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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

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Contents

Page

Foreword v

Introduction vi

1 Scope 1

2 Normative references 1

3 Abbreviations, terms and definitions 1
3.1 Abbreviations 1
3.2 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 and verifying the sterilization dose 7
5.1 Nature of product 7
5.2 Sample item portion (SIP) 8
5.3 Manner of sampling 8
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 $\geqslant$ 1,0 for multiple production batches 11
7.3 Procedure for Method 1 for product with an average bioburden $\geqslant$ 1,0 for a single production batch 16
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 18

8 Method 2: Dose setting using fraction positive information from incremental dosing to determine an extrapolation factor 18
8.1 Rationale 18
8.2 Procedure for Method 2A 19
8.3 Procedure for Method 2B 22

9 Method VD_{max} — Substantiation of 25 kGy or 15 kGy as the sterilization dose 25
9.1 Rationale 25
9.2 Procedure for Method VD_{max}^{25} for multiple production batches 26
9.3 Procedure for Method VD_{max}^{25} for a single production batch 29
9.4 Procedure for Method VD_{max}^{15} for multiple production batches 30
9.5 Procedure for Method VD_{max}^{15} for a single production batch 33

10 Auditing sterilization dose 34
10.1 Purpose and frequency 34

10.2 Procedure for auditing a sterilization dose established using Method 1 or Method 2 35
10.3 Procedure for auditing a sterilization dose substantiated using VD_{max} 37

11 Worked examples 41
11.1 Worked examples for Method 1 41
11.2 Worked examples for Method 2 44
11.3 Worked examples for Method VD_{max} 53
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 55
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 56
11.6 Worked example of a sterilization dose audit for a sterilization dose substantiated using Method VD_{max}[25] 58

Bibliography 59

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 first edition, together with ISO 11137-1 and ISO 11137-3, cancels and replaces ISO 11137:1995.

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*

This corrected version of ISO 11137-2:2006 incorporates changes in the following subclauses:

4.3.1.3, 5.1.1, 7.1, 7.2.3.2, 7.3.4.2, 7.4, 8.1, 8.2.3.1.1, 8.2.3.3.1, 8.2.6.3, 8.3.3.3.1, 8.3.6.3, 9.2.3.2, 9.2.4, 9.3.4.2, 9.3.5, 9.3.6.2, 9.4.1.2, 9.4.3.2, 9.4.5.2, 9.5.2.2, 9.5.4.2, 9.5.6.2, 10.2.5.2, 10.2.6.1, 10.3.3.2, 10.3.6.4.2, 11.3.

Introduction

This part of ISO 11137 describes methods that may 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:

a) dose setting to obtain a product-specific dose;

b) 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 (Tallentire, 1973 [17]; Tallentire, Dwyer and Ley, 1971 [18]; Tallentire and Khan, 1978 [19]). Subsequently, standardized protocols were developed (Davis *et al*., 1981 [8]; Davis, Strawderman and Whitby, 1984 [9]) which formed the basis of the dose setting methods detailed in the AAMI *Recommended Practice for Sterilization by Gamma Radiation* (AAMI 1984, 1991 [4], [6]).

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 may 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 $\leqslant$ 25 kGy. The basis of the method devised specifically for substantiation of 25 kGy, Method VD_{max}, was put forward by Kowalski and Tallentire (1999) [14]. Subsequent evaluations involving computational techniques demonstrated that the underlying principles were soundly based (Kowalski, Aoshuang and Tallentire, 2000) [13] 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 (Kowalski *et al*., 2002) [16].

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}* (AAMI TIR27:2001) [5], 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 kGy, is included as a superscript to the VD_{max} symbol. Thus, for substantiation of a sterilization dose of 25 kGy the method is designated VD_{max}^{25}.

Method VD_{max}^{15} is based on the same principles as Method VD_{max}^{25} described above. The test procedure is the same as Method VD_{max}^{25}, but VD_{max}^{15} is limited to product with average bioburden $\leqslant$ 1,5. The outcomes of these tests are used to substantiate that 15 kGy achieves a sterility assurance level of 10^{-6}.

This part of ISO 11137 also describes methods that may 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 of 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 dose auditing in order to demonstrate the continued effectiveness of the sterilization dose.

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

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 the population of microorganisms on product*

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

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

3 Abbreviations, terms and definitions

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

3.1 Abbreviations

3.1.1
A
dose to adjust the median ffp dose downwards, to the FFP dose

3.1.2
*CD**
number of positive tests of sterility obtained from tests performed individually on 100 product items irradiated in a Method 2 verification dose experiment

3.1.3
*d**
dose derived from an incremental dose experiment performed on product items drawn from a given production batch

3.1.4
*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 3 *d** values derived for a given product.

