

# American National Standard



## ANSI/AAMI/ ISO 11137-2: 2013/(R)2019

Sterilization of health care  
products—Radiation—  
Part 2: Establishing the  
sterilization dose

# Objectives and uses of AAMI standards and recommended practices

It is most important that the objectives and potential uses of an AAMI product standard or recommended practice are clearly understood. The objectives of AAMI's technical development program derive from AAMI's overall mission: the advancement of medical instrumentation. Essential to such advancement are (1) a continued increase in the safe and effective application of current technologies to patient care, and (2) the encouragement of new technologies. It is AAMI's view that standards and recommended practices can contribute significantly to the advancement of medical instrumentation, provided that they are drafted with attention to these objectives and provided that arbitrary and restrictive uses are avoided.

A voluntary *standard* for a *medical device* recommends to the manufacturer the information that should be provided with or on the product, basic safety and performance criteria that should be considered in qualifying the device for clinical use, and the measurement techniques that can be used to determine whether the device conforms with the safety and performance criteria and/or to compare the performance characteristics of different products. Some standards emphasize the information that should be provided with the device, including performance characteristics, instructions for use, warnings and precautions, and other data considered important in ensuring the safe and effective use of the device in the clinical environment. Recommending the disclosure of performance characteristics often necessitates the development of specialized test methods to facilitate uniformity in reporting; reaching consensus on these tests can represent a considerable part of committee work. When a drafting committee determines that clinical concerns warrant the establishment of *minimum* safety and performance criteria, referee tests must be provided and the reasons for establishing the criteria must be documented in the rationale.

A *recommended practice* provides guidelines for the use, care, and/or processing of a medical device or system. A recommended practice does not address device performance *per se*, but rather procedures and practices that will help ensure that a device is used safely and effectively and that its performance will be maintained.

Although a device standard is primarily directed to the manufacturer, it may also be of value to the potential purchaser or user of the device as a frame of reference for device evaluation. Similarly, even though a recommended practice is usually oriented towards healthcare professionals, it may be useful to the manufacturer in better understanding the environment in which a medical device will be used. Also, some recommended practices, while not addressing device performance criteria, provide guidelines to industrial personnel on such subjects as sterilization processing, methods of collecting data to establish safety and efficacy, human engineering, and other processing or evaluation techniques; such guidelines may be useful to health care professionals in understanding industrial practices.

In determining whether an AAMI standard or recommended practice is relevant to the specific needs of a potential user of the document, several important concepts must be recognized:

All AAMI standards and recommended practices are *voluntary* (unless, of course, they are adopted by government regulatory or procurement authorities). The application of a standard or recommended practice is solely within the discretion and professional judgment of the user of the document.

Each AAMI standard or recommended practice reflects the collective expertise of a committee of health care professionals and industrial representatives, whose work has been reviewed nationally (and sometimes internationally). As such, the consensus recommendations embodied in a standard or recommended practice are intended to respond to clinical needs and, ultimately, to help ensure patient safety. A standard or recommended practice is limited, however, in the sense that it responds generally to perceived risks and conditions that may not always be relevant to specific situations. A standard or recommended practice is an important *reference* in responsible decision-making, but it should never *replace* responsible decision-making.

Despite periodic review and revision (at least once every five years), a standard or recommended practice is necessarily a static document applied to a dynamic technology. Therefore, a standards user must carefully review the reasons why the document was initially developed and the specific rationale for each of its provisions. This review will reveal whether the document remains relevant to the specific needs of the user.

Particular care should be taken in applying a product standard to existing devices and equipment, and in applying a recommended practice to current procedures and practices. While observed or potential risks with existing equipment typically form the basis for the safety and performance criteria defined in a standard, professional judgment must be used in applying these criteria to existing equipment. No single source of information will serve to identify a particular product as "unsafe". A voluntary standard can be used as one resource, but the ultimate decision as to product safety and efficacy must take into account the specifics of its utilization and, of course, cost-benefit considerations. Similarly, a recommended practice should be analyzed in the context of the specific needs and resources of the individual institution or firm. Again, the rationale accompanying each AAMI standard and recommended practice is an excellent guide to the reasoning and data underlying its provision.

In summary, a standard or recommended practice is truly useful only when it is used in conjunction with other sources of information and policy guidance and in the context of professional experience and judgment.

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# **Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose**

Approved 2 July 2013 by  
**AAMI**

Approved 10 July 2013 and reaffirmed 1 May 2019 by  
**American National Standards Institute, Inc.**

**Abstract:** Describes methods that can be used to determine the minimum dose necessary to achieve the specified requirement for sterility, including methods to substantiate 25 kGy as the sterilization dose.

