ISO TIR10993-20:2006	Identical
ISO 11135:1994	ANSI/AAMI/ISO 11135:1994	Identical
ISO 11137-1:2006	ANSI/AAMI/ISO 11137-1:2006	Identical
ISO 11137-2:2006 (2006-08-01 corrected version)	ANSI/AAMI/ISO 11137-2:2006	Identical
ISO 11137-3:2006	ANSI/AAMI/ISO 11137-3:2006	Identical
ISO 11138-1: 2006	ANSI/AAMI/ISO 11138-1:2006	Identical
ISO 11138-2: 2006	ANSI/AAMI/ISO 11138-2:2006	Identical
ISO 11138-3: 2006	ANSI/AAMI/ISO 11138-3:2006	Identical
ISO 11138-4: 2006	ANSI/AAMI/ISO 11138-4:2006	Identical
ISO 11138-5: 2006	ANSI/AAMI/ISO 11138-5:2006	Identical
ISO/TS 11139:2006	ANSI/AAMI/ISO 11139:2006	Identical
ISO 11140-1:2005	ANSI/AAMI/ISO 11140-1:2005	Identical
ISO 11140-5:2000	ANSI/AAMI ST66:1999	Major technical variations
ISO 11607-1:2006	ANSI/AAMI/ISO 11607-1:2006	Identical
ISO 11607-2:2006	ANSI/AAMI/ISO 11607-2:2006	Identical
ISO 11737-1: 2006	ANSI/AAMI/ISO 11737-1:2006	Identical
ISO 11737-2:1998	ANSI/AAMI/ISO 11737-2:1998	Identical
ISO 11737-3:2004	ANSI/AAMI/ISO 11737-3:2004	Identical
ISO 13485:2003	ANSI/AAMI/ISO 13485:2003	Identical
ISO 13488:1996	ANSI/AAMI/ISO 13488:1996	Identical
ISO 14155-1:2003	ANSI/AAMI/ISO 14155-1:2003	Identical
ISO 14155-2:2003	ANSI/AAMI/ISO 14155-2:2003	Identical
ISO 14160:1998	ANSI/AAMI/ISO 14160:1998	Identical
ISO 14161:2000	ANSI/AAMI/ISO 14161:2000	Identical
ISO 14937:2000	ANSI/AAMI/ISO 14937:2000	Identical
ISO/TR 14969:2004	ANSI/AAMI/ISO TIR14969:2004	Identical
ISO 14971:2000 and A1:2003	ANSI/AAMI/ISO 14971:2000 and A1:2003	Identical
ISO 15223:2000, A1:2002, and A2:2004	ANSI/AAMI/ISO 15223:2000, A1:2001, and A2:2004	Identical
ISO 15225:2000 and A1:2004	ANSI/AAMI/ISO 15225:2000/(R)2006 and A1:2004/(R)2006	Identical
ISO 15674:2001	ANSI/AAMI/ISO 15674:2001	Identical
ISO 15675:2001	ANSI/AAMI/ISO 15675:2001	Identical
ISO/TS 15843:2000	ANSI/AAMI/ISO TIR15843:2000	Identical
ISO 15882:2003	ANSI/AAMI/ISO 15882:2003	Identical
ISO/TR 16142:2006	ANSI/AAMI/ISO TIR16142:2006	Identical
ISO 17664:2004	ANSI/AAMI ST81:2004	Major technical variations
ISO 17665-1:2006	ANSI/AAMI/ISO 17665-1:2006	Identical
ISO 18472:2006	ANSI/AAMI/ISO 18472:2006	Identical
ISO/TS 19218:2005	ANSI/AAMI/ISO 19218:2005	Identical
ISO 25539-1:2003 and A1:2005	ANSI/AAMI/ISO 25539-1:2003 and A1:2005	Identical

[1]In production
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Introduction

This document is intended to be used in conjunction with ANSI/AAMI/ISO 11137, *Sterilization of health care products Radiation sterilization* (series). 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 11137-2:2006 includes Method VD_{max} for the substantiation of 25 kGy as a sterilization dose (termed VD_{max}^{25}) for products with an average bioburden less than or equal to 1,000, and VD_{max}^{15} for the substantiation of 15 kGy as a sterilization dose for products with low average bioburden (less than or equal to 1.5).

