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

Stérilisation des produits de santé — Irradiation — Justification de la dose stérilisante choisie: Méthode DV_{max}^{DS}

Reference number
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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.

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

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

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

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

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

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

The main changes are as follows:

— guidance is offered for determination of an SIP for bulk materials such as powders, liquids and gels;

— 5.3.3 and 5.3.4 have been reworded to match language in ISO 11137-2;

— the NOTE in 5.4.1 has been removed;

— 7.2 has been replaced with a reference to requirements in ISO 11137-1;

— guidance has been added for when to re-substantiate the sterilization dose based on shifts in bioburden.

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

Introduction

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

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

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

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

The method described in this document is for substantiation of a selected sterilization dose to achieve a sterility assurance level (SAL) of 10^{-6} or less at that dose (e.g. Method VD_{max}^{20} for a selected sterilization dose of 20 kGy). The application of the method is not limited by production batch size or production frequency, and the number of product items irradiated in the verification dose experiment remains constant. The method is founded on and embodies the following three principles:

— existence of a direct link between the outcome of the verification dose experiment and the attainment of an SAL of 10^{-6} at the selected sterilization dose;

— possession of a level of conservativeness at least equal to that of the standard distribution of resistances (SDR);

— for a given bioburden, use of a maximal verification dose (VD_{max}) corresponding to substantiation of a selected sterilization dose.

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

The method described here and designated Method VD_{max}^{SD} procedurally comprises elements that closely parallel those of dose setting Method 1 described in ISO 11137-2. One key area of difference is the number of product items used in the verification dose experiment. In the computer evaluations referred to above, changing the verification SAL value had little effect on the substantiation outcome and this finding led to a sample size of 10 product items being chosen for subsequent field evaluations and, ultimately, for inclusion in this document.

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

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

1 Scope

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

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

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

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

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

2 Normative references

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

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

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

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

3 Terms and definitions

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

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

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
absorbed dose
dose
quantity of ionizing radiation energy imparted per unit mass of a specified material

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

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

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

3.2
batch
defined quantity of a product intended or purported to be uniform in character and quality, produced during a specified cycle of manufacture

[SOURCE: ISO 11139:2018, 3.21]

3.3
bioburden
population of viable *microorganisms* (3.11) on or in a product and/or *sterile barrier system* (3.16)

[SOURCE: ISO 11139:2018, 3.23]

3.4
correction
action to eliminate a detected nonconformity

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

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

3.5
corrective action
action to eliminate the cause of a nonconformity and to prevent recurrence

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

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

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

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

3.6
dose mapping
measurement of dose distribution and variability in material irradiated under specified conditions

[SOURCE: ISO 11139:2018, 3.87]

3.7
false positive
test result interpreted as growth arising from product, or portion thereof, tested when either growth resulted from extraneous microbial contamination or turbidity occurred from interaction between the product, or portions thereof, and the test medium

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

3.8
health care product(s)
medical device (3.9), including in vitro diagnostic medical device, or medicinal product, including biopharmaceutical

[SOURCE: ISO 11139:2018, 3.132]

3.9
medical device
instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, or software material, or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

— diagnosis, prevention, monitoring, treatment, or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of, or compensation for an injury;

— investigation, replacement, modification, or support of the anatomy, or of a physiological process;

— supporting or sustaining life;

— control of conception;

— disinfection of medical devices;

— providing information by means of in vitro examination of specimens derived from the human body;

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

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

3.10
Method VD_{max}
procedure for sterilization dose substantiation that uses the maximal *verification dose* (3.23) for a given *bioburden* (3.3), consistent with the attainment of a sterility assurance level (SAL) of 10^{-6} at a selected sterilization dose

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

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

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

3.11
microorganism
entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

Note 1 to entry: A specific standard might not require demonstration of the effectiveness of the sterilization process in inactivating all types of microorganisms, identified in the definition above, for validation and/or routine control of the sterilization process.

