BS EN ISO 11137-2:2015+A1:2023

BSI Standards Publication

Sterilization of health care products — Radiation

Part 2: Establishing the sterilization dose

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National foreword

This British Standard is the UK implementation of EN ISO 11137-2:2015+A1:2023. It is identical to ISO 11137-2:2013 incorporating amendment 1:2022. It supersedes BS EN ISO 11137-2:2015, which is withdrawn.

The start and finish of text introduced or altered by amendment is indicated in the text by tags. Tags indicating changes to ISO text carry the number of the ISO amendment. For example, text altered by ISO amendment 1 is indicated by A1 A1.

The UK participation in its preparation was entrusted to Technical Committee CH/198, Sterilization and Associated Equipment and Processes.

A list of organizations represented on this committee can be obtained on request to its committee manager.

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Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose (ISO 11137-2:2013)

Stérilisation des produits de santé - Irradiation - Partie 2: Établissement de la dose stérilisante (ISO 11137-2:2013)

Sterilisation von Produkten für die Gesundheitsfürsorge - Strahlen - Teil 2: Festlegung der Sterilisationsdosis (ISO 11137-2:2013)

This European Standard was approved by CEN on 20 May 2015.

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Foreword

The text of ISO 11137-2:2013 has been prepared by Technical Committee ISO/TC 198 “Sterilization of health care products” of the International Organization for Standardization (ISO) and has been taken over as EN ISO 11137-2:2015 by Technical Committee CEN/TC 204 “Sterilization of medical devices” the secretariat of which is held by BSI.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by December 2015, and conflicting national standards shall be withdrawn at the latest by December 2015.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN [and/or CENELEC] shall not be held responsible for identifying any or all such patent rights.

This document supersedes EN ISO 11137-2:2013.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directives.

For relationship with EU Directives, see informative Annexes ZA, ZB and ZC, which are integral parts of this document.

The following referenced documents are indispensable for the application of this document. For undated references, the edition of the referenced document (including any amendments) listed below applies. For dated references, only the edition cited applies. However, for any use of this standard within the meaning of Annex ZA, ZB or ZC, the user should always check that any referenced document has not been superseded and that its relevant contents can still be considered the generally acknowledged state-of-art.

When an IEC or ISO standard is referred to in the ISO standard text, this should be understood as a normative reference to the corresponding EN standard, if available, and otherwise to the dated version of the ISO or IEC standard as listed below.

NOTE The way in which these referenced documents are cited in normative requirements determines the extent (in whole or in part) to which they apply.

Table — Correlation between normative references and dated EN and ISO standards

Normative references as listed in Clause 2 of the ISO standard	Equivalent dated standard	
	EN	ISO
ISO 11137	EN ISO 11137-1:2006/A1:2013	ISO 11137-1:2006/A1:2013
ISO 11737-1	EN ISO 11737-1:2006 + AC:2009	ISO 11737-1:2006 + Cor 1:2007
ISO 11737-2	EN ISO 11737-2:2009	ISO 11737-2:2009

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Endorsement notice

The text of ISO 11137-2:2013 has been approved by CEN as EN ISO 11137-2:2015 without any modification.

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European foreword to amendment A1

This document (EN ISO 11137-2:2015/A1:2023) has been prepared by Technical Committee ISO/TC 198 "Sterilization of health care products" in collaboration with Technical Committee CEN/TC 204 “Sterilization of medical devices” the secretariat of which is held by BSI.

This Amendment to the European Standard EN ISO 11137-2:2015 shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by October 2023, and conflicting national standards shall be withdrawn at the latest by October 2023.

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This document has been prepared under a standardization request M/575 of 14.4.2021 given to CEN by the European Commission and supports general safety and performance requirements of EU Regulations(s).

For the relationship with EU Directive(s) see informative Annex ZA and Annex ZB, which are an integral part of this document.

Any feedback and questions on this document should be directed to the users’ national standards body/national committee. A complete listing of these bodies can be found on the CEN website.

The following referenced documents are indispensable for the application of this document. For undated references, the edition of the referenced document (including any amendments) listed below applies. For dated references, only the edition cited applies. However, for any use of this standard within the meaning of Annex ZA or ZB, the user should always check that any referenced document has not been superseded and that its relevant contents can still be considered the generally acknowledged state-of-art.

When an IEC or ISO standard is referred to in the ISO standard text, this should be understood as a normative reference to the corresponding EN standard, if available, and otherwise to the dated version of the ISO or IEC standard as listed below.

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Endorsement notice

The text of ISO 11137-2:2013/Amd 1:2022 has been approved by CEN as EN ISO 11137-2:2015/A1:2023 without any modification.

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Annex ZA
(informative)

Relationship between this European Standard and the General Safety and Performance Requirements of Regulation (EU) 2017/745 aimed to be covered

This European standard has been prepared under M/575 to provide one voluntary means of conforming to the General Safety and Performance Requirements of Regulation (EU) 2017/745 of 5 April 2017 concerning medical devices [OJ L 117] and to system or process requirements including those relating to quality management systems, risk management, post-market surveillance systems, clinical investigations, clinical evaluation or post-market clinical follow-up.