3.1.5
*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

3.1.6
*DD**
dose delivered in a Method 2 verification dose experiment

3.1.7
DS
estimate of D_{10} value of microorganisms present on product after exposure to *DD**

3.1.8
***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]

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

3.1.9
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

3.1.10
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 3 ffp doses

3.1.11
First No Positive dose
FNP
estimate of the dose to provide an SAL of 10^{-2} for the test items, which is used in the calculation of *DS*

3.1.12
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

3.1.13
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

3.2 Terms

3.2.1
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]

3.2.2
bioburden
population of viable microorganisms on or in product and/or sterile barrier system

[ISO/TS 11139:2006]

3.2.3
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

3.2.4
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

3.2.5
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

3.2.6
negative test of sterility
test result for which there is no detectable microbial growth from product, or portion thereof, subjected to a test of sterility

3.2.7
packaging system
combination of the sterile barrier system and protective packaging

[ISO/TS 11139:2006]

3.2.8
positive test of sterility
test result for which there is detectable microbial growth from product, or portion thereof, subjected to a test of sterility

3.2.9
sample item portion
SIP
defined portion of a health care product that is tested

3.2.10
sterile barrier system
minimum package that prevents ingress of microorganisms and allows aseptic presentation of product at the point of use

3.2.11
sterility assurance level
SAL
probability of a single viable microorganism occurring on an item after sterilization

[ISO/TS 11139:2006]

NOTE The term sterility assurance level 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}.

3.2.12
sterilization dose audit
exercise undertaken to confirm the appropriateness of an established sterilization dose

3.2.13
verification dose
dose of radiation predicted to give a predetermined SAL $\geqslant 10^{-2}$ used in establishing the sterilization dose

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 number and types of microorganism present on or in product (the bioburden). The type of microorganism is indicative of its resistance to radiation. Variables such as density and product configuration within its packaging system are not considered in the establishment of these product families because they are not factors that influence bioburden.

In using product families in establishing the sterilization dose and for sterilization dose auditing, it is important to be aware of risks such as reduction in the ability to detect an inadvertent change within the manufacturing process that influences the effectiveness of sterilization. Furthermore, the use of a single product to represent the product family might not detect changes that occur in other members of the product family. The risk associated with a reduction in ability to detect changes in other members of the product family should be evaluated and a plan for maintaining product families 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 process;

e) manufacturing equipment;

f) manufacturing environment;

g) manufacturing location.

The outcome of the assessment and considerations shall be recorded (see 4.1.2 of ISO 11137-1:2006).

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 4.1.2 of ISO 11137-1:2006). 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 microorganism on or in product shall be used as the basis for selecting product to represent a product family.

4.3.1.2 A product family shall be represented by:

a) the master product (see 4.3.2)

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) numbers of microorganisms comprising the bioburden;

b) types of microorganism comprising the bioburden;

c) the 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 product family in accordance with 4.3.3.

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 planned schedule to include different members of the product family. The manufacturing volume and availability of product should be considered in the selection of the equivalent product to represent the product family.

4.3.4 Simulated product

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

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

A simulated product may be:

a) one 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 which 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 assure 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 review shall be performed at least annually. The outcome of the review shall be recorded in accordance with 4.1.2 of ISO 11137-1:2006.

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 4.1.2 of ISO 11137-1:2006).

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

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

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

5.1 Nature of product

5.1.1 Product for sterilization can consist of:

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 dose setting and dose substantiation shall be taken in accordance with Table 1.

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

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

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

EXAMPLE If the product has a label claim of sterility for the fluid path only, the sterilization dose may be established based on bioburden determinations and outcomes of tests of sterility performed on the fluid path.

5.2 Sample item portion (SIP)

5.2.1 For product with an average bioburden equal to or greater than 1,0, whenever practicable, an entire product (SIP equal to 1,0) should be used for testing in accordance with Table 1. When the use of an entire product is not practicable, a selected portion of product (sample item portion) may be substituted. The SIP should be as large a portion of item as practicable in order to manipulate in the laboratory, and should be of a size that can be handled during testing.

5.2.2 For a product with an average bioburden equal to or less than 0,9, an entire product (SIP equal to 1,0) shall be used for testing in accordance with Table 1.

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

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 SIP

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

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

5.2.5 The adequacy of a selected SIP shall be demonstrated. The bioburden of the SIP shall be such that tests of sterility performed individually on 20 non-irradiated SIP items yield a minimum of 17 positive tests of sterility (i.e. 85 % positives). If the criterion is not achieved, a SIP larger than that examined originally and that meets the criterion shall be used. If an entire product is tested (SIP equal to 1,0), the criterion of a minimum of 17 positive tests of sterility observed out of 20 tests of sterility performed does not have to be met.

5.3 Manner of sampling

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

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

5.4 Microbiological testing

5.4.1 Bioburden determinations and tests of sterility shall be conducted in accordance with 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, e.g., Herring et al, 1974 [12]; Favero, 1971 [10]; NHB 5340.1A, 1968 [7].

Whenever practicable, product the should be irradiated in its original form and package system. However, to reduce the possibility of false positives in the test of sterility, an item may be disassembled and repackaged prior to irradiation. 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). Materials for repackaging product items for irradiation shall be capable of withstanding the doses delivered and subsequent handling, thereby minimizing the likelihood of contamination.

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

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

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) Method 2A (see 8.2),

c) Method 2B (see 8.3)

or

d) a method providing equivalent assurance to that of a), b) or c) above in achieving the specified requirements for sterility.