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

3.12
packaging system
combination of the *sterile barrier system* (3.16) and protective packaging

[SOURCE: ISO 11139:2018, 3.192]

3.13
positive test of sterility
test result for which there is detectable microbial growth from product, or portion thereof, subjected to a *test of sterility* (3.22)

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

3.14
product
tangible result of a process

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

[SOURCE: ISO 11139:2018, 3.217]

3.15
sample item portion
SIP
specified part of a *health care product* (3.8) that is tested

[SOURCE: ISO 11139:2018, 3.240]

3.16
sterile barrier system
minimum package that minimizes the risk of ingress of *microorganisms* (3.11) and allows aseptic presentation of the sterile contents at the point of use

[SOURCE: ISO 11139:2018, 3.272]

3.17
sterility
state of being free from viable *microorganisms* (3.11)

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

[SOURCE: ISO 11139:2018, 3.274]

3.18
sterility assurance level
SAL
probability of a single viable *microorganism* (3.11) occurring on an item after sterilization

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

[SOURCE: ISO 11139:2018, 3.275

3.19
sterilization
validated process used to render product free from viable *microorganisms* (3.11)

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

[SOURCE: ISO 11139:2018, 3.277]

3.20
sterilization dose
SD
D_{ster}
minimum dose to achieve the specified requirements for *sterility* (3.17)

[SOURCE: ISO 11139:2018, 3.280]

3.21
sterilization dose audit
exercise undertaken to confirm the appropriateness of an established sterilization dose

[SOURCE: ISO 11139:2018, 3.281]

3.22
test of sterility
technical operation performed as part of development, validation or requalification to determine the presence or absence of viable *microorganisms* (3.11) on product or portion thereof

[SOURCE: ISO 11139:2018, 3.299]

3.23
verification dose
dose of radiation predicted to give a predetermined *sterility assurance level (SAL)* (3.18) greater than or equal to 10^{-2} used in establishing the sterilization dose

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

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

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

4.1 General

The establishment of a sterilization dose, for which sterilization dose selection and substantiation can be undertaken, and the carrying out of sterilization dose audits are activities that are part of process definition and maintaining process effectiveness (see ISO 11137-1). For these activities, product may be grouped into families. Definition of product families is based principally on the numbers and types of microorganisms on or in product (the bioburden), the type being indicative of the microorganism's resistance to radiation (see ISO 11737-1). Variables such as density and product configuration within its packaging system are not considered in the establishment of these product families because they are not factors that influence bioburden.

In using product families for establishing the sterilization dose and for carrying out sterilization dose audits, it is important to be aware of the reduction in the ability to detect an inadvertent change within the manufacturing process that influences the effectiveness of sterilization. Furthermore, with the use of a single product to represent the product family, it is possible that changes that occur in other members of the product family will not be detected. The effect of a reduction on ability to detect changes in other members of the product family should be evaluated and a plan for maintaining product families developed and implemented before proceeding.

4.2 Defining product families

4.2.1 The criteria for defining a product family shall be documented. Product shall be assessed against these criteria and the similarities between potential product family members considered.

Consideration shall include all product-related variables that affect bioburden, including, but not limited to:

a) nature and sources of raw materials, including the effect, if any, of raw materials that can be sourced from more than one location;

b) components;

c) product design and size;

d) manufacturing processes;

e) manufacturing equipment;

f) manufacturing environment;

g) manufacturing location.

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

4.2.2 Product shall only be included in a product family if it is demonstrated that the product-related variables (see 4.2.1) are similar and under control.

4.2.3 To include product within a product family, it shall be demonstrated that bioburden comprises similar numbers and types of microorganisms.

4.2.4 Inclusion of product from more than one manufacturing location in a product family shall be specifically justified and recorded in accordance with ISO 11137-1:2006, 4.1.2. Consideration shall be given to the effect on bioburden of:

a) geographic and/or climatic differences between locations;

b) any differences in the control of the manufacturing processes or environment;

c) sources of raw materials and processing adjuvants (e.g. water).

4.3 Designation of product to represent a product family

4.3.1 Product to represent a product family

4.3.1.1 The number and types of microorganisms on or in product shall be used as the basis for selecting product to represent a product family.

4.3.1.2 A product family shall be represented by:

a) a master product (see 4.3.2), or

b) an equivalent product (see 4.3.3), or

c) a simulated product (see 4.3.4).

4.3.1.3 A formal, documented assessment shall be undertaken to decide which of the three potential representative products in 4.3.1.2 is appropriate. In this assessment, consideration shall be given to the following:

a) number of microorganisms comprising the bioburden;

b) types of microorganisms comprising the bioburden;

c) environment in which the microorganisms occur;

d) size of product;

e) number of components;

f) complexity of product;

g) degree of automation during manufacture;

h) manufacturing environment.