**Keywords:** health care products, medical equipment, sterilization, radiation, gamma, electron beam, bremsstrahlung, x-ray, dose, dose-setting

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## Glossary of equivalent standards

International Standards adopted in the United States may include normative references to other International Standards. AAMI maintains a current list of each International Standard that has been adopted by AAMI (and ANSI). Available on the AAMI website at the address below, this list gives the corresponding U.S. designation and level of equivalency to the International Standard.

[www.aami.org/standards/glossary.pdf](http://www.aami.org/standards/glossary.pdf)



## Committee representation

### Association for the Advancement of Medical Instrumentation

#### Radiation Sterilization Working Group

The adoption of ISO 11137-2, Third edition, as an AAMI Standard was initiated by the U.S. TAG for ISO/TC 198 and the AAMI Radiation Sterilization Working Group, which also functions as the U.S. Technical Advisory Group to the relevant work in the International Organization for Standardization (ISO). U.S. representatives from the AAMI Radiation Sterilization Working Group (U.S. Sub-TAG for ISO/TC 198/WG 2, Radiation Sterilization) played an active role in developing the International Standard.

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

|                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Cochairs</i>   | Victoria M. Hitchins, PhD, FDA/CDRH<br>Michael H. Scholla, Dupont Protection Technologies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <i>Members</i>    | Janet Prust , 3M Healthcare<br>Byron Lambert , Abbott Laboratories<br>Jeff Martin , Alcon Laboratories Inc.<br>Ramona Conner , Association of Perioperative Registered Nurses<br>Patrick McCormick , Bausch & Lomb Inc.<br>Mark Seybold , Baxter Healthcare Corporation<br>Lisa Macdonald , Becton Dickinson & Company<br>Christopher Anderson , Boston Scientific Corporation<br>Trabue Bryans , BryKor LLC<br>Rey Lopez , Cardinal Health (MP&S)<br>Phil Cogdill , Covidien<br>Kim Darnell , CR Bard<br>Mark Smith , Getinge USA<br>Deborah Havlik , Hospira Worldwide Inc.<br>Sue Klacik , IAHCSMM<br>Joyce Hansen , Johnson & Johnson<br>Lisa Foster , Medpoint LLC<br>Nancy Rakiewicz , Moog Medical Devices<br>Joel Gorski , NAMSA<br>Martell Winters , Nelson Laboratories Inc.<br>Andrew Sharavara , Propper Manufacturing Co Inc.<br>Jackie Daley , Sinai Hospital of Baltimore<br>Nancy Chobin , St Barnabas Healthcare System<br>Bill Young , Sterigenics International<br>Doug Harbrecht , Sterility Assurance LLC<br>Gerald McDonnell , Steris Corporation<br>Colleen Landers , Timmins & District Hospital |
| <i>Alternates</i> | Craig Wallace , 3M Healthcare<br>David McGoldrick , Abbott Laboratories<br>Jim Kaiser , Bausch & Lomb Inc.<br>Mike Sadowski , Baxter Healthcare Corporation<br>Glenn Calvert , Becton Dickinson & Company<br>Ralph Makinen , Boston Scientific Corporation<br>Dave Dion , Cardinal Health (MP&S)<br>Lloyd Brown , Covidien<br>Mary Mayo , CR Bard<br>Karen Polkinghorne , Dupont Protection Technologies<br>Natalie Lind , IAHCSMM<br>Tom Frazar , Johnson & Johnson<br>Patrick Polito , Moog Medical Devices<br>Shaundrea Rechsteiner , NAMSA<br>Jerry Nelson , Nelson Laboratories Inc.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

Martha Kadas , Sterigenics International  
Pete Burke , Steris Corporation  
Gordon Ely , WuXi AppTec Inc.

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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.