Once this standard is cited in the Official Journal of the European Union under that Regulation, compliance with the normative clauses of this standard given in Table ZA.1 and application of the edition of the normatively referenced standards as given in Table ZA.2 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding General Safety and Performance Requirements of that Regulation, and associated EFTA Regulations.

Where a definition in this standard differs from a definition of the same term set out in Regulation (EU) 2017/745, the differences shall be indicated in this Annex Z. For the purpose of using this standard in support of the requirements set out in Regulation (EU) 2017/745, the definitions set out in this Regulation prevail.

Where the European standard is an adoption of an International Standard, the scope of this standard can differ from the scope of the European Regulation that it supports. As the scope of the applicable regulatory requirements differ from nation to nation and region to region, the standard can only support European regulatory requirements to the extent of the scope of the European regulation for medical devices (EU) 2017/745).

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with Regulation (EU) 2017/745. This means that risks have to be 'reduced as far as possible', 'reduced to the lowest possible level', 'reduced as far as possible and appropriate', 'removed or reduced as far as possible', 'eliminated or reduced as far as possible', 'removed or minimized as far as possible', or 'minimized', according to the wording of the corresponding General Safety and Performance Requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with General Safety and Performance Requirements 1, 2, 3, 4, 5, 8, 9, 10, 11, 14, 16, 17, 18, 19, 20, 21 and 22 of the Regulation.

NOTE 3 When a General Safety and Performance Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

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Table ZA.1 – Correspondence between this European standard and Annex I of Regulation (EU) 2017/745 [OJ L 117]

General Safety and Performance Requirements of Regulation (EU) 2017/745	Clause(s) / sub-clause(s) of this EN	Remarks / Notes
11.4 first sentence only	4,5,6,7,8,9,10	This standard provides requirements for the establishment of the sterilization dose in the development, validation and routine control of a sterilization process using ionising radiation for medical devices. This General Safety and Performance Requirement is addressed only with regard to devices for which sterilization by ionising radiation is appropriate and only in conjunction with EN ISO 11137-1. This relevant General Safety and Performance Requirement is only partly addressed in this European Standard. Design and packaging for maintenance of sterility during transportation and storage are not covered. Aspects of manufacture other than those related to attainment of sterility by ionising radiation are not covered. Evidence that the integrity of the packaging is maintained to the point of use is not covered.
11.5	4,5,6,7,8,9,10	This standard provides requirements for the establishment of the sterilization dose in the development, validation and routine control of a sterilization process ionising radiation for medical devices. This General Safety and Performance Requirement is addressed only with regard to devices for which sterilization by ionising radiation is appropriate and only in conjunction with EN ISO 11137-1. This relevant General Safety and Performance Requirement is only partly addressed in this European Standard. Packaging for maintenance of sterility is not covered. Aspects of manufacture other than those related to attainment of sterility by ionising radiation are not covered.

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Table ZA.2 — Applicable Standards to confer presumption of conformity as described in this Annex ZA

Reference in Clause 2	International Standard Edition	Title	Corresponding European Standard Edition
ISO 11137-1:2006/Amd1:2013	ISO 11137-1:2006/Amd1:2013	Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices	EN ISO 11137-1:2006+A1:2013
ISO 11137-1:2006/Amd2:2018	ISO 11137-1:2006/Amd2:2018	Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices	EN ISO 11137-1:2015+A2:2019
ISO 11737-1	ISO 11737-1:2018	Sterilization of health care products — Microbiological methods — Part 1: Determination of a population of microorganisms on products	EN ISO 11737-1:2018+A1:2021
ISO 11737-2	ISO 11737-2:2019	Sterilization of health care products — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process	EN ISO 11737-2:2020
ISO 13004	ISO 13004:2022	Sterilization of health care products — Radiation — Substantiation of selected sterilization dose: Method VDmaxSD	Previous edition published is CEN ISO/TS 13004:2014

The documents listed in the Column 1 of table ZA.2, in whole or in part, are normatively referenced in this document and are indispensable for its application. The achievement of the presumption of conformity is subject to the application of the edition of Standards as listed in Column 4 or, if no European Standard Edition exists, the International Standard Edition given in Column 2 of table ZA.2.

WARNING 1 — Presumption of conformity stays valid only as long as a reference to this European Standard is maintained in the list published in the Official Journal of the European Union. Users of this standard should consult frequently the latest list published in the Official Journal of the European Union.

WARNING 2 — Other Union legislation may be applicable to the product(s) falling within the scope of this standard.

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Annex ZB
(informative)

Relationship between this European Standard and the General Safety and Performance Requirements of Regulation (EU) 2017/746 aimed to be covered

This European standard has been prepared under M/575 to provide one voluntary means of conforming to the General Safety and Performance Requirements of Regulation (EU) 2017/746 of 5 April 2017 concerning *in vitro* diagnostic medical devices [OJ L 117] and to system or process requirements including those relating to quality management systems, risk management, post-market surveillance systems, performance studies, clinical evidence or post-market performance follow-up.