4.3.2 Master product

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

a) at random, or

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

4.3.3 Equivalent product

A group of product shall only be considered equivalent if assessment (see 4.3.1.3) indicates that group members require the same sterilization dose. Selection of the equivalent product to represent the family shall be either

a) at random, or

b) in accordance with a documented procedure to include different members of the product family. The manufacturing volume and availability of product should be considered in the selection of the equivalent product to represent the product family.

4.3.4 Simulated product

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

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

A simulated product may be:

a) one that is similar to the actual product in terms of materials and size, and subjected to similar manufacturing processes, e.g. a piece of the material, used for implants, that goes through the entire manufacturing process, or

b) a combination of components from product within the product family that would not typically be combined for use, e.g. a tubing set containing multiple filters, clamps and stopcocks that are components of other products within the product family.

4.4 Maintaining product families

4.4.1 Periodic review

Review shall be performed at a specified frequency to ensure that product families and product used to represent each product family remain valid. Responsibility for reviews of either product or processes, or both that can affect membership of product families shall be allocated to competent personnel. Such review shall be performed at least annually. The outcome of the review shall be recorded in accordance with ISO 11137-1:2006, 4.1.2.

4.4.2 Modification to either product or manufacturing process, or both

Modifications to product, such as raw materials (nature and source), components or product design (including size), and/or modifications to the manufacturing process, e.g. equipment, environment or location, shall be assessed through a formal, documented change control system. Such modifications can alter the basis on which the product family was defined or the basis on which the selection of product to represent the product family was made. Significant changes can require definition of a new product family or the selection of a different representative product.

4.4.3 Records

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

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

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

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

5.1 Nature of product

5.1.1 Product for sterilization can consist of:

a) an individual health care product in its packaging system;

b) a set of components presented in a packaging system, which are assembled at the point of use to form the health care product, together with accessories required to use the assembled product;

c) a number of identical health care products in their packaging system;

d) a kit comprising a variety of procedure-related health care products.

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

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

Product type	Item for bioburden determination and verification dose experiment	Rationale
Individual health care product in its packaging system	Individual health care product	Each health care product is used independently in clinical practice.
Set of components in a packaging system	Combination of all components of the product	Components are assembled as a product and used together in clinical practice.
Number of identical health care products in their packaging system	Single health care product taken from the packaging system	Each health care product is used independently in clinical practice; the SAL of an individual health care product within the packaging system meets the selected SAL, although the overall SAL associated with the packaging system can be higher.
Kit of procedure-related health care products [a]	Each type of health care product comprising the kit	Each health care product is used independently in clinical practice.

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

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

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

5.2 Sample item portion (SIP)

5.2.1 For product with an average bioburden greater than or equal to 1,0, whenever practicable, an entire product (SIP equal to 1,0) should be used for testing according to Table 1. When the use of an entire product is not practicable, a sample item portion (SIP) of product 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 1,0, an entire product (SIP equal to 1,0) shall be used for testing in accordance with Table 1.

NOTE When testing products with low average bioburden, it is possible that an SIP will not always be the portion of the product item possessing microorganisms. Therefore, the entire product (SIP = 1,0) is used for products with an average bioburden less than 1,0.

5.2.3 If the bioburden is evenly distributed either on the item or in the item, or both, 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 SIP

Basis for SIP	Product
Length	Tubing (consistent diameter) Rolls of bandage
Mass	Powders Gowns
Volume	Liquids
Surface area	Surgical drapes Tubing (variable diameter)

For bulk type materials, a representative sample may be considered as an SIP of 1,0 for the product (i.e. powder, gels and liquids). The rationale for the selected sample size should be documented.

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 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 one 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 than 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.

NOTE When performing a bioburden determination on bulk materials such as powder, gels and liquids (see ISO 11737-1:2018, B.3.3), it is not necessary to demonstrate the adequacy of the SIP used in the bioburden determination.

5.2.6 The same 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.

If the SIP used in the performance of tests of sterility is different from that used in the determination of bioburden, caution should be exercised when selecting the sterilization dose and when calculating the value of SIP VD_{max}^{SD}. In carrying out these two activities, two separate determinations of bioburden are required: one for the SIP used to obtain the bioburden for the entire product item employed in the selection of the sterilization dose and the other for the SIP used to obtain the value of SIP VD_{max}^{SD} employed in the performance of the verification dose experiment.

5.3 Manner of sampling

5.3.1 Product for sterilization dose substantiation and for sterilization dose auditing shall be representative of that subjected to routine manufacturing procedures and conditions.