This TIR parallels and extends ANSI/AAMI/ISO 11137-2; it provides a methodology for the substantiation of a range of sterilization doses. Included are 15, 17.5, 20, 22.5, 25, 27.5, 30, 32.5, and 35 kGy; each of these sterilization doses is valid only for a specified unique range of average bioburden on product.

The method described in this report is a simple approach to dose substantiation to attain a sterility assurance level (SAL) of 10^{-6} at the selected sterilization dose, (e.g. 25 kGy for VD_{max}^{25}). 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 the sterilization dose.

— 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 a selected sterilization dose.

This approach to sterilization dose substantiation 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); application of the VD_{max} approach to doses other than 25 kGy is discussed in Kowalski and Tallentire (2003).

The method described here and designated 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 is substantiated by this method. In particular, one requirement states that products shall be manufactured in circumstances such that the bioburden is controlled. Compliance with the requirements for properly controlling the quality of raw materials and the manufacturing environment, and for establishing the basic properties of the packaging material, is essential.

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1 Scope

1.1 Inclusions

This technical information report (TIR) describes a method of substantiating a selected dose for a sterility assurance level (SAL) of 10^{-6} for radiation sterilization of health care products. This TIR also specifies a method of dose auditing to demonstrate the continued effectiveness of the sterilization dose.

NOTE 1—This method of sterilization dose substantiation may be used to meet the product qualification requirements specified in ANSI/AAMI/ISO 11137.

NOTE 2—This TIR is considered informative, and use of the terms shall, should, and so forth should be considered only within the context of this TIR. That is, if the decision is made to use this method of substantiation, then this method should be followed according to the requirements (shall) and recommendations (should) set forth in this TIR.

1.2 Exclusions

This method, as described, is for the substantiation of the specified doses only and cannot be used to substantiate other sterilization doses. The method cannot be used for the substantiation of a selected dose when the average bioburden estimate of the entire product unit does not meet the requirements for the selected dose.

2 Normative references

The following normative documents contain provisions that, through reference in this text, constitute provisions of this TIR. For dated references, subsequent amendments to or revisions of any of these publications do not apply. However, parties to agreements based on this TIR 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 AAMI standards.

ANSI/AAMI/ISO 11137-1, *Sterilization of health care products—Radiation—Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices*

ANSI/AAMI/ISO 11137-2, *Sterilization of health care products—Radiation—Part 2: Establishing the sterilization dose*

ANSI/AAMI/ISO 11137-3, *Sterilization of health care products—Radiation—Part 3: Guidance on dosimetric aspects*

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

ANSI/AAMI/ISO 11737-2, *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 TIR the following terms and definitions apply.

3.1 absorbed dose: Quantity of ionizing radiation energy imparted per unit mass of matter.

NOTE—The unit of absorbed dose is the gray (Gy), where 1 gray is equivalent to absorption of 1 joule per kilogram.

[ANSI/AAMI/ISO 11137-1]

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3.2 batch: Defined quantity of product, intended or purported to be uniform in character and quality, which has been produced during a defined cycle of manufacture.

[ANSI/AAMI/ISO TIR11139]

3.3 bioburden: Population of viable microorganisms on or in product and/or sterile barrier system.

[ANSI/AAMI/ISO TIR11139]

3.4 change control: Assessment and determination of the appropriateness of a proposed alteration to product or procedure.

[ANSI/AAMI/ISO TIR11139]

3.5 corrective action: Action to eliminate the cause of a detected nonconformity or other undesirable situation.

NOTE 1—There can be more than one cause for a nonconformity.

NOTE 2—Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence.

NOTE 3—There is a distinction between correction and corrective action.