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

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|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Cochairs</i> | Trabue Bryans, BryKor LLC<br>Lisa Foster, Medpoint LLC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <i>Members</i>  | Simon Bogdansky, Allo Source<br>Curt Bogue, Cook Inc.<br>Anne Booth, Booth Scientific Inc.<br>Harry Bushar, Bushar, Harry - 1166<br>Glenn Calvert, Becton Dickinson & Company<br>Rebecca Campbell, Sterigenics International<br>Vin Caputo, WL Gore & Associates Inc.<br>Denise Cleghorn, Boston Scientific Corporation<br>Gary Cranston, Consulting & Technical Services/PCS<br>Emily Craven, Nordion Inc.<br>Greg Crego, Moog Medical Devices<br>Elaine Daniell, CR Bard<br>Douglas Davie, Sterilization Validation Services<br>Staci DeMoss, NAMSA<br>Darci Diage, Direct Flow Medical Inc.<br>April Doering, St Jude Medical Inc.<br>William FitzGerald, FitzGerald & Associates Ltd<br>Sarah Gagnon, Microtest Laboratories Inc.<br>Chris Haas, Covidien<br>Joyce Hansen, Johnson & Johnson<br>Thomas Hansen, Terumo Americas Corporate<br>Doug Harbrecht, Sterility Assurance LLC<br>Deborah Havlik, Hospira Worldwide Inc.<br>Betty Howard, Steris Corporation<br>Brent Huberty, Medtronic Inc WHQ Campus<br>Jim Kaiser, Bausch & Lomb Inc.<br>David King, Tandem Diabetes Care Inc.<br>Carolyn Kinsley, LexaMed Ltd<br>John Kowalski, MicroGAMMA LLC<br>Byron Lambert, Abbott Laboratories<br>Rey Lopez, Cardinal Health (MP&S)<br>Ronald Lulich, 3M Healthcare<br>Jeff Martin, Alcon Laboratories Inc.<br>Joseph Mello, Ethide Laboratories Inc.<br>Rusty Mills, GE Healthcare<br>Larry Nichols, Nutek Corporation<br>Gerry O'Dell, Gerry O'Dell Consulting<br>Dave Parente, Ecolab<br>Michelle Peterson, Stryker Instruments Division<br>Rudy Pina, Dynatec Scientific Labs Inc.<br>Manneu Saavedra, Kimberly-Clark Corporation<br>Jon Seulean, Terumo BCT<br>Harry Shaffer, Sterilization Consulting Services<br>Ian Shorr, CareFusion<br>Sopheak Srun, Quality Tech Services Inc.<br>Fenil Sutaria, Medline Industries Inc.<br>Bud Weisman, Fresenius Medical Care Renal Therapies Group |

Pat Weixel, FDA/CDRH  
John Williams, Baxter Healthcare Corporation  
Martell Winters, Nelson Laboratories Inc.

*Alternates*

Marjean Boyter, Fresenius Medical Care Renal Therapies Group  
Claudia Camp, Stryker Instruments Division  
David Cardin, Zimmer Inc.  
Jessica Desmond, Microtest Laboratories Inc.  
John DiCaro, Covidien  
Dave Dion, Cardinal Health (MP&S)  
Brian Drumheller, CR Bard  
Niki Fidopiastis, Sterigenics International  
Shelley Green, WuXi AppTec Inc.  
Chris Johnson, Steris Corporation  
Chris Kobus, GE Healthcare  
Ezra Koski, Terumo BCT  
Maggie Ladd, Kimberly-Clark Corporation  
Antonio Lopez-Feliciano, Lopez-Feliciano, Antonio - 440392  
Jody Markling, St Jude Medical Inc.  
Patrick McCormick, Bausch & Lomb Inc.  
Alan Montgomery, Becton Dickinson & Company  
Kimberly Patton, Becton Dickinson & Company  
Michelle Pierce, NAMSA  
Nancy Rakiewicz, Moog Medical Devices  
Robert Reich, LexaMed Ltd  
Reginald Roberts, Medline Industries Inc.  
Matt Roybal, Johnson & Johnson  
Jody Rupert, WL Gore & Associates Inc.  
Mark Seybold, Baxter Healthcare Corporation  
Michael Sprague, Ethide Laboratories Inc.  
Wendy Wangsgard, Nelson Laboratories Inc.  
Cas Woss, FitzGerald & Associates Ltd

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## Background of ANSI/AAMI adoption of ISO 11137-2:2013

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 Technical Committee 198, Sterilization of health care products, WG 2, Radiation sterilization.

U.S. participation in ISO/TC 198/WG 2 is organized through the U.S. Technical Advisory Group to ISO/TC 198/WG 2, administered by the Association for the Advancement of Medical Instrumentation. Experts from the United States made a considerable contribution to this standard.

ANSI/AAMI/ISO 11137-2:2013 was approved by the American National Standards Institute (ANSI) on 10 July 2013.

The majority of the changes throughout the 2012 version of ISO 11137-2 were to harmonize parallel sections for the numerous Methods in order to provide improved clarity, readability and precision of terminology. Additional changes rationalized tolerances around Method 2 incremental doses and DD\* and provided requirements for documenting rationale for actions following a dose audit failure requiring re-establishment of dose. This 2013 edition incorporates minor revisions, which are noted in the ISO foreword.

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

AAMI (and ANSI) have adopted other ISO standards. See the Glossary of Equivalent Standards for a list of ISO standards adopted by AAMI, which gives the corresponding U.S. designation and the level of equivalency with the ISO standard.

As used within the context of this document, “shall” indicates requirements strictly to be followed to conform to the standard. “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.

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 come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 4301 N. Fairfax Dr, Suite 301, Arlington, VA 22203-1633.

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NOTE—Beginning with the ISO foreword on page x, this American National Standard is identical to ISO 11137-2:2013.

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## Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 11137-2 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This third edition cancels and replaces the second edition (ISO 11137 2:2012), of which it constitutes a minor revision with the following changes:

- addition of the word “and” in 9.1, second paragraph, third sentence;
- addition of the word “not” in 10.3.4.1, third paragraph;
- correction of the language used to describe requirements for interpretation of results during a verification dose experiment in the second paragraph in 7.2.6.2, 7.3.7.2, 9.2.6.3, 9.3.7.3, 9.4.6.3, and 9.5.7.3.