5.3.2 Each product item used in the determination of bioburden or in the performance of a test of sterility should be taken, where applicable (see Table 1), from a separate packaging system.

5.3.3 For product capable of supporting microbial growth, the maximum allowable amount of time from manufacture to sterilization of product shall be determined. Storage conditions (including refrigeration of product, if applicable) should be considered as part of this determination. The period of time between the taking of product items from production and the determination of bioburden or

the performance of the verification dose experiment should be reflective of the maximum allowable holding time.

The manufacturing step to use in this determination of the maximum allowable holding time should be the last step before the product would be capable of supporting microbial growth (e.g. the last mixing step for a liquid formulation), and in many cases this might not be the very last manufacturing step prior to sterilization of product.

5.3.4 Product items may be selected from product rejected during the manufacturing process provided that they have been subjected to the same manufacturing procedures and conditions as the remainder of production, including packaging.

5.4 Microbiological testing

5.4.1 Bioburden determinations and performance of tests of sterility shall be conducted in accordance with ISO 11737-1 and ISO 11737-2, respectively.

To reduce the possibility of false positives in carrying out tests of sterility, items may be disassembled and repackaged prior to irradiation. Manipulations prior to irradiation shall not 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).

5.4.2 Bioburden determinations shall be carried out on product that has undergone the packaging process.

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

5.5 Irradiation

5.5.1 Irradiation of product in performing sterilization dose substantiation and sterilization dose auditing shall be conducted in an irradiator that has undergone installation qualification and operational 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, sufficient performance qualification dose mapping shall be carried out to identify the highest and the lowest doses delivered to product.

5.5.4 Whenever practicable, for the performance of a verification dose experiment, product should be irradiated in its original form and in its packaging system.

5.5.5 Materials for repackaging product items for irradiation, if applicable (see 5.4.1), shall be capable of withstanding the doses delivered and subsequent handling, thereby minimizing the likelihood of contamination.

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

6 Method VD_{max}^{SD} — Substantiation of a selected sterilization dose of 17,5 kGy, 20 kGy, 22,5 kGy, 27,5 kGy, 30 kGy, 32,5 kGy or 35 kGy

6.1 Rationale

Operationally, the method of substantiation for a selected sterilization dose is similar to dose setting Method 1 of ISO 11137-2; it too requires a determination of bioburden and the performance of a verification dose experiment.

In carrying out substantiation, the method verifies that bioburden present on product prior to sterilization is less resistant to radiation than a microbial population of maximal resistance consistent with the attainment of an SAL of 10^{-6} at the selected sterilization dose; verification is conducted through performance of a verification dose experiment at an SAL of 10^{-1} using 10 product items. The dose at an SAL of 10^{-1} for a population having this resistance (maximal verification dose, VD_{max}) is characteristic of the bioburden level, the sterilization dose and the associated maximal resistance. In establishing the maximal resistance for a particular bioburden level and sterilization dose, due account has been taken of the various resistance components of the SDR, the latter being the basis of Method 1. Components of the SDR of high resistance that have significant effect on the attainment of an SAL of 10^{-6} have been used to define the maximal resistances on which this substantiation method is based. In this way, the level of conservativeness of the SDR, and thus of Method 1, is preserved. See Kowalski and Tallentire[7]; Kowalski, Aoshuang, and Tallentire[8]; Kowalski and Tallentire[11].

In practice, a determination is made of the average bioburden. Based on this average value, a sterilization dose is selected from a table listing the upper limits of average bioburden that apply to specified selected sterilization doses. These upper limits are the numbers of microorganisms possessing a given maximal resistance commensurate with the attainment of a SAL of 10^{-6} at the selected sterilization dose. The VD_{max} dose corresponding to the selected sterilization dose and the average bioburden is read from a second table; it is the dose at which the verification dose experiment is carried out. Ten product items, or portions thereof (if applicable, see 5.2), are exposed to the VD_{max}^{SD} dose and each item is subjected individually to a test of sterility. If there is no more than one positive test of sterility in the 10 tests, the pre-selected sterilization dose is substantiated.

The VD_{max} methods given in this document are for selected sterilization doses of 17,5 kGy, 20 kGy, 22,5 kGy, 27,5 kGy, 30 kGy, 32,5 kGy and 35 kGy. To distinguish these applications of Method VD_{max} and their associated sets of values of verification dose, a superscript has been added to the term VD_{max} where appropriate, i.e.. VD_{max}^{SD}, where SD is the selected sterilization dose.

