



American
National
Standard

ANSI/AAMI/ISO 13004:2022

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

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

Approved 18 December 2023 by
AAMI

Approved 9 February 2024 by
American National Standards Institute

Abstract: This document describes a method for substantiating a select sterilization dose that achieves a sterility assurance level of 10^{-6} or less for radiation sterilization of health care products. This document also specifies a method of sterilization dose audit used to demonstrate the continued effectiveness of the substantiated sterilization dose.

Keywords: radiation sterilization, sterilization dose, sterility assurance level

AAMI Standard

This Association for the Advancement of Medical Instrumentation (AAMI) standard implies a consensus of those substantially concerned with its scope and provisions. The existence of an AAMI standard does not in any respect preclude anyone, whether they have approved the standard or not, from manufacturing, marketing, purchasing, or using products, processes, or procedures not conforming to the standard. AAMI standards are subject to periodic review, and users are cautioned to obtain the latest editions.

CAUTION NOTICE: This AAMI standard may be revised or withdrawn at any time. AAMI procedures require that action be taken to reaffirm, revise, or withdraw this standard no later than 5 years from the date of publication. Interested parties may obtain current information on all AAMI standards by calling or writing AAMI.

All AAMI standards, recommended practices, technical information reports, and other types of technical documents developed by AAMI are *voluntary*, and their application is solely within the discretion and professional judgment of the user of the document. Occasionally, voluntary technical documents are adopted by government regulatory agencies or procurement authorities, in which case the adopting agency is responsible for enforcement of its rules and regulations.

Published by

AAMI

901 N. Glebe Road, Suite 300
Arlington, VA 22203

© 2024 by the Association for the Advancement of Medical Instrumentation

All Rights Reserved

This publication is subject to copyright claims of ISO and AAMI. No part of this publication may be reproduced or distributed in any form, including an electronic retrieval system, without the prior written permission of AAMI. All requests pertaining to this draft should be submitted to AAMI. It is illegal under federal law (17 U.S.C. § 101, *et seq.*) to make copies of all or any part of this document (whether internally or externally) without the prior written permission of the Association for the Advancement of Medical Instrumentation. Violators risk legal action, including civil and criminal penalties, and damages of \$100,000 per offense. For permission regarding the use of all or any part of this document, contact the Copyright Clearance Center.

Printed in the United States of America

ISBN 978-1-57020-888-1

Contents

Page

Committee representation.....	iv
Background of ANSI/AAMI adoption of ISO 13004:2022	ix
Foreword.....	x
Introduction	xi
1 Scope	1
2 Normative references	1
3 Terms and definitions.....	1
4 Definition and maintenance of product families for sterilization dose substantiation and sterilization dose auditing.....	6
5 Selection and testing of product for substantiating and auditing a selected sterilization dose	9
6 Method VD_{max}^{SD} —Substantiation of a selected sterilization dose of 17,5 kGy, 20 kGy, 22,5 kGy, 27,5 kGy, 30 kGy, 32,5 kGy or 35 kGy	12
7 Maintaining process effectiveness	21
8 Tables of values for SIP	26
9 Worked examples	57
Bibliography	61

Committee representation

Association for the Advancement of Medical Instrumentation

Radiation Sterilization Working Group

The adoption of ISO 13004:2022 as an American National Standard was initiated by the AAMI Radiation Sterilization Working Group (AAMI ST-WG02). AAMI ST-WG02 provides input to the Sterilization Standards Committee (AAMI ST), which is the responsible group for providing the U.S. input to the relevant group in ISO/TC 198. U.S. representatives from AAMI ST-WG02 and the Technical Advisory Group (TAG) played an active part in developing the ISO document.