ISO 11137 consists of the following parts, under the general title *Sterilization of health care products — Radiation*:

- *Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*
- *Part 2: Establishing the sterilization dose*
- *Part 3: Guidance on dosimetric aspects*

## Introduction

This part of ISO 11137 describes methods that can be used to establish the sterilization dose in accordance with one of the two approaches specified in 8.2 of ISO 11137-1:2006. The methods used in these approaches are:

- dose setting to obtain a product-specific dose;
- dose substantiation to verify a preselected dose of 25 kGy or 15 kGy.

The basis of the dose setting methods described in this part of ISO 11137 (Methods 1 and 2) owe much to the ideas first propounded by Tallentire<sup>[19][20][21]</sup>. Subsequently, standardized protocols were developed<sup>[10][11]</sup>, which formed the basis of the dose setting methods detailed in the AAMI Recommended Practice for Sterilization by Gamma Radiation<sup>[6][8]</sup>.

Methods 1 and 2 and the associated sterilization dose audit procedures use data derived from the inactivation of the microbial population in its natural state on product. The methods 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 such species has its own unique  $D_{10}$  value. In the model, the probability that an item will possess a surviving microorganism after exposure to a given dose of radiation is defined in terms of the initial number of microorganisms on the item prior to irradiation and the  $D_{10}$  values of the microorganisms. The methods involve performance of tests of sterility on product items that have received doses of radiation lower than the sterilization dose. The outcome of these tests is used to predict the dose needed to achieve a predetermined sterility assurance level (SAL).

Methods 1 and 2 can also be used to substantiate 25 kGy if, on performing a dose setting exercise, the derived sterilization dose for an SAL of  $10^{-6}$  is less than or equal to 25 kGy. The basis of the method devised specifically for substantiation of 25 kGy, Method  $VD_{max}$ , was put forward by Kowalski and Tallentire<sup>[16]</sup>. Subsequent evaluations involving computational techniques demonstrated that the underlying principles were soundly based<sup>[15]</sup> and field trials confirmed that Method  $VD_{max}$  is effective in substantiating 25 kGy for a wide variety of medical devices manufactured and assembled in different ways<sup>[18]</sup>.

A standardized procedure for the use of  $VD_{max}$  for substantiation of a sterilization dose of 25 kGy has been published in the AAMI Technical Information Report *Sterilization of health care products — Radiation sterilization — Substantiation of 25 kGy as a sterilization dose — Method  $VD_{max}$* <sup>[7]</sup>, a text on which the method described herein is largely based. Method  $VD_{max}$  is founded on dose setting Method 1 and, as such, it possesses the high level of conservativeness characteristic of Method 1. In a similar manner to the dose setting methods, it involves performance of tests of sterility on product items that have received a dose of radiation lower than the sterilization dose. The outcomes of these tests are used to substantiate that 25 kGy achieves an SAL of  $10^{-6}$ .

To link the use of  $VD_{max}$  for the substantiation of a particular preselected sterilization dose, the numerical value of the latter, expressed in kilograys, is included as a superscript to the  $VD_{max}$  symbol. Thus, for substantiation of a sterilization dose of 25 kGy, the method is designated Method  $VD_{max}^{25}$ .

Method  $VD_{max}^{15}$  is based on the same principles as Method  $VD_{max}^{25}$ . The test procedure is similar to that of Method  $VD_{max}^{25}$ , but Method  $VD_{max}^{15}$  is limited to product with an average bioburden less than or equal to 1.5. The outcomes of the associated tests of sterility are used to substantiate that 15 kGy achieve a sterility assurance level of  $10^{-6}$ .

This part of ISO 11137 also describes methods that can be used to carry out sterilization dose audits in accordance with ISO 11137-1:2006, Clause 12. Following establishment of the sterilization dose, sterilization dose audits are performed routinely to confirm that the sterilization dose continues to achieve the desired SAL.

# Sterilization of health care products — Radiation —

## Part 2: Establishing the sterilization dose

### 1 Scope

This part of ISO 11137 specifies methods for determining the minimum dose needed to achieve a specified requirement for sterility and methods to substantiate the use of 25 kGy or 15 kGy as the sterilization dose to achieve a sterility assurance level, SAL, of  $10^{-6}$ . This part of ISO 11137 also specifies methods of sterilization dose audit used to demonstrate the continued effectiveness of the sterilization dose.

This part of ISO 11137 defines product families for sterilization dose establishment and sterilization dose audit.

### 2 Normative references

The following referenced documents are indispensable for the application 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 the development, validation and routine control of a sterilization process for medical devices*

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

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

### 3 Terms, definitions and abbreviated terms

For the purposes of this document, the terms and definitions given in ISO 11137-1 and the following apply.