NOTE Inspection of the values of the VD_{max}^{SD} for the various levels of average bioburden given in each of the tables in Clause 8 reveals a change in the relationship between the bioburden level and the value of VD_{max}^{SD}. With increasing bioburden up to a certain level, values progressively increase, as can be expected. However, at a particular bioburden level, the VD_{max}^{SD} takes a maximum, and for higher bioburden levels, the corresponding VD_{max}^{SD} values progressively decrease. For example, for Method $VD_{max}^{17,5}$, $VD_{max}^{17,5}$ values progressively increase up to a bioburden level of 2,5. However, at a bioburden of 2,5, the value of $VD_{max}^{17,5}$ takes a maximum, and for higher bioburden levels, the corresponding $VD_{max}^{17,5}$ values decrease. A similar increase, followed by a decrease, is seen with the other VD_{max}^{SD} methods. This behaviour is not the result of an error in either the tables or the calculation of the VD_{max} values. It is an inevitable outcome of building into Method VD_{max}^{SD} the same degree of conservativeness as that in Method 1 (see Kowalski and Tallentire[11]).

6.2 Procedure for Method VD_{max}^{SD} for multiple production batches

6.2.1 General

6.2.1.1 In applying Method VD_{max}^{SD} for product with an average bioburden less than 1,0, the entire product item shall be used, whereas for product with an average bioburden greater than or equal to 1,0, an SIP may be used (see 5.2.5).

6.2.1.2 In applying Method VD_{max}^{SD}, the six stages below shall be followed.

NOTE For worked examples, see 9.1 and 9.2.

6.2.2 Stage 1: Obtain samples of product

Select 10 product items from each of three independent production batches, in accordance with 5.1, 5.2 (if applicable) and 5.3.

Product will also be needed to perform the verification dose experiment (see 6.2.6.1) and it is possible that additional product will be needed to validate the adequacy of an SIP less than one (see 5.2.5) or to perform a confirmatory verification dose experiment (see 6.2.7.2 and 6.2.8).

6.2.3 Stage 2: Determine average bioburden

6.2.3.1 Apply the correction factor in the determination of bioburden (see ISO 11737-1).

6.2.3.2 Determine the bioburden of each of the selected product items and calculate:

a) the average bioburden per item for each of the three batches of product items (batch average bioburden);

b) the average bioburden per item for all selected product items (overall average bioburden).

Bioburden is generally determined on individual product items, but when the bioburden is low (e.g. less than 10), it is permissible to pool the 10 product items for the determination of average bioburden. This guidance does not apply to SIP; SIPs should not be pooled, rather a larger SIP should be chosen (see 5.2.5).

NOTE An observation of no colonies in the determination of bioburden is sometimes expressed as less than the limit of detection. Use of the limit of detection as a bioburden value in calculating average bioburden can lead to an overestimation of average bioburden. Overestimation can lead to selection of too high a sterilization dose and, in consequence, a high value for $VD_{max}{}^{SD}$, thereby affecting the validity of the verification dose experiment. The use of an approach for bioburden determination having a low limit of detection can reduce such overestimation (see ISO 11737-1:2018, A.6.1.1).

For an SIP less than 1,0, calculate the average bioburden for the entire product item (SIP equal to 1,0) by dividing each of the three SIP batch average bioburdens and the overall SIP average bioburden by the SIP value.

6.2.4 Stage 3: Obtain the selected sterilization dose

6.2.4.1 In obtaining the selected sterilization dose, values of average bioburden for the entire product item (SIP equal to 1,0) shall be used (see 6.2.3.2).

6.2.4.2 From Table 3, obtain the selected sterilization dose. In obtaining this dose, all three batch average bioburdens (SIP equal to 1,0) determined in Stage 2 shall be below or equal to the associated upper limit of the average bioburden given in Table 3.

6.2.4.3 A sterilization dose greater than the lowest dose consistent with meeting the requirement in 6.2.4.2 may be selected. A rationale for selecting a greater dose can be based on factors such as:

a) the difference between the average bioburden and the upper limit associated with the selected sterilization dose;

b) available data on the variation in the numbers and types of microorganisms that comprise the bioburden;

c) available data on the microbiological quality of similar products including the results of sterilization dose audits;

d) the materials comprising the product and the control of the microbiological quality of materials;

e) the manufacturing process and associated control and monitoring procedures, particularly steps that affect bioburden or its resistance; and

f) the manufacturing environment, particularly the extent of microbiological control and monitoring, and available data on the stability of the manufacturing environment over time.