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

Cochairs: Elaine Daniell
Niki Fidopiastis

Members: Jennifer Asleson, Quality, Microbiology & Sterilization Services LLC
Dean Bird, Olympus America Inc
Jody Birks, Eagle Medical Inc
Tim Bollnow, Intuitive Surgical Inc
Trabue Bryans, BryKor LLC
Nicholas Brydon, NextBeam [Nick Brydon Consulting LLC]
Richard Burgess, BSI Healthcare
Nicole Burns, Ecolab
Linnette Cachares, Arthrex Inc
Glenn Calvert, West Pharmaceutical Services, Inc.
Denise Cleghorn, Boston Scientific Corporation
Lisa Cook, B Braun of America Inc
Elaine Daniell, EDan-SA LLC
Douglas Davie, Sterilization Validation Services
Brian Davis, Stryker
Michael Douthit, Minus 6 Sterilization Consulting
Niki Fidopiastis, Medtronic Inc Campus
Michael Flanagan, Zimmer Biomet
Jacob Gibbons, Genentech Inc
Becky Gilsdorf, Healthmark Industries Company Inc
Amy Gravley, DEKRA Certification
Michael Graybill, 3M Health Care
Chris Haas, Getinge USA
Douglas Harbrecht, Sterility Assurance LLC
Deborah Havlik, DA Havlik Consulting
Mollie Holter, MicroBio Consulting LLC
Betty Howard, STERIS Corporation | Healthcare
Manuel Saavedra Jr., Avanos Medical
Jeffrey Karp, AbbVie
Ezra Koski, Terumo BCT
Mark Krocko, Mevex Corporation
Vu Le, Abbott Laboratories
Cathy Leckwart, WuXi AppTec Inc
John Logar, Johnson & Johnson
Randy Mack, Pfizer Parenteral Center of Excellence

Jeffrey Martin, Sterilization and Quality System Consulting LLC
 Patrick McCormick, Bausch & Lomb Inc
 Susan Messier, Ethide Laboratories
 Marina Milenkovic, Edwards Lifesciences
 Carolyn Braithwaite-Nelson, Philips
 Larry Nichols, Steri-Tek
 Susumu Nozawa, Siemens Healthineers
 Gerry O'Dell, Gerry O'Dell Consulting
 Kevin O'Hara, Sotera Health LLC
 David Parente, Sterwell LLC
 Kimberly Patton, Performance Review Institute MedAccred
 Michelle Pierce, NAMSA
 Rudy Pina, Dynatec Scientific Labs Inc
 Nicole Robichaud, Mesa Laboratories Biological Indicator Division- Bozeman Facility
 Tyrone Rouse, Owens & Minor
 Jody Rupert, WL Gore & Associates Inc
 Mara Senescu, Baxter Healthcare Corporation
 Harry Shaffer, Sterilization Consulting Services
 Paul Sordellini, Integra LifeSciences Corporation
 Mauricio Martinez Sr, Smiths Medical
 Molly Swanson, Quality Tech Services LLC
 Stephanie Volk, Convatec
 Wendy Wangsgard, ICU Medical Inc
 Richard Weisman, Fresenius Medical Care
 Scott Weiss, Alcon Laboratories Inc
 Patrick Weixel, FDA/CDRH
 Beverly Whitaker, Indigo Consulting Group LLC
 James Whitcomb, LexaMed Ltd
 Jarl Yeager, Powder River Medical Resources

Alternates: Christopher Anderson, Johnson & Johnson
 Agnieszka Baczek, Medline Industries Inc
 Vincent Bartoletti, Terumo BCT
 Curt Bogue, Cook Medical - Bloomington
 David Brodersen, Getinge USA
 Bethany Daniell, EDan-SA LLC
 Martin Dawson, BSI Healthcare
 Steven DeGraff, Boston Scientific Corporation
 Zachary Dukerich, Arthrex Inc
 Gordon Ely, LexaMed Ltd
 Shawn Engberg, MD Furniture & Supply
 Michael Groendyk, West Pharmaceutical Services, Inc.
 Sreekanth Gutala, FDA/CDRH
 Trang Hoang, Edwards Lifesciences
 Kenneth Aston II, Intuitive Surgical Inc
 Nichole Jackson, Ecolab
 Tara Jacobson, Abbott Laboratories
 Satu King, Philips
 Sarath Koruprolu, Ethide Laboratories
 Wendy Mach, Integra LifeSciences Corporation
 James Maher, Becton Dickinson & Company
 Consuelo Lorraine McChesney, Alcon Laboratories Inc
 Tom McElroy, IUVO BioScience

