INTERNATIONAL STANDARD

ISO 11137-2

Third edition
2013-06-01

Sterilization of health care products — Radiation —

Part 2: Establishing the sterilization dose

Stérilisation des produits de santé — Irradiation —

Partie 2: Établissement de la dose stérilisante

Reference number
ISO 11137-2:2013(E)

© ISO 2013



COPYRIGHT PROTECTED DOCUMENT

© ISO 2013

All rights reserved. Unless otherwise specified, no part of this publication may be reproduced or utilized otherwise in any form or by any means, electronic or mechanical, including photocopying, or posting on the internet or an intranet, without prior written permission. Permission can be requested from either ISO at the address below or ISO's member body in the country of the requester.

ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

Published in Switzerland

Contents

Page

Foreword ... **v**

Introduction ... **vi**

1 Scope ... **1**

2 Normative references ... **1**

3 Terms, definitions, and abbreviated terms ... **1**
3.1 Terms and definitions ... 1
3.2 Abbreviated terms ... 3

4 Definition and maintenance of product families for dose setting, dose substantiation, and sterilization dose auditing ... **4**
4.1 General ... 4
4.2 Defining product families ... 4
4.3 Designation of product to represent a product family for performance of a verification dose experiment or sterilization dose audit ... 5
4.4 Maintaining product families ... 6
4.5 Effect of failure of establishment of sterilization dose or of a sterilization dose audit on a product family ... 7

5 Selection and testing of product for establishing the sterilization dose ... **7**
5.1 Nature of product ... 7
5.2 Sample item portion (SIP) ... 8
5.3 Manner of sampling ... 9
5.4 Microbiological testing ... 9
5.5 Irradiation ... 9

6 Methods of dose establishment ... **9**

7 Method 1: dose setting using bioburden information ... **10**
7.1 Rationale ... 10
7.2 Procedure for Method 1 for product with an average bioburden greater than or equal to 1,0 for multiple production batches ... 11
7.3 Procedure for Method 1 for product with an average bioburden greater than or equal to 1,0 for a single production batch ... 17
7.4 Procedure for Method 1 for product with an average bioburden in the range 0,1 to 0,9 for multiple or single production batches ... 19

8 Method 2: Dose setting using fraction positive information from incremental dosing to determine an extrapolation factor ... **20**
8.1 Rationale ... 20
8.2 Procedure for Method 2A ... 21
8.3 Procedure for Method 2B ... 24

9 Method VD_{max} — Substantiation of 25 kGy or 15 kGy as the sterilization dose ... **28**
9.1 Rationale ... 28
9.2 Procedure for Method $VD_{max}25$ for multiple production batches ... 29
9.3 Procedure for Method $VD_{max}25$ for a single production batch ... 34
9.4 Procedure for Method $VD_{max}15$ for multiple production batches ... 37
9.5 Procedure for Method $VD_{max}15$ for a single production batch ... 40

10 Sterilization dose audit ... **43**
10.1 Purpose and frequency ... 43
10.2 Procedure for auditing a sterilization dose established using Method 1, Method 2A, or Method 2B ... 43
10.3 Procedure for auditing a sterilization dose substantiated using Method $VD_{max}25$ or Method $VD_{max}15$ ... 46
10.4 Failure of a sterilization dose audit ... 52

11 Worked examples ... **52**

© ISO 2013 – All rights reserved

11.1 Worked examples for Method 1 52
11.2 Worked examples for Method 2 54
11.3 Worked examples for Method VD_{max} 62
11.4 Worked example of a sterilization dose audit for a dose established using Method 1, the findings from which necessitated augmentation of the sterilization dose 64
11.5 Worked example of a sterilization dose audit for a dose established using Method 2A, the findings from which necessitated augmentation of the sterilization dose 64
11.6 Worked example of a sterilization dose audit for a sterilization dose substantiated using Method VD_{max}^{25} 65

Bibliography **67**

 © ISO 2013 – All rights reserved

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*

© ISO 2013 – All rights reserved

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[19][20][21]. Subsequently, standardized protocols were developed[10][11], which formed the basis of the dose setting methods detailed in the AAMI Recommended Practice for Sterilization by Gamma Radiation[6][8].

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[16]. Subsequent evaluations involving computational techniques demonstrated that the underlying principles were soundly based[15] 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[18].

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}[7], 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 achieves 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.

 © ISO 2013 – All rights reserved

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 documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. 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]

© ISO 2013 – All rights reserved

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 1 to entry: 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

© ISO 2013 – All rights reserved

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 1 to entry: 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_{10} **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 1 to entry: For the purposes of this part of ISO 11137, D_{10} applies to the radiation dose only and not to time.

© ISO 2013 – All rights reserved

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;

© ISO 2013 – All rights reserved