Table 3 — Upper limit of average bioburden for selection of a given sterilization dose

Upper limit for average bioburden (SIP equal to 1,0)	Selected sterilization dose (kGy)
9,0	17,5
45	20
220	22,5
5 000	27,5
23 000	30
100 000	32,5
440 000	35

6.2.5 Stage 4: Obtain VD_{max}^{SD}

6.2.5.1 From Table 4, identify the table in Clause 8 that gives values of SIP equal to 1,0 VD_{max}^{SD}, SIP dose reduction factor and dose augmentation value, corresponding to different values of average bioburden, for the selected sterilization dose.

Table 4 — Table in Clause 8 corresponding to the selected sterilization dose

Selected sterilization dose (kGy)	Corresponding table in Clause 8
17,5	Table 5
20	Table 6
22,5	Table 7
27,5	Table 8
30	Table 9
32,5	Table 10
35	Table 11

6.2.5.2 Compare the three batch average bioburdens to the overall average bioburden found in Stage 2 and determine whether any one of the batch average bioburdens is two or more times greater than the overall average bioburden.

6.2.5.3 From the identified table in Clause 8, obtain the value of SIP equal to 1,0 VD_{max}^{SD} using one of the following as the average bioburden:

a) if a batch average bioburden is two or more times greater than the overall average bioburden, use the highest batch average bioburden, or

b) if each of the batch average bioburdens is less than two times the overall average bioburden, use the overall average bioburden.

For an SIP equal to 1,0, if the average bioburden is not given in the identified table in Clause 8, use the closest tabulated value greater than the average bioburden to locate the value of SIP equal to 1,0 VD_{max}^{SD}.

For an SIP less than 1,0, use the average bioburden for the entire product item (SIP equal to 1,0), calculated in Stage 2 (6.2.3.2), to enter the identified table in Clause 8. If the calculated average bioburden is not given in the identified table in Clause 8, use the closest tabulated value greater than the average bioburden to locate the value of SIP equal to 1,0 VD_{max}^{SD} and the corresponding SIP dose reduction factor. Use Formula (1) to calculate the SIP VD_{max}^{SD} (see Kowalski and Tallentire[11]).

$$\text{SIP } VD_{max}^{SD} = (\text{SIP equal to 1,0 } VD_{max}^{SD}) + (\text{SIP dose reduction factor} \times \log \text{SIP}) \quad (1)$$

Use of an SIP less than 1,0 is not permitted for product with an average bioburden less than 1,0 (see 6.2.1.1).

6.2.6 Stage 5: Perform verification dose experiment

6.2.6.1 Select 10 product items from a single batch of product. The 10 product items for the performance of Stage 5 may be selected from one of the batches on which a bioburden determination was carried out in Stage 2, or from a fourth batch manufactured under conditions that are representative of normal production (see 5.3).

6.2.6.2 Irradiate these product items at VD_{max}^{SD} obtained from the identified table in Clause 8 or calculated using Formula (1), whichever is appropriate.

The highest dose to product items shall not exceed VD_{max}^{SD} by more than 10 % or 0,1 kGy, whichever is greater.

A tolerance of 0,1 kGy is allowed in order to accommodate the ability and practicality of irradiation facilities to deliver and measure VD_{max}^{SD} doses below 1,0 kGy.

The arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of VD_{max}^{SD}.

Determine the dose delivered (see 5.5).

If the highest dose to product items exceeds VD_{max}^{SD} by more than 10 % or 0,1 kGy, whichever is greater, the verification dose experiment shall be repeated.

If the arithmetic mean of the highest and lowest doses to product items is less than 90 % of VD_{max}^{SD}, the verification dose experiment may be repeated. If this mean dose is less than 90 % of VD_{max}^{SD} and, on performance of tests of sterility, acceptable results are observed (see 6.2.7), the verification dose experiment need not be repeated.

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

6.2.7 Stage 6: Interpretation of results

6.2.7.1 If no more than one positive test of sterility is obtained from the 10 tests carried out, accept verification and thereby substantiate the selected sterilization dose.

6.2.7.2 If two positive tests of sterility are obtained, perform a confirmatory verification dose experiment (see 6.2.8).

6.2.7.3 If three or more positive tests of sterility are obtained, do not accept verification as the selected sterilization dose can be inadequate.