Jeff One, AbbVie
 Kyrstan Polaski, STERIS Corporation | Healthcare
 Hudson Santos, WuXi AppTec Inc
 Michael Schoene, Bausch & Lomb Inc
 Kristen Spigiel, Stryker
 Sopheak Srun, Quality Tech Services LLC
 Abigail Stein, Zimmer Biomet
 Justin Tettenborn, Fresenius Medical Care
 Ileana Toro-Guzman, Avanos Medical
 Julie Tuinstra, NAMS
 Wayne Usher, 3M Health Care
 Peter Veselovsky, Mevex Corporation
 Jill Warren, Siemens Healthineers
 John Williams, Medtronic Inc Campus
 Martell Winters, Sotera Health LLC
 Dan Wojtczak, Baxter Healthcare Corporation
 Frank Yanocha, Cordis US Corp

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

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

Cochairs: Janet M. Prust

Members: Gregory Darnall Aldrich, Gregory Aldrich (Individual Expert)
 Anas Aljabo, SteriLabs Canada Inc.
 Eseosa Tony Amenaghawon, Cincinnati Childrens Hospital Medical Center
 Brett Anderson, Cochlear Ltd
 Jennifer R. Asleson, Quality, Microbiology & Sterilization Services LLC
 Richard Bancroft, STERIS Corporation | Healthcare
 Leigh Anne Bartlett, Leigh Anne Bartlett (Individual Expert)
 Marie K. Brewer, UnityPoint Health - St. Luke's Hospital
 Trabue Daley Bryans, BryKor LLC
 Nicholas Brydon, NextBeam LLC
 Jonathan Burdach, Nanosonics Limited
 Rai Chowdhary, The KPI System
 Emily Craven, Boston Scientific Corporation
 Jacqueline A. Daley, Providence St Joseph Health System
 Christophe Deneux, Becton Dickinson & Company
 Kumbirai Dhliwayo, Kumbirai Dhliwayo (Individual Expert)
 Chase Elms, Chase Elms (Individual Expert)
 Gordon M. Ely, LexaMed Ltd
 Afif Jhoel Escheik, Crothall Healthcare
 Deannard Esnard, Deannard Esnard (Individual Expert)
 Nicole Felderman, CIVCO Medical Solutions
 Brian J. Fortier, Aorta Medical Inc
 Daniel Fowler, WuXi AppTec Inc
 Jacqueline Gosier, Jacqueline Gosier (Individual Expert)
 Suzanne Goss, Suzanne Goss (Individual Expert)
 Magnus Graham, BSI Healthcare
 Shelley Hagan, Henry Ford Health