#### 3.1 Terms and definitions

##### 3.1.1

##### **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

[ISO/TS 11139:2006, definition 2.1]

### **3.1.2**

#### **bioburden**

population of viable microorganisms on or in product and/or sterile barrier system

[ISO/TS 11139:2006, definition 2.2]

### **3.1.3**

#### **false positive**

test result interpreted as growth arising from the 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

### **3.1.4**

#### **fraction positive**

quotient in which the number of positive tests of sterility is given by the numerator and the number of tests performed is given by the denominator

### **3.1.5**

#### **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

### **3.1.6**

#### **negative test of sterility**

test result for which there is no detectable microbial growth from product, or portions thereof, subjected to a test of sterility

### **3.1.7**

#### **packaging system**

combination of the sterile barrier system and protective packaging

[ISO/TS 11139:2006, definition 2.28]

### **3.1.8**

#### **positive test of sterility**

test result for which there is detectable microbial growth from product, or portions thereof, subjected to a test of sterility

### **3.1.9**

#### **sample item portion**

##### **SIP**

defined portion of a health care product that is tested

### **3.1.10**

#### **standard distribution of resistances**

##### **SDR**

reference set of resistances of microorganisms and corresponding probabilities of occurrence

### **3.1.11**

#### **sterile barrier system**

minimum package that prevents ingress of microorganisms and allows aseptic presentation of product at the point of use

### **3.1.12**

#### **sterility assurance level**

##### **SAL**

probability of a single viable microorganism occurring on an item after sterilization

**NOTE** The term SAL takes a quantitative value, generally  $10^{-6}$  or  $10^{-3}$ . When applying 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  $10^{-3}$ .

[ISO/TS 11139:2006, definition 2.46]

### **3.1.13**

#### **sterilization dose audit**

exercise undertaken to confirm the appropriateness of an established sterilization dose

### **3.1.14**

#### **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

[ISO/TS 11139:2006, definition 2.54]

### **3.1.15**

#### **verification dose**

dose of radiation predicted to give a predetermined SAL greater than or equal to  $10^{-2}$  used in establishing the sterilization dose

## **3.2 Abbreviated terms**

### **3.2.1**

*A*

dose to adjust the median ffp dose downwards to the FFP dose

### **3.2.2**

*CD\**

number of positive tests of sterility obtained from tests performed individually on 100 product items irradiated in a Method 2 verification dose experiment

### **3.2.3**

*d\**

dose derived from an incremental dose experiment performed on product items drawn from a given production batch

### **3.2.4**

*D\**

initial estimate of the dose to provide an SAL of  $10^{-2}$  for the test items

**NOTE** Generally, it is the median of the three *d\** values derived for a given product.

### **3.2.5**

*D\*\**

final estimate of the dose to provide an SAL of  $10^{-2}$  for the test items, which is used in the calculation of the sterilization dose

### 3.2.6

*DD\**

highest dose delivered in a Method 2 verification dose experiment

### 3.2.7

*DS*

estimate of the  $D_{10}$  value of microorganisms present on product after exposure to *DD\**

### 3.2.8

*D value*

*D*<sub>10</sub> **value**

time or dose required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions

[ISO/TS 11139:2006, definition 2.11]

NOTE For the purposes of this part of ISO 11137,  $D_{10}$  applies to the radiation dose only and not to time.

### 3.2.9

**first fraction positive dose**

**ffp**

lowest dose of an incremental dose series, applied to product items drawn from a given production batch, at which at least one of the associated 20 tests of sterility is negative

### 3.2.10

**First Fraction Positive dose**

**FFP**

dose at which 19 positives out of the 20 tests of sterility are expected to occur, calculated by subtracting *A* from the median of three ffp doses

### 3.2.11

**First No Positive dose**

**FNP**

estimate of the dose to provide an SAL of  $10^{-2}$  for the test items, that is used in the calculation of *DS*

### 3.2.12

$VD_{\max}^{15}$

maximal verification dose for a given bioburden, consistent with the attainment of an SAL of  $10^{-6}$  at a specified sterilization dose of 15 kGy

### 3.2.13

$VD_{\max}^{25}$

maximal verification dose for a given bioburden, consistent with the attainment of an SAL of  $10^{-6}$  at a specified sterilization dose of 25 kGy

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

### 4.1 General

The establishment of a sterilization dose and the carrying out of sterilization dose audits are activities that are part of process definition (see Clause 8 of ISO 11137-1:2006) and maintaining process effectiveness (see Clause 12 of ISO 11137-1:2006). For these activities, product may be grouped into families; definition of product families is based principally on the numbers and types of microorganisms 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 for establishing the sterilization dose and for carrying out sterilization dose audits, 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 developed and implemented before proceeding.