[ANSI/AAMI/ISO TIR11139]

3.6 dose: See absorbed dose.

NOTE—The term dose is used as a synonym for the defined term “absorbed dose.”

[ANSI/AAMI/ISO 11137-1]

3.7 dose mapping: Measurement of dose distribution and variability in material irradiated under defined conditions.

[ANSI/AAMI/ISO 11137-1]

3.8 D value (D_{10} value): Time or dose required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions.

[ANSI/AAMI/ISO TIR11139]

NOTE—For the purposes of this TIR, D_{10} applies to the radiation dose only and not time.

3.9 false positive: Test result interpreted as growth arising from product, or portions thereof, tested when either growth resulted from extraneous microbial contamination or turbidity occurred from interaction between the product, or portions thereof, and the test medium.

[ANSI/AAMI/ISO 11137-2]

3.10 health care product: Medical device(s), including in vitro diagnostic medical device(s), or medicinal product(s), including biopharmaceutical(s).

[ANSI/AAMI/ISO TIR11139]

3.11 incremental dose: Dose within a series of doses applied to a number of product, or portions thereof, and used in a dose-setting method to obtain or confirm the sterilization dose.

[ANSI/AAMI/ISO 11137-2]

3.12 medical device: Instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material, or other related article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purposes of

a) diagnosing, preventing, monitoring, treating, or alleviating disease;

b) diagnosing, monitoring, treating, alleviating, of or compensating for an injury;

c) investigating, replacing, modifying, or supporting of the anatomy or a physiological process;

d) supporting or sustaining life;

e) controlling conception;

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f) disinfecting medical devices; or

g) providing information for medical purposes by means of in vitro examination of specimens derived from the human body;

and that does not achieve its primary intended action in or on the human body by pharmacological, immunological, or metabolic means, but that may be assisted in its function by such means.

[ANSI/AAMI/ISO 13485]

3.13 microorganism: Entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses.

NOTE—A specific standard might not require demonstration of the effectiveness of the sterilization process in inactivating all types of microorganisms, identified in the definition above, for validation and/or routine control of the sterilization process.

[ANSI/AAMI/ISO TIR11139]

3.14 negative test of sterility: Test result for which there is no detectable microbial growth from product, or portion thereof, subjected to a test of sterility

[ANSI/AAMI/ISO 11137-2]

3.15 packaging system: Combination of the sterile barrier system and protective packaging.

[ANSI/AAMI/ISO TIR11139]

3.16 positive test of sterility: Test result for which there is detectable microbial growth from product, or portion thereof, subjected to a test of sterility.

[ANSI/AAMI/ISO 11137-2]

3.17 product: Result of a process.

[ISO 9000:2000]

NOTE—For the purposes of sterilization standards, product is tangible and can be raw materials, intermediates, sub-assemblies or health care products.

3.18 product family: Group of different product that can be given the same sterilization dose.

[ANSI/AAMI/ISO 11137-1]

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

[ANSI/AAMI/ISO 11137-2]

3.20 sterile barrier system: Minimum package that prevents ingress of microorganisms and allows aseptic presentation of product at the point of use.

[ANSI/AAMI/ISO TIR11139]

3.21 sterility: State of being free from viable microorganisms.

NOTE—In practice, no such absolute statement regarding the absence of microorganisms can be proven (see sterilization).

[ANSI/AAMI/ISO TIR11139]

3.22 sterility assurance level (SAL): Probability of a single viable microorganism occurring on an item after sterilization.

[ANSI/AAMI/ISO TIR11139]

NOTE—The term SAL takes a quantitative value, generally 10^{-6} or 10^{-3}. When this quantitative value to assurance of sterility, an SAL of 10^{-6} has a lower value but provides a greater assurance of sterility than an SAL of 10^{-3}.

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3.23 sterilization: Validated process used to render product free from viable microorganisms.

NOTE—In a sterilization process, the nature of microbial inactivation is exponential; thus, the survival of a microorganism on an individual item can be expressed in terms of probability. Although this probability can be reduced to a very low number, it can never be reduced to zero see sterility assurance level, 3.22.