Ashley Hammer, Washington Regional Medical Center
 Douglas F. Harbrecht, Sterility Assurance LLC
 Jeanetta Harris, Jeanetta Harris (Individual Expert)
 Deborah A. Havlik, DA Havlik Consulting
 Amani Hawsawi, Amani Hawsawi (Individual Expert)
 Crystal Heishman, U of L Hospital - University of Louisville
 Tisza Holt, Insulet Corporation
 Mollie J. Holter, MicroBio Consulting LLC
 Stephanie Jean Homuth, Hennepin County Medical Center Warehouse
 Clark W. Houghtling, Cosmed Group Inc
 Angela G. Jensen, Rush Foundation Hospital
 Nicholas Kalanta, McLane Children's Hospital
 Susan G. Klacik, Healthcare Sterile Processing Association (HSPA)
 Erin A. Kyle, Association of Perioperative Registered Nurses (AORN)
 Byron J. Lambert, Abbott Laboratories
 Stacey Law, Stacey Law (Individual Expert)
 Alaina N Lett, Alaina Lett (Individual Expert)
 Marissa Jones Lewis, Veterans Administration (VA) Central Office
 Emily Lorcheim, ClorDiSys Solutions, Inc
 Jonathan Manuel, Jonathan Manuel (Individual Expert)
 Kelly Marcum, HCA Healthcare
 John L. Mazzilli, Saddleback Memorial Medical Center
 Patrick J. McCormick, Bausch & Lomb Inc
 Gerald E. McDonnell, Johnson & Johnson
 Russell (Rusty) Mills, Zimmer Biomet
 Leslie Nichols, Mayo Clinic
 Atila Nozari, 3M Health Care
 Gerry A. O'Dell, Gerry O'Dell Consulting
 James O'Reilly, St Joseph Health System - Trinity Health
 Ken Paddock, Baxter Healthcare Corporation
 Alberto Guzman Paret, Cordis US Corp
 Kia Parker, The Ohio State Wexner Medical Center-University Hospital
 Kimberly Patton, Performance Review Institute MedAccred
 Annemarie Pelloso, Michigan Medicine (University of Michigan Health System)
 Nancy Pickens, Nancy Pickens (Individual Expert)
 Karana M Pierre, Karana M Pierre (Individual Expert)
 Dawn Pierson, CS Medical LLC
 Julissa Pina, Instylla, Inc.
 Shane Pinkston, Getinge USA
 Janet M. Prust, St. Croix Standards Consulting LLC
 Beth Rayfield, IU Health North Hospital
 Joan E. Rickard, Montefiore Medical Center
 Viktoria (Tori) Ruiz, Sutter Health
 Angela Salmen, Angela Salmen (Individual Expert)
 Linda Sue Schultz, Northside Hospital Surgical Services Atlanta
 Ebow Holdbrook-Smith, WellSpan Health
 Joan M. Spear, Joan M. Spear (Individual Expert)
 Sopheak Srun, Quality Tech Services LLC
 Mark Swanson, Quality and Regulatory Expert Partners (QRX)
 Sherri Taylor, Sherri Taylor (Individual Expert)
 Julie TerWee, Pfizer Parenteral Center of Excellence
 James Treharn, St. Peter's Health
 Melissa Vargas, Christiana Care Health Services
 Sara Vinson, University of Florida
 Wendy Wangsgard, ICU Medical Inc

Adrienne C. Watson, Adrienne Watson (Individual Expert)
James Sidney Wiggs, Legacy Health System
Martell Winters, Sotera Health LLC
Roberto Zumbado, Philips

Alternates: Kendall Ashe, CS Medical LLC
Jennifer Benolken, DuPont Tyvek Medical and Pharmaceutical Protection
Damien S. Berg, Healthcare Sterile Processing Association (HSPA)
Mark Bogs, ICU Medical Inc
Stacy Bohl, Boston Scientific Corporation
Kevin Bovee, Insulet Corporation
Richard Burgess, BSI Healthcare
Densley Coke, Densley Coke (Individual Expert)
Aaron David DeMent, Sotera Health LLC
April Doering, 3M Health Care
Mary Ann Drosnock, Getinge USA
Anna M. Grayson, Grayson Associates
Rhashamekia Law, Rhashamekia Law (Individual Expert)
Cathy Leckwart, WuXi AppTec Inc
Paul Lorcheim, ClorDiSys Solutions, Inc
Michelle (Shelly) Luebke, Baxter Healthcare Corporation
James A. Maher, Becton Dickinson & Company
Shaun McGinley, Zimmer Biomet
David Ford McGoldrick, Abbott Laboratories
Christine L. Render, Cosmed Group Inc
Petra Richards, Kaiser Foundation Health Plan/Hospitals
Susan Rogers, Veterans Administration (VA) Central Office
Krista Schulte, Quality Tech Services LLC
Lisa Ward, STERIS Corporation | Healthcare

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

Background of ANSI/AAMI adoption of ISO 13004:2022

As indicated in the foreword to the main body of this document (page x), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO/TC 198 to Sterilization of health care products — Radiation — Substantiation of selected sterilization dose: Method VD_{max}^{SD}. When ISO 13004 was published in 2013, AAMI adopted it as a Technical Information Report. In 2022, ISO 13004 was finalized as an ISO standard. This document is to be used with ISO 11137-1, which has been adopted by AAMI. Therefore, it was determined that the adoption of ISO 13004:2022 is in line with AAMI's work program and adoption process.

U.S. participation in ISO/TC 198 is organized through the U.S. Technical Advisory Group, AAMI ST, administered by the Association for the Advancement of Medical Instrumentation. Experts from the United States made a considerable contribution to this standard.