If the occurrence of these positive tests of sterility can be ascribed to incorrect performance of the determination of bioburden, incorrect performance of tests of sterility or incorrect delivery of VD_{max}^{SD} or a specific bioburden-related cause, implement corrective action and repeat the verification

dose experiment using a further 10 product items from a batch manufactured under conditions that are representative of normal production. If, as a result of corrective action, the estimate of average bioburden changes, for the repeat verification dose experiment use the VD_{max}^{SD} (6.2.5) that corresponds to the changed average bioburden. If the estimate of average bioburden is unchanged, use the same VD_{max}^{SD} as that used in the verification dose experiment that was not accepted. Interpret the results of the repeat verification dose experiment in accordance with 6.2.7.

If the occurrence of these positive tests of sterility cannot be ascribed to incorrect performance of the determination of bioburden, incorrect performance of tests of sterility or incorrect delivery of VD_{max}^{SD} or a specific bioburden-related cause, the selected sterilization dose is not substantiated and another approach for establishing a sterilization dose shall be used. Other approaches are:

a) selection and substantiation of a higher sterilization dose than that for which verification was not accepted using Method VD_{max}^{SD}, starting at Stage 3 (6.2.4);

b) Method 1;

c) Method 2; and

d) a method providing assurance, in regard to achieving maximally an SAL of 10^{-6}, equivalent to that of other methods of dose establishment.

6.2.8 Confirmatory verification dose experiment

6.2.8.1 General

If a confirmatory verification dose experiment is to be carried out (see 6.2.7.2), the three stages below shall be followed.

6.2.8.2 Stage 1: Obtain samples of product

Select 10 product items from a single batch of product. The 10 product items for the performance of the confirmatory verification dose experiment may be selected from one of the batches on which a bioburden determination was carried out in Stage 2 (see 6.2.3), from the fourth batch used in Stage 5 (see 6.2.6.1) or from a batch manufactured under conditions that are representative of normal production (see 5.3).

6.2.8.3 Stage 2: Perform confirmatory verification dose experiment

6.2.8.3.1 Irradiate these product items at VD_{max}^{SD} obtained in 6.2.5.

The highest dose to product items shall not exceed VD_{max}^{SD} by more than 10 % or 0,1 kGy, whichever is greater.

A tolerance of 0,1 kGy is allowed in order to accommodate the ability and practicality of irradiation facilities to deliver and measure VD_{max}^{SD} doses below 1,0 kGy.

The arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of VD_{max}^{SD} .

Determine the dose delivered (see 5.5).

If the highest dose to product items exceeds VD_{max}^{SD} by more than 10 % or 0,1 kGy, whichever is greater, the verification dose experiment shall be repeated.

If the arithmetic mean of the highest and lowest doses to product items is less than 90 % of VD_{max}^{SD} , the confirmatory verification dose experiment may be repeated. If this mean dose is less than 90 % of VD_{max}^{SD} and, on performance of tests of sterility, acceptable results are observed (see 6.2.8.4), the confirmatory verification dose experiment need not be repeated.

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

6.2.8.4 Stage 3: Interpretation of results

6.2.8.4.1 If there are no positive tests of sterility from the 10 tests carried out, accept confirmatory verification and thereby substantiate the selected sterilization dose.

6.2.8.4.2 If any positive tests of sterility are obtained, do not accept confirmatory verification as the selected sterilization dose can be inadequate.

If the occurrence of these positive tests of sterility can be ascribed to incorrect performance of tests of sterility or incorrect delivery of VD_{max}^{SD}, or a specific bioburden-related cause, implement corrective action and repeat the confirmatory verification dose experiment using a further 10 product items from a batch manufactured under conditions that are representative of normal production and the same VD_{max}^{SD} as that used originally. Interpret the results of the repeat confirmatory verification dose experiment in accordance with 6.2.8.4.

If the occurrence of these positive tests of sterility cannot be ascribed to incorrect performance of tests of sterility or incorrect delivery of VD_{max}^{SD}, or a specific bioburden-related cause, the selected sterilization dose is not substantiated and another approach for establishing a sterilization dose shall be used. Other approaches are:

a) selection and substantiation of a higher sterilization dose than that for which verification was not accepted using Method VD_{max}^{SD}, starting at Stage 3 (6.2.4);

b) Method 1;

c) Method 2; and

d) a method providing assurance, in regard to achieving maximally an SAL of 10^{-6}, equivalent to that of other methods of dose establishment.