Once this standard is cited in the Official Journal of the European Union under that Regulation, compliance with the normative clauses of this standard given in Table ZB.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding General Safety and Performance Requirements of that Regulation, and associated EFTA Regulations.

Where a definition in this standard differs from a definition of the same term set out in Regulation (EU) 2017/746, the differences shall be indicated in the Annex Z. For the purpose of using this standard in support of the requirements set out in Regulation (EU) 2017/746, the definitions set out in this Regulation prevail.

Where the European standard is an adoption of an International Standard, the scope of this standard can differ from the scope of the European Regulation that it supports. As the scope of the applicable regulatory requirements differ from nation to nation and region to region, the standard can only support European regulatory requirements to the extent of the scope of the In vitro Diagnostic Regulation (EU) 2017/746).

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with Regulation (EU) 2017/746. This means that risks have to be 'reduced as far as possible', 'reduced to a level as low as reasonably practicable', 'reduced to the lowest possible level', 'reduced as far as possible and appropriate', 'removed or reduced as far as possible', 'eliminated or reduced as far as possible', 'prevented' or 'minimized', according to the wording of the corresponding General Safety and Performance Requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with General Safety and Performance Requirements 1, 2, 3, 4, 5, 8, 10, 11, 13, 15, 16, 17, 18 and 19 of the Regulation.

NOTE 3 When a General Safety and Performance Requirement does not appear in Table ZB.1, it means that it is not addressed by this European Standard.

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Table ZB.1 – Correspondence between this European standard and Annex I of Regulation (EU) 2017/746 [OJ L 117]

General Safety and Performance Requirements of Regulation (EU) 2017/746	Clause(s) / sub-clause(s) of this EN	Remarks / Notes
11.3	4,5,6,7,8,9,10	This standard provides requirements for the establishment of the sterilization dose in the development, validation and routine control of a sterilization process using ionising radiation for medical devices. This General Safety and Performance Requirement is addressed only with regard to devices for which sterilization by ionising radiation is appropriate and only in conjunction with EN ISO 11137-1. This relevant General Safety and Performance Requirement is only partly addressed in this European Standard. Design and packaging for maintenance of sterility during transportation and storage are not covered. Aspects of manufacture other than those related to attainment of sterility by ionising radiation are not covered. Evidence that the integrity of the packaging is maintained to the point of use is not covered.

WARNING 1: Presumption of conformity stays valid only as long as a reference to this European standard is maintained in the list published in the Official Journal of the European Union. Users of this standard should consult frequently the latest list published in the Official Journal of the European Union.

WARNING 2: Other Union legislation may be applicable to the product(s) falling within the scope of this standard.

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Annex ZC
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 98/79/EC on *in vitro* diagnostic medical devices

This European Standard has been prepared under a mandate given to CEN/CENELEC by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 98/79/EC on in vitro diagnostic medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the normative clauses of this standard given in Table ZC.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with 98/79/EC. This means that risks have to be reduced 'as far as possible', 'to a minimum', 'to the lowest possible level', 'minimized' or 'removed', according to the wording of the corresponding essential requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with essential requirements Part A: 1, 2 and 5; Part B: 1.2, 2, 3, 5, 6, and 7 of the Directive.

NOTE 3 This Annex ZA is based on normative references according to the table of references in the European foreword, replacing the references in the core text.

NOTE 4 When an Essential Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

Table ZC.1 — Correspondence between this European Standard and Directive 98/79/EC

Clauses of this European Standard	Essential Requirements (ERs) of EU Directive 98/79/EC	Qualifying remarks/Notes
4, 5, 6, 7, 8, 9, 10	B.2.3	Only a sterilization process using inoizing radiation is considered by this standard. This relevant ER is only partly addressed in this International Standard and only in conjunction with ISO 11137-1. Design and packaging for maintenance of sterility during transportation and storage are not covered. Aspects of manufacture other than those related to sterilization are not covered.

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4, 5, 6, 7, 8, 9, 10	B.2.4	This relevant Essential requirement is addressed in this International Standard in conjunction with ISO 11137-1 and only with regard to: - sterilization, not covering other special microbiological state - devices for which sterilization by radiation is appropriate .

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this standard.

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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*

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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.

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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*

〈A1〉 ISO 11137-1:2006/Amd1: 2013, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices — Amendment 1*

ISO 11137-1:2006/Amd2: 2018, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices — Amendment 2: Revision to 4.3.4 and 11.2*

ISO 13004: 20—[1]), *Sterilization of health care products — Radiation — Substantiation of selected sterilization dose: Method* VD_{max}^{SD} 〈A1〉

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]

〈A1〉 1) Under preparation. Stage at the time of publication: ISO/DIS 13004. 〈A1〉

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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

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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.

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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;

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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;

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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

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

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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) Rolls of bandage
Mass	Powders Gowns
Volume	Liquids
Surface area	Surgical drapes 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 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.

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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 ± 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:

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