[ANSI/AAMI/ISO TIR11139]

3.24 sterilization dose: Minimum dose to achieve the specified requirements for sterility.

[ANSI/AAMI/ISO 11137-1]

3.25 sterilization dose audit: Exercise undertaken to confirm the appropriateness of an established sterilization dose.

[ANSI/AAMI/ISO 11137-2]

3.26 test of sterility: Technical operation performed as part of development, validation, or requalification to determine the presence or absence of viable microorganisms on product or portions thereof.

[ANSI/AAMI/ISO TIR11139]

3.27 verification dose: Dose of radiation predicted to give a predetermined SAL $\geq 10^{-2}$; used in establishing the sterilization dose.

[ANSI/AAMI/ISO 11137-2]

3.28 VD_{max}: Maximal verification dose for a given bioburden, consistent with the attainment of a SAL of 10^{-6} at a specified sterilization dose.

NOTE—The method is generally referred to as VD_{max}^{SD}, where SD is replaced with the sterilization dose that is being validated.

4 Definition and maintenance of product families for dose setting, dose substantiation, and sterilization dose auditing

4.1 General

Establishing a sterilization dose and carrying out sterilization dose audits are part of process definition (see Clause 8 of ANSI/AAMI/ISO 11137-1) and maintenance of process effectiveness (see Clause 12 of ANSI/AAMI/ISO 11137-1). For these activities, product may be grouped into families; definition of product families is based principally on the number and types of microorganism present on or in product (the bioburden). The type of microorganism is indicative of its resistance to radiation. Variables such as density and product configuration within its packaging system are not considered in the establishment of these product families because they are not factors that influence bioburden.

In using product families in establishing the sterilization dose and for sterilization dose auditing, it is important to be aware of risks such as reduction in the ability to detect an inadvertent change within the manufacturing process that influences the effectiveness of sterilization. Furthermore, the use of a single product to represent the product family might 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 should be developed and implemented before proceeding.

NOTE—See ANSI/AAMI/ISO 14971 for guidance related to risk management.

4.2 Defining product families

4.2.1 The criteria for defining a product family shall be documented. Product shall be assessed against these criteria, and the similarities between potential product family members shall be considered. Consideration shall include all product-related variables that affect bioburden, including, but not limited to,

a) nature and sources of raw materials, including the effect, if any, of raw materials that might be sourced from more than one location;

b) components;

c) product design and size;

d) manufacturing process;

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e) manufacturing equipment;

f) manufacturing environment; and

g) manufacturing location.

The outcome of the assessment and considerations shall be recorded (see 4.1.2 of ANSI/AAMI/ISO 11137-1).

4.2.2 Product shall be included in a product family if it is demonstrated that the product-related variables (see 4.2.1) are similar and under control.

4.2.3 Before product is included in a product family. It shall be demonstrated that bioburden comprises similar numbers and types of microorganisms

4.2.4 Inclusion of product from more than one manufacturing location in a product family shall be specifically justified and recorded (see 4.1.2 of ANSI/AAMI/ISO 11137-1). Consideration shall be given to the effect on bioburden of

a) geographic and climatic differences between locations,

b) any differences in the control of the manufacturing processes or environment, and

c) sources of raw materials and processing adjuvants (e.g., water).

4.3 Designation of product to represent a product family for performance of a verification dose experiment or sterilization dose audit

4.3.1 Product to represent a product family

4.3.1.1 The number and types of microorganism on or in product shall be used as the basis for selecting product to represent a product family.

4.3.1.2 A product family shall be represented by

a) the master product (see 4.3.2),

b) an equivalent product (see 4.3.3), or

c) a simulated product (see 4.3.4).

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

a) numbers of microorganisms comprising the bioburden,

b) types of microorganisms comprising the bioburden,

c) environment in which the microorganisms occur,

d) size of product,

e) number of components,

f) complexity of product,

g) degree of automation during manufacture, and

h) manufacturing environment.