AAMI encourages its committees to harmonize their work with International Standards in the area of Sterilization of health care products — Radiation — Substantiation of selected sterilization dose: Method VD_{max}^{SD}. Upon review of ISO 13004:2022, the U.S. TAG to ISO/TC 198 and the AAMI Radiation Sterilization Working Group decided to adopt it verbatim, as a revision of ANSI/AAMI/ISO TIR13004:2013/(R)2016.

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every five years to reflect technological advances that may have occurred since publication.

As used within the context of this document, “shall” indicates requirements strictly to be followed to conform to the recommended practice. “Should” indicates that among several possibilities, one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action should be avoided but is not prohibited.

“May” is used to indicate that a course of action is permissible within the limits of the standard. “Can” is used as a statement of possibility and capability. Finally, “must” is used only to describe “unavoidable” situations, including those mandated by government regulation.

NOTE Users of this standard are advised that this document is an AAMI identical adoption of an ISO document and that the following international conventions have been carried over to the AAMI publication:

- British English spelling (e.g. colour instead of color)
- Use of SI units (e.g. metres instead of feet, Celsius instead of Fahrenheit, etc.)
- Decimal comma instead of a decimal point (e.g. 1 000,15 instead of 1,000.15)

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data comes to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 901 N. Glebe Road, Suite 300, Arlington, VA 22203.

NOTE—Beginning with the ISO foreword on page x, this American National Standard is identical to ISO 13004:2022.

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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

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

This first edition cancels and replaces ISO/TS 13004:2013.

The main changes are as follows:

- guidance is offered for determination of an SIP for bulk materials such as powders, liquids and gels;
- 5.3.3 and 5.3.4 have been reworded to match language in ISO 11137-2;
- the NOTE in 5.4.1 has been removed;
- 7.2 has been replaced with a reference to requirements in ISO 11137-1;
- guidance has been added for when to re-substantiate the sterilization dose based on shifts in bioburden.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

This document is intended to be used in conjunction with ISO 11137-1. One of the activities encompassed within process definition in ISO 11137-1 is the option to select and substantiate a sterilization dose to be applied to health care products.

ISO 11137-2 includes Method VD_{max}^{SD} for the substantiation of 25 kGy as a sterilization dose (termed Method VD_{max}^{25}) for product with an average bioburden less than or equal to 1 000 and Method VD_{max}^{15} for the substantiation of 15 kGy as a sterilization dose for product with an average bioburden less than or equal to 1,5.

This document extends the methods of selection and substantiation of a sterilization dose specified in ISO 11137-2. It provides a methodology for the substantiation of selected sterilization doses of 17,5 kGy, 20 kGy, 22,5 kGy, 27,5 kGy, 30 kGy, 32,5 kGy and 35 kGy, each of which is valid only for a specified upper limit of average bioburden.

NOTE Selected sterilization doses of 25 kGy and 15 kGy are not included in this document. The seven methods in this document follow the same technical steps as the methods given in ISO 11137-2 for selection and substantiation of sterilization doses of 25 kGy and 15 kGy. However, the descriptive text in this document has been modified to better communicate the methods and hence the text occasionally differs from that in ISO 11137-2.

The method described in this document is for substantiation of a selected sterilization dose to achieve a sterility assurance level (SAL) of 10^{-6} or less at that dose (e.g. Method VD_{max}^{20} for a selected sterilization dose of 20 kGy). The application of the method is not limited by production batch size or production frequency, and the number of product items irradiated in the verification dose experiment remains constant. The method is founded on 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 selected sterilization dose;
- possession of a level of conservativeness at least equal to that of the standard distribution of resistances (SDR);
- for a given bioburden, use of a maximal verification dose (VD_{max}) corresponding to substantiation of a selected sterilization dose.