NOTE See 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 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 processes;
- e) manufacturing equipment;
- f) manufacturing environment;
- g) manufacturing location.

The outcome of the assessment and considerations shall be recorded (see 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 (see 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 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 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) the 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 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 could be considered as the master product. In such circumstances, any one of these products may be selected as the master product to represent the family, either a) at random, or b) according to a documented procedure to include the different products that could be considered as master products.

#### **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) according to 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 might be:

- a) one which 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 product and/or processes that might affect membership of product families shall be allocated to competent personnel. Such a 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 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 the selection of a different representative product.

##### **4.4.3 Records**

Records of product families shall be retained (see ISO 11137-1:2006, 4.1.2).

#### **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 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 product comprising the product family.

## 5 Selection and testing of product for establishing the 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 the performance of sterilization dose establishment shall be taken in accordance with Table 1.

**Table 1 — Nature of product items for establishing 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 overall SAL associated with the packaging system might be higher |
| Kit of procedure-related health care products <sup>a</sup>                                                                                      | Each type of health care product comprising the kit                            | Each health care product is used independently in clinical practice                                                                                                                                                                                 |
| NOTE 1 See 5.2 for guidance on the use of SIP for product characterized in 5.1.1 b).                                                            |                                                                                |                                                                                                                                                                                                                                                     |
| NOTE 2 See Clause 4 for the use of product families for product characterized in 5.1.1 d).                                                      |                                                                                |                                                                                                                                                                                                                                                     |
| <sup>a</sup> 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 can 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 can 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 in accordance with Table 1. When the use of an entire product is not practicable, a selected portion of product (SIP) may be substituted. The SIP should be as large a portion of the item as practicable and should be of a size that can be handled during testing.

**5.2.2** For a 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 either a) portions of product selected at random that proportionally represent each of the materials from which the product is made, or b) the portion of the product that is considered to be the most severe challenge to the sterilization process.

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

**Table 2 — Examples for calculation of an SIP**

| Basis for SIP | Product                                          |
|---------------|--------------------------------------------------|
| Length        | Tubing (consistent diameter)<br>Rolls of bandage |
| Mass          | Powders<br>Gowns                                 |
| Volume        | Liquids                                          |
| Surface area  | Surgical drapes<br>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 the 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 at least 17 of the 20 non-irradiated SIPs yield positive tests of sterility, or a bioburden of 1.0 or more is found on at least 85 % of 20 or more SIPs. If neither of these criteria is met, an SIP that is different from that examined originally and that meets one of the above criteria shall be used. If an entire product is tested (SIP equal to 1.0), the criteria specified above do not apply.

**5.2.6** The same portion of product item (SIP) should be used in the performance of tests of sterility when carrying out the verification dose experiment as that used in the determination of bioburden when obtaining the verification dose.

**NOTE** If a different portion of product item (SIP) is used in the performance of tests of sterility from that used in the determination of bioburden, caution should be exercised when obtaining the verification and sterilization doses.

### 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. 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 taking of product from production and the performance of the verification dose experiment 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 ISO 11737-1 and ISO 11737-2, respectively.

Soybean Casein Digest Broth, with an incubation temperature of  $30 \pm 2$  °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 References [9], [12] and [14]).

Manipulations prior to 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). Whenever practicable, for the performance of a verification dose experiment, product should be irradiated in its original form and in its packaging system. However, to reduce the possibility of false positives in carrying out tests of sterility, product may be disassembled and repackaged prior to irradiation. Materials for repackaging product 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 a product that has undergone the packaging process.

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

### 5.5 Irradiation

**5.5.1** Irradiation of product in establishing the sterilization dose shall be conducted in an irradiator that has undergone installation qualification, operational qualification and performance qualification, in accordance with ISO 11137-1.

**5.5.2** Measurement of dose and the use of radiation sources shall be in accordance with ISO 11137-1.

**5.5.3** 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 delivered to product.

**NOTE** See ISO 11137-3 for guidance on dosimetric aspects of radiation sterilization.

## 6 Methods of dose establishment

**6.1** If a sterilization dose is established in accordance with 8.2.2 a) of ISO 11137-1:2006 (product-specific sterilization dose), it shall be set by one of the following methods:

- a) Method 1 for multiple and single batches (see Clause 7),
- b) Methods 2A and 2B (see Clause 8), or
- c) a method providing equivalent assurance to that of a) or b) above in achieving the specified requirements for sterility.

**6.2** If a sterilization dose of 25 kGy is established in accordance with 8.2.2 b) of ISO 11137-1:2006 (dose substantiation), it shall be substantiated by one of the following methods:

- a) Method  $VD_{max}^{25}$  (see 9.2 and 9.3), for product with an average bioburden less than or equal to 1,000,
- b) Method 1 (see Clause 7), subject to the derived sterilization dose taking a value less than or equal to 25 kGy and achieving maximally an SAL of  $10^{-6}$ ,
- c) Method 2 (see Clause 8), subject to the derived sterilization dose taking a value less than or equal to 25 kGy and achieving an SAL of  $10^{-6}$ ,
- d) a method providing equivalent assurance to that of a), b) or c) above in achieving maximally an SAL of  $10^{-6}$ .