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4.3.2 Master product

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

4.3.3 Equivalent product

A group of product shall be considered equivalent only if assessment (see 4.3.1.3) indicates that group members require the same sterilization dose. Selection of the equivalent product to represent the family shall be either at random or according to a planned schedule to include different members of the product family. The manufacturing volume and availability of product should be considered in the selection of the equivalent product to represent the product family.

4.3.4 Simulated product

A simulated product shall represent a product family only if it constitutes an equivalent or greater challenge to the sterilization process than that provided by members of the product family. Simulated product shall be packaged the manner the same way and with materials used for the actual product.

NOTE—A simulated product is not intended for clinical use; it is fabricated solely for the establishment or maintenance of the sterilization dose.

A simulated product may be

a) one that is similar to the actual product in terms of materials and size and that is subjected to similar manufacturing processes (for example, a piece of the material used for implants that goes through the entire manufacturing process), or

b) a combination of components from product within the product family that would not typically be combined for use (for example, a tubing set containing multiple filters or clamps and stopcocks that are components of other products within the product family).

4.4 Maintaining product families

4.4.1 Periodic review

Review shall be performed at a specified frequency to ensure that product families and product used to represent each product family remain valid. Responsibility for review of product and/or processes that might affect membership of product families shall be allocated to competent personnel. Such reviews shall be performed at least annually. The outcome of the review shall be recorded in accordance with 4.1.2 of ANSI/AAMI/ISO 11137-1.

4.4.2 Modification to product and/or manufacturing process

Modifications to product, 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 assessed through a formal, documented change control system. Such modifications can alter the basis on which the product family was defined or the basis on which the selection of product to represent the product family was made. Significant changes can require definition of a new product family or selection of a different representative product.

4.4.3 Records

Records of product families shall be retained (see 4.1.2 of ANSI/AAMI/ISO 11137-1).

4.5 Effect of failure of establishment of sterilization dose or of a sterilization dose audit on a product family

In the event of failure during establishment of the sterilization dose or sterilization dose audit for a product family, all members of that family shall be considered to be affected. Subsequent actions shall apply to all product comprising the product family.

5 Selection and testing of product for establishing and verifying the sterilization dose

5.1 Nature of product

5.1.1 Product for sterilization can consist of

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a) an individual health care product in their packaging system;

b) a set of components presented in a packaging system 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 in its packaging system; and

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

Product items for dose setting and dose substantiation shall be selected in accordance with Table 1.

Table 1—Nature of product items for establishing and verifying the sterilization dose

Product type	Item for bioburden estimation, verification, and/or incremental dose experiment	Rationale
Individual health care product in its packaging system	Individual health care product	Each health care product is used independently in clinical practice.
Set of components in a packaging system	Combination of all components of the product	Components are assembled as a product and used together in clinical practice.
Number of identical health care products in their packaging system	Single health care product taken from the packaging system	Each health care product is used independently in clinical practice. The SAL of an individual health care product within the packaging system meets the selected SAL, although the SAL associated with that packaging system might be higher.
Kit of procedure-related health care products*	Each type of health care product in the kit	Each health care product is used independently in clinical practice.

* In dose setting, the sterilization dose is chosen based on the health care product requiring the highest sterilization dose.

NOTE 1—See 5.2 for guidance on the use of sample item portion for product characterized in 5.1.1 b).

NOTE 2—See 4 for the use of Product Families for product characterized in 5.1.1 d).

5.1.2 If the product has a claim of sterility for part of the product, the sterilization dose may be established on the basis of that part only.

NOTE—For example, if the product has a label claim of sterility for the fluid path only, the sterilization dose may be established basis of bioburden determinations and outcomes of tests of sterility performed on the fluid path.

5.2 Sample item portion (SIP)

5.2.1 For product with an average bioburden greater than or equal to 1.0, whenever practicable, an entire product (SIP equal to 1.0) should be used for testing in accordance with Table 1. When the use of an entire product is not practicable, a selected portion of product (sample item portion, SIP) may be substituted. The SIP should be as large a portion of the item as practicable to manipulate in the laboratory and should be of a size that can be handled during testing.