This approach to sterilization dose substantiation was first outlined by Kowalski and Tallentire^[7] and, from subsequent evaluations involving computational techniques (Kowalski, Aoshuang and Tallentire^[8]) and field evaluations (Kowalski et al.^[9]), it was concluded that the method is soundly based. An overview of the method and aspects of implementation are provided in Kowalski and Tallentire.^{[10][11]} Application of the Method VD_{max}^{SD} approach to doses other than 25 kGy is discussed in Kowalski and Tallentire^{[12][13]}.

The method described here and designated Method VD_{max}^{SD} procedurally comprises elements that closely parallel those of dose setting Method 1 described in ISO 11137-2. One key area of difference is the number of product items 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 items being chosen for subsequent field evaluations and, ultimately, for inclusion in this document.

Manufacturers of health care products who intend to use this specification are reminded that the requirements contained in the ISO 11137 series apply to the manufacture and control of production batches destined for radiation sterilization. In particular, one requirement states that products have to be manufactured in circumstances such that the bioburden is controlled. The control of the quality of raw materials, the manufacturing environment, the health, hygiene and attire of personnel and for establishing the basic properties of packaging material should be maintained.

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

1 Scope

This document describes a method for substantiating a selected sterilization dose of 17,5 kGy, 20 kGy, 22,5 kGy, 27,5 kGy, 30 kGy, 32,5 kGy or 35 kGy that achieves a sterility assurance level (SAL) of 10^{-6} or less for radiation sterilization of health care products. This document also specifies a method of sterilization dose audit used to demonstrate the continued effectiveness of the substantiated sterilization dose.

NOTE 1 Selection and substantiation of the sterilization dose is used to meet the requirements for establishing the sterilization dose within process definition in ISO 11137-1.

This document does not apply to other sterilization doses than the substantiation of a selected sterilization dose of 17,5 kGy, 20 kGy, 22,5 kGy, 27,5 kGy, 30 kGy, 32,5 kGy or 35 kGy. The method is not used for the substantiation of a selected sterilization dose if the average bioburden of the entire product item exceeds the limit specified for the selected sterilization dose (see Table 3).

NOTE 2 The methods for substantiation of selected sterilization doses of 25 kGy and 15 kGy are not included in this document. They are described in ISO 11137-2.

If the decision is made to use this method of sterilization dose establishment, the method is intended to be followed in accordance with the requirements (shall) and guidance (should) stipulated herein.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 11137-1:2006, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11737-1:2018, *Sterilization of health care products — Microbiological methods — Part 1: Determination of a population of microorganisms on products*

ISO 11737-2, *Sterilization of health care products — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process*

3 Terms and definitions

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

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

- ISO Online browsing platform: available at <https://www.iso.org/obp>
- IEC Electropedia: available at <https://www.electropedia.org/>

3.1

absorbed dose

dose

quantity of ionizing radiation energy imparted per unit mass of a specified material

Note 1 to entry: The unit of absorbed dose is the gray (Gy), where 1 Gy is equivalent to the absorption of 1 J/kg.

Note 2 to entry: For the purposes of this document, the term dose is used to mean absorbed dose.

[SOURCE: ISO 11139:2018, 3.3, modified — The term "dose" was added. Notes 1 to 2 to entry were added.]

3.2

batch

defined quantity of a product intended or purported to be uniform in character and quality produced during a specified cycle of manufacture

[SOURCE: ISO 11139:2018, 3.21]

3.3

bioburden

population of viable *microorganisms* (3.11) on or in a product and/or *sterile barrier system* (3.16)

[SOURCE: ISO 11139:2018, 3.23]

3.4

correction

action to eliminate a detected nonconformity

Note 1 to entry: A correction can be made in conjunction with *corrective action* (3.5).

[SOURCE: ISO 11139:2018, 3.64, modified — In the Note 1 to entry, "in advance of, in conjunction with, or after" has been replaced by "in conjunction with".]

3.5

corrective action

action to eliminate the cause of a nonconformity and to prevent recurrence

Note 1 to entry: There can be more than one cause for a nonconformity.

Note 2 to entry: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence.

Note 3 to entry: There is a distinction between *correction* (3.4) and *corrective action* (3.5).

[SOURCE: ISO 11139:2018, 3.65, modified — Note 3 to entry has been added.]