**6.3** If a sterilization dose of 15 kGy is established in accordance with 8.2.2 b) of ISO 11137-1:2006 (dose substantiation), it shall be substantiated by one of the following methods:

- a) Method  $VD_{max}^{15}$  (see 9.4 and 9.5), for product with an average bioburden less than or equal to 15,
- b) Method 1 (see Clause 7), subject to the derived sterilization dose taking a value less than or equal to 15 kGy and achieving maximally an SAL of  $10^{-6}$ ,
- c) Method 2 (see Clause 8), subject to the derived sterilization dose taking a value less than or equal to 15 kGy and achieving an SAL of  $10^{-6}$ , or
- d) a method providing equivalent assurance to that of a), b) or c) above in achieving maximally an SAL of  $10^{-6}$ .

## 7 Method 1: dose setting using bioburden information

### 7.1 Rationale

This method of establishing a sterilization dose depends upon experimental verification that the radiation resistance of the bioburden is less than or equal to the resistance of a microbial population having the standard distribution of resistances (SDR).

A rationalized choice has been made for the SDR. The SDR specifies resistances of microorganisms in terms of  $D_{10}$  values and the probability of occurrence of values in the total population (see Table 3). Using computational methods, the individual doses, required to achieve values of SAL of  $10^{-2}$ ,  $10^{-3}$ ,  $10^{-4}$ ,  $10^{-5}$

and  $10^{-6}$  for increasing levels of average bioburden having the SDR, have been calculated. The calculated dose values for given average bioburdens are tabulated in Tables 5 and 6.

**NOTE** Table B.1 of ISO 11137:1995, giving verification and sterilization doses for Method 1, was compiled using regularly increasing doses to give corresponding increasing average bioburden values. The dose increment was 0.1 kGy and the average bioburden values increased in a non-regular fashion and included both whole and fractional numbers (i.e. 104; 112.6; 121.9; 131.9; etc.). In order to improve the table, making it easier to use and interpret, the average bioburden values in Table 5 of this part of ISO 11137 are expressed as regularly increasing whole numbers. The incremental increases in the bioburden values are chosen to yield increases in the verification dose of around 0.1 kGy, the verification doses being rounded to one decimal place. Regular increases in average bioburden values have been similarly included in Table 6.

**Table 3 — Standard distribution of resistances (SDR) used in Method 1 (see Reference [10])**

| $D_{10}$<br>(kGy)  | 1.0    | 1.5    | 2.0   | 2.5   | 2.8   | 3.1   | 3.4   | 3.7   | 4.0   | 4.2   |
|--------------------|--------|--------|-------|-------|-------|-------|-------|-------|-------|-------|
| Probability<br>(%) | 65.487 | 22.493 | 6.302 | 3.179 | 1.213 | 0.786 | 0.350 | 0.111 | 0.072 | 0.007 |

In practice, the average bioburden is determined. The dose that gives an SAL of  $10^{-2}$  at this average bioburden is read from Table 5 or Table 6. This dose is designated as the verification dose and it represents the dose that will reduce a microbial population having the SDR to a level that gives an SAL of  $10^{-2}$ . One hundred product items are then exposed to the selected verification dose and each item is individually subjected to a test of sterility. If there are not more than two positive tests out of the 100 tests, the average bioburden in Table 5 or Table 6 is again used to provide the sterilization dose for any desired SAL.

The rationale for allowing two positives is based upon the assumption that the probabilities of occurrence of numbers of positives around an average of one positive are distributed according to the Poisson distribution. With this distribution, there is a 92 % probability that zero, one or two positives will occur (see Table 4).

**Table 4 — Probabilities of occurrence of numbers of positives around an average of one, distributed according to the Poisson distribution**

| Number of positives | 0    | 1    | 2    | 3   | 4   | 5   | 6    | 7     | 8      |
|---------------------|------|------|------|-----|-----|-----|------|-------|--------|
| Probability<br>(%)  | 36.6 | 37.0 | 18.5 | 6.1 | 1.5 | 0.3 | 0.05 | 0.006 | 0.0007 |

## 7.2 Procedure for Method 1 for product with an average bioburden greater than or equal to 1.0 for multiple production batches

### 7.2.1 General

In applying Method 1, the six stages below shall be followed.

**NOTE** For a worked example, see 11.1.

## 7.2.2 Stage 1: Select SAL and obtain samples of product

**7.2.2.1** Record the SAL for the intended use of the product.

**7.2.2.2** Select 10 product items from each of three independent production batches, in accordance with 5.1, 5.2 and 5.3.