5.2.2 For product with an average bioburden less than or equal to 0.9, an entire product (SIP equal to 1.0) shall be used for testing in accordance with Table 1.

5.2.3 If the bioburden is evenly distributed on and/or in the item, the SIP may be selected from any portion of the item. If the bioburden is not evenly distributed, the SIP shall consist of portions of product selected at random that proportionally represent each of the materials from which the product is made. If the bioburden distribution is known, the SIP may be selected from the portion of the product that is considered to be the most severe challenge to the sterilization process.

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The SIP can be calculated on the basis of length, mass, volume, or surface area (see Table 2 for examples).

Table 2—Examples for SIP calculation

Basis for SIP	Product
Length	Tubing (consistent diameter)
Mass	Powders Gowns Implants (absorbable)
Volume	Fluid
Surface area	Implants (non-absorbable) Tubing (variable diameter)

5.2.4 The preparation and packaging of an SIP shall be carried out under conditions that minimize alterations to bioburden. Environmentally controlled conditions should be used for preparation of SIPs and, whenever possible, packaging materials should be equivalent to those used for the finished product.

5.2.5 The adequacy of a selected SIP shall be demonstrated. The bioburden of the SIP shall be such that either (a) presterilization counts show ≥ 1 cfu/SIP on at least 85 % of the SIP items, or (b) tests of sterility performed individually on 20 nonirradiated SIP items yield a minimum of 17 positive tests of sterility (i.e., 85 % positives). If the criterion is not achieved, an SIP that is larger the one examined originally and that meets the criterion shall be used. If an entire product is tested (SIP equal to 1.0), the criterion of a minimum of 17 positive tests of sterility observed out of 20 tests of sterility performed does not have to be met.

5.3 Manner of sampling

5.3.1 Product for establishing or auditing the sterilization dose shall be representative of that subjected to routine processing procedures and conditions. Generally, each product item used for a bioburden determination or in the performance of a test of sterility should be taken from a separate packaging system.

5.3.2 The period of time that elapses between the selection of product samples and the determination of bioburden should reflect the time period between completion of the last manufacturing step and sterilization of product. Product items may be selected from product rejected during the manufacturing process provided that they have been subjected to the same processing and conditions as the remainder of production.

5.4 Microbiological testing

5.4.1 Bioburden determinations and tests of sterility shall be conducted in accordance with ANSI/AAMI/ISO 11737-1 and ANSI/AAMI/ISO 11737-2, respectively.

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 for the performance of tests of sterility. If there is reason to suspect that this medium and temperature do not support the growth of microorganisms present, other appropriate media and incubation conditions should be used. (See Herring, et al. 1974; Favero, 1971; and NHB 5340.1A, 1968.)

Whenever practicable, product should be irradiated in its original form and package system. However, to reduce the possibility of false positives in the test of sterility, an item may be disassembled and repackaged before irradiation. Manipulations before irradiation are not acceptable if they change the magnitude of the bioburden or its response to radiation (i.e., manipulations that alter the chemical environment in the vicinity of the microorganisms, typically oxygen tension). Materials for repackaging product items for irradiation shall be capable of withstanding the doses delivered and subsequent handling, thereby minimizing the likelihood of contamination.

5.4.2 Bioburden determinations shall be carried out on product that has undergone the packaging process.

NOTE—Generally, it is sufficient to perform a bioburden determination on product after its removal from its packaging system and to omit the packaging system from the determination.

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5.5 Irradiation

5.5.1 Irradiation of product in establishing and verifying the sterilization dose shall be conducted in an irradiator that has undergone Installation Qualification, Operational Qualification, and Performance Qualification in accordance with ANSI/AAMI/ISO 11137-1. For the performance of a verification dose experiment or an incremental dose experiment, sufficient dose mapping shall be carried out to identify the highest and the lowest doses received by product.