3.6

dose mapping

measurement of dose distribution and variability in material irradiated under specified conditions

[SOURCE: ISO 11139:2018, 3.87]

3.7

false positive

test result interpreted as growth arising from product, or portion 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

[SOURCE: ISO 11137-2:2013, 3.1.3]

3.8

health care product(s)

medical device (3.9), including in vitro diagnostic medical device, or medicinal product, including biopharmaceutical

[SOURCE: ISO 11139:2018, 3.132]

3.9

medical device

instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, or software material, or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

- diagnosis, prevention, monitoring, treatment, or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of, or compensation for an injury;
- investigation, replacement, modification, or support of the anatomy, or of a physiological process;
- supporting or sustaining life;
- control of conception;
- disinfection of medical devices;
- providing information by means of in vitro examination of specimens derived from the human body;

and does not achieve its primary intended action by pharmacological, immunological, or metabolic means, but which may be assisted in its intended function by such means

[SOURCE: ISO 11139:2018, 3.166, modified — Note 1 to entry has been deleted.]

3.10

Method VD_{max}

procedure for sterilization dose substantiation that uses the maximal *verification dose* (3.23) for a given *bioburden* (3.3), consistent with the attainment of a sterility assurance level (SAL) of 10^{-6} at a selected sterilization dose

Note 1 to entry: The substantiation method is generally referred to as Method VD_{max}^{SD} , where SD takes the value of the selected sterilization dose.

Note 2 to entry: VD_{max}^{SD} is the maximal *verification dose* (3.23) for a particular selected sterilization dose (SD) obtained in using Method VD_{max}^{SD} .

Note 3 to entry: The term VD_{max}^{SD} may be used interchangeably with the term VD_{max}^{Dster} .

3.11

microorganism

entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

Note 1 to entry: 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.

[SOURCE: ISO 11139:2018, 3.176, modified — Note 1 to entry was added.]

3.12

packaging system

combination of the *sterile barrier system* (3.16) and protective packaging

[SOURCE: ISO 11139:2018, 3.192]

3.13

positive test of sterility

test result for which there is detectable microbial growth from product, or portion thereof, subjected to a *test of sterility* (3.22)

[SOURCE: ISO 11137-2:2013, 3.1.8]

3.14

product

tangible result of a process

EXAMPLE Raw material(s), intermediate(s), sub-assembly(ies), *health care product(s)* (3.8).

[SOURCE: ISO 11139:2018, 3.217]

3.15

sample item portion

SIP

specified part of a *health care product* (3.8) that is tested

[SOURCE: ISO 11139:2018, 3.240]

3.16

sterile barrier system

minimum package that minimizes the risk of ingress of *microorganisms* (3.11) and allows aseptic presentation of the sterile contents at the point of use

[SOURCE: ISO 11139:2018, 3.272]

3.17

sterility

state of being free from viable *microorganisms* (3.11)

Note 1 to entry: In practice, no such absolute statement regarding the absence of microorganisms can be proven [see *sterilization* (3.19)].

[SOURCE: ISO 11139:2018, 3.274]

3.18

sterility assurance level

SAL

probability of a single viable *microorganism* (3.11) occurring on an item after sterilization

Note 1 to entry: It is expressed as the negative exponent to the base 10.

[SOURCE: ISO 11139:2018, 3.275]

3.19

sterilization

validated process used to render product free from viable *microorganisms* (3.11)

Note 1 to entry: In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number it can never be reduced to zero [see *sterility assurance level* (3.18)].

[SOURCE: ISO 11139:2018, 3.277]

3.20

sterilization dose

SD

D_{ster}

minimum dose to achieve the specified requirements for *sterility* (3.17)

[SOURCE: ISO 11139:2018, 3.280]

3.21

sterilization dose audit

exercise undertaken to confirm the appropriateness of an established sterilization dose

[SOURCE: ISO 11139:2018, 3.281]

3.22

test of sterility

technical operation performed as part of development, validation or requalification to determine the presence or absence of viable *microorganisms* (3.11) on product or portion thereof

[SOURCE: ISO 11139:2018, 3.299]

3.23

verification dose

dose of radiation predicted to give a predetermined *sterility assurance level (SAL)* (3.18) greater than or equal to 10^{-2} used in establishing the sterilization dose

Note 1 to entry: For the purpose of this document, this predetermined SAL is 10^{-1} .