**NOTE** Additional product might be needed to validate the adequacy of an SIP of less than one (see 5.2.5).

## 7.2.3 Stage 2: Determine average bioburden

**7.2.3.1** Decide if a correction factor is to be applied in the determination of bioburden.

**NOTE** ISO 11737-1 utilizes a correction factor derived from the validation of the bioburden technique to compensate for incomplete removal of microorganisms from product. The performance of dose establishment using Method 1 may use a bioburden determination without the application of the correction factor. When a correction factor is not used, the bioburden might be underestimated. Failure to apply the bioburden correction factor could increase the risk of failure of the verification dose experiment.

**7.2.3.2** Determine the bioburden of each of the selected product items and calculate:

- a) the average bioburden per item for each of the three batches of product items (batch average bioburden);
- b) the average bioburden per item for all selected product items (overall average bioburden).

**NOTE 1** Bioburden is generally determined on individual product items unless the bioburden is low (e.g. less than 10), in which case it is permissible to pool the 10 product items for the determination of batch average bioburden. This guidance does not apply to SIPs, which should not be pooled; instead a larger SIP should be chosen (see 5.2.5).

**NOTE 2** When no colonies are observed in the determination of bioburden, this is sometimes expressed as being below the limit of detection. Use of the limit of detection as a bioburden value in calculating average bioburden could lead to an overestimation. Overestimation could affect the validity of the verification dose experiment.

**7.2.3.3** Compare the three batch average bioburdens with the overall average bioburden and determine whether any one of the batch average bioburdens is two or more times greater than the overall average bioburden.

## 7.2.4 Stage 3: Obtain verification dose

Obtain the dose for an SAL of  $10^{-2}$  from Table 5 using one of the following as the average bioburden:

- a) if a batch average bioburden is two or more times greater than the overall average bioburden, use the highest batch average bioburden, or
- b) if each of the batch average bioburdens is less than two times the overall average bioburden, use the overall average bioburden.

If the average bioburden is not given in Table 5, use the closest tabulated value greater than the average bioburden.

Designate this dose as the verification dose.

If SIPs are to be used in the performance of tests of sterility, use the highest SIP batch average bioburden or the overall SIP average bioburden, as appropriate, to obtain the verification dose.

### 7.2.5 Stage 4: Perform verification dose experiment

**7.2.5.1** Select 100 product items from a single batch of product. The 100 product items for the performance of Stage 4 may be selected from one of the batches on which a bioburden determination was carried out in Stage 2, or from a fourth batch manufactured under conditions that are representative of normal production (see 5.3).

**7.2.5.2** Irradiate these product items at the verification dose.

The highest dose to product items shall not exceed the verification dose by more than 10 %.

The arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of the verification dose.

Determine the dose delivered (see 5.5).

If the highest dose to product items exceeds the verification dose by more than 10 %, the verification dose experiment shall be repeated.

If the arithmetic mean of the highest and lowest doses to product items is less than 90 % of the verification dose, the verification dose experiment may be repeated. If this mean dose is less than 90 % of the verification dose and, on performance of tests of sterility, acceptable results are observed (see 7.2.6.1), the verification dose experiment need not be repeated.

**7.2.5.3** Subject each irradiated product item individually to a test of sterility (see 5.4.1) and record the number of positive tests of sterility.

### 7.2.6 Stage 5: Interpretation of results

**7.2.6.1** If no more than two positive tests of sterility are obtained from the 100 tests carried out, accept verification.

**7.2.6.2** If three or more positive tests of sterility are obtained, do not accept verification.

If the occurrence of these positive tests of sterility can be ascribed to incorrect performance of the determination of bioburden, incorrect performance of tests of sterility or incorrect delivery of the verification dose, or a specific bioburden-related cause, implement corrective action and repeat the verification dose experiment using a further 100 product items. If, as a result of corrective action, the estimate of average bioburden changes, use the verification dose (7.2.4) that corresponds to the changed average bioburden. If the estimate of average bioburden is unchanged, use the same verification dose as that used in the verification dose experiment that was not accepted. Interpret the results of the repeat verification dose experiment in accordance with 7.2.6.

If the occurrence of these positive tests of sterility cannot be ascribed to incorrect performance of the determination of bioburden, incorrect performance of tests of sterility or incorrect delivery of the verification dose, or a specific bioburden-related cause, this method of dose setting is not valid and an alternative method for establishing a sterilization dose shall be used (see Clause 6).

### 7.2.7 Stage 6: Establish sterilization dose

**7.2.7.1** If the entire product is used and verification is accepted, obtain the sterilization dose for the product from Table 5 by entering the table at the tabulated value equal to the average bioburden used in Stage 3. Alternatively, if the average bioburden is not given in Table 5, enter the table at the closest tabulated value greater than the average bioburden and read the dose necessary to achieve the desired SAL.