5.5.2 Dose measurements and the use of radiation sources shall be in accordance with ANSI/AAMI/ISO 11137-1.

NOTE—See ANSI/AAMI/ISO 11137-3 for guidance on dosimetric aspects of radiation sterilization.

6 Method VD_{max}—Substantiation of a selected sterilization dose

6.1 Rationale

Operationally, this method of substantiation for a selected sterilization dose is similar to dose-setting Method 1 of ANSI/AAMI/ISO 11137-2. It also requires a determination of bioburden and the performance of a verification dose experiment.

In carrying out substantiation, the method verifies that bioburden present on product before sterilization is less resistant to radiation than a microbial population of maximum resistance consistent with the attainment of a SAL of 10^{-6} at the selected sterilization dose. Verification is conducted at a SAL of 10^{-1}, with 10 product items irradiated in the performance of the verification dose experiment. The dose corresponding to this SAL, (VD_{max}) is characteristic of both the bioburden level and the associated maximum resistance. In establishing the maximum resistance for a particular bioburden level, due account has been taken of the various resistance components of the standard distribution of resistances (SDR), which is the basis of Method 1. High-resistance components of the SDR that have significant effect on the attainment of a SAL of 10^{-6} have been used to define the maximum 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. (See Kowalski and Tallentire, 1999; Kowalski, Aoshuang, and Tallentire, 2000; and Kowalski and Tallentire, 2003.)

In practice, a determination is made of the average bioburden. A sterilization dose is selected on the basis of average bioburden value and other relevant information (see 6.2.4.2). The VD_{max} dose corresponding to this average for the selected sterilization dose is read from a table; it is the dose at which the verification dose experiment is carried out. Ten product items, or portions thereof, are exposed to the VD_{max} dose, and each item is subjected individually to a test of sterility. If there is no more than one positive test of sterility in the 10 tests, the selected sterilization dose is substantiated. The VD_{max} methods given in this TIR are for selected sterilization doses of 15, 17.5, 20, 22.5, 25, 27.5, 30, 32.5, and 35 kGy. Each of these sterilization doses has an associated unique range of applicable average bioburden on product. The method for 25 kGy is applicable to product having an average bioburden less than or equal to 1000. To distinguish these applications of Method VD_{max} and their associated sets of values of verification dose, a superscript has been added to the term *VD_{max}* where appropriate, such as VD_{max}^{15} or $VD_{max}^{27.5}$; so that readers can identify values of VD_{max} that are associated with a selected sterilization dose, a superscript '^{SD}' is used, viz. VD_{max}^{SD}.

NOTE—Inspection of the values of the VD_{max} verification dose for the various levels of average bioburden given in the tables in Annex A reveals a change in the relationship between the bioburden level and the value of the VD_{max} verification dose. With increasing bioburden up to a certain level, values progressively increase, as might be expected. However, at the particular bioburden level, the VD_{max} verification dose takes a maximum, and for higher bioburden levels, the corresponding the VD_{max} verification dose values decline. For example, for VD_{max}^{25}, values progressively increase up to a bioburden level of 80. However, at a bioburden of 80, VD_{max}^{25} takes a maximum, and for higher bioburden levels, the corresponding VD_{max} values decline. This behavior is not the result of an error in either the tables or the calculation of the VD_{max} values. It is an inevitable outcome of building into Method VD_{max} the same degree of conservativeness as that in Method 1 (see Kowalski and Tallentire 2003).

6.2 Procedure for Method VD_{max} for multiple production batches

6.2.1 General

6.2.1.1 In applying VD_{max} for product with an average bioburden less than or equal to 0.9 inclusive, the entire product item shall be used, whereas for product with an average bioburden greater than 0.9, an SIP may be used. In the case of VD_{max}^{15}, an SIP equal to 1.0 shall be used.

6.2.1.2 In applying Method VD_{max}, the six stages below shall be followed.

NOTE—For worked examples, see clause 9.

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