[SOURCE: ISO 11139:2018, 3.315, modified — Note 1 to entry was added.]

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

4.1 General

The establishment of a sterilization dose, for which sterilization dose selection and substantiation can be undertaken, and the carrying out of sterilization dose audits are activities that are part of process definition and maintaining process effectiveness (see ISO 11137-1). For these activities, product may be grouped into families. Definition of product families is based principally on the numbers and types of microorganisms on or in product (the bioburden), the type being indicative of the microorganism's resistance to radiation (see ISO 11737-1). 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 for establishing the sterilization dose and for carrying out sterilization dose audits, it is important to be aware of the reduction in the ability to detect an inadvertent change within the manufacturing process that influences the effectiveness of sterilization. Furthermore, with the use of a single product to represent the product family, it is possible that changes that occur in other members of the product family will not be detected. The effect of a reduction on ability to detect changes in other members of the product family should be evaluated and a plan for maintaining product families developed and implemented before proceeding.

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 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 can be sourced from more than one location;
- b) components;
- c) product design and size;
- d) manufacturing processes;
- e) manufacturing equipment;
- f) manufacturing environment;
- g) manufacturing location.

The outcome of the assessment and considerations shall be recorded in accordance with ISO 11137-1:2006, 4.1.2.

4.2.2 Product shall only 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 To include product within 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 in accordance with ISO 11137-1:2006, 4.1.2. Consideration shall be given to the effect on bioburden of:

- a) geographic and/or climatic differences between locations;

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

4.3 Designation of product to represent a product family

4.3.1 Product to represent a product family

4.3.1.1 The number and types of microorganisms 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) a master product (see 4.3.2), or
- 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) number 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;
- h) manufacturing environment.

4.3.2 Master product

A member of a product family shall only be considered a master product if assessment (see 4.3.1.3) indicates that the member presents a challenge to the sterilization process that is greater than that of all other product family members. In some situations, there can be several products within the product family, each of which can 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, either

- a) at random, or
- b) according to a documented procedure to include the different products each of which can be considered as the master product.

4.3.3 Equivalent product

A group of product shall only be considered equivalent 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

- a) at random, or
- b) in accordance with a documented procedure 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 only represent a product family 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 in a manner 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 subjected to similar manufacturing processes, e.g. 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, e.g. a tubing set containing multiple filters, 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 reviews of either product or processes, or both that can affect membership of product families shall be allocated to competent personnel. Such review shall be performed at least annually. The outcome of the review shall be recorded in accordance with ISO 11137-1:2006, 4.1.2.

4.4.2 Modification to either product or manufacturing process, or both

Modifications to product, such as raw materials (nature and source), components or product design (including size), and/or modifications to the manufacturing process, e.g. 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 the selection of a different representative product.

4.4.3 Records

Records of product families shall be retained in accordance with ISO 11137-1:2006, 4.1.2.

4.5 Consequence of failure of sterilization dose substantiation or sterilization dose audit

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

5 Selection and testing of product for substantiating and auditing a selected sterilization dose

5.1 Nature of product

5.1.1 Product for sterilization can consist of:

- a) an individual health care product in its packaging system;
- b) a set of components presented in a packaging system, 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 in their packaging system;
- d) a kit comprising a variety of procedure-related health care products.

Product items for sterilization dose substantiation and for sterilization dose auditing shall be taken in accordance with Table 1.

Table 1 — Nature of product items for sterilization dose substantiation and for sterilization dose auditing

Product type	Item for bioburden determination and verification 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 overall SAL associated with the packaging system can be higher.
Kit of procedure-related health care products ^a	Each type of health care product comprising the kit	Each health care product is used independently in clinical practice.

^a In dose establishment, the sterilization dose is chosen based on the health care product requiring the highest sterilization dose.

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.

EXAMPLE If the product has a label claim of sterility for the fluid path only, the sterilization dose may be established based on 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 according to Table 1. When the use of an entire product is not practicable,