6.3 Procedure for Method VD_{max}^{SD} for a single production batch

6.3.1 Rationale

This method is an adaptation of Method VD_{max}^{SD} and is intended to be used only for the substantiation of a selected sterilization dose for a single production batch.

6.3.2 General

6.3.2.1 In applying Method VD_{max}^{SD} for product with an average bioburden less than 1,0, the entire product item shall be used, whereas for product with an average bioburden greater than 0,9, an SIP may be used (see 5.2.5).

6.3.2.2 Product capable of supporting microbial growth should be stored under conditions that inhibit such growth for the time between manufacture of the single production batch and sterilization.

6.3.2.3 In applying Method VD_{max}^{SD}, the six stages below shall be followed.

6.3.3 Stage 1: Obtain samples of product

Select 10 product items from the single production batch, in accordance with 5.1, 5.2 (if applicable) and 5.3.

Product will also be needed to perform the verification dose experiment (see 6.3.7) and additional product can be needed to validate the adequacy of an SIP less than one (see 5.2.5) or to perform a confirmatory verification dose experiment (see 6.3.9).

6.3.4 Stage 2: Determine average bioburden

6.3.4.1 Apply the correction factor in the determination of bioburden (see ISO 11737-1).

6.3.4.2 Determine the bioburden of each of the selected product items and calculate the average bioburden.

Bioburden is generally determined on individual product items, but when the bioburden is low (e.g. less than 10), it is permissible to pool the 10 product items for the determination of average bioburden. This guidance does not apply to SIP; SIPs should not be pooled, rather a larger SIP should be chosen (see 5.2.5).

NOTE An observation of no colonies in the determination of bioburden is sometimes expressed as less than the limit of detection. Use of the limit of detection as a bioburden value in calculating average bioburden can lead to an overestimation of average bioburden. Overestimation can lead to selection of too high a sterilization dose and, in consequence, a high value of VD_{max}^{SD}, thereby affecting the validity of the verification dose experiment. The use of an approach for bioburden determination having a low limit of detection can reduce such overestimation (see ISO 11737-1:2018, A.6.1.1).

For an SIP less than 1,0, calculate the average bioburden for the entire product item (SIP equal to 1,0) by dividing the SIP batch average bioburden by the SIP value.

6.3.5 Stage 3: Obtain the selected sterilization dose

6.3.5.1 In obtaining the selected sterilization dose, the value of average bioburden for the entire product item (SIP equal to 1,0) shall be used (see 6.3.4.2).

6.3.5.2 From Table 3, obtain the selected sterilization dose. In obtaining this dose, the batch average bioburden (SIP equal to 1,0) determined in Stage 2 shall be less than or equal to the associated upper limit of the average bioburden given in Table 3.

6.3.5.3 A sterilization dose greater than the lowest dose consistent with meeting the requirement in 6.3.5.2 may be selected. A rationale for selecting a greater dose can be based on factors such as:

a) the difference between the average bioburden and the upper limit associated with the selected sterilization dose;

b) available data on the variation in the numbers and types of microorganisms that comprise the bioburden;

c) available data on the microbiological quality of similar products including the results of sterilization dose audits;

d) the materials comprising the product and the control of the microbiological quality of materials;

e) the manufacturing process and associated control and monitoring procedures, particularly steps that affect bioburden or its resistance; and

f) the manufacturing environment, particularly the extent of microbiological control and monitoring, and available data on the stability of the manufacturing environment over time.

6.3.6 Stage 4: Obtain VD_{max}^{SD}

6.3.6.1 From Table 4, identify the table in Clause 8 that gives the values of SIP equal to 1,0 VD_{max}^{SD}, SIP dose reduction factor and dose augmentation value, corresponding to different values of average bioburden, for the selected sterilization dose.

6.3.6.2 From the identified table, obtain the value of SIP equal to 1,0 VD_{max}^{SD} using the average bioburden for the entire product item (SIP equal to 1,0).

For an SIP equal to 1,0, if the average bioburden is not given in the identified table in Clause 8, use the closest tabulated value greater than the average bioburden to locate the value of SIP equal to 1,0 VD_{max}^{SD}.

For an SIP less than 1,0, use the average bioburden for the entire product item (SIP equal to 1,0), calculated in Stage 2 (6.3.4.2), to enter the identified table in Clause 8. If the calculated average bioburden is not given in the table, use the closest tabulated value greater than the average value to locate the value of SIP equal to 1,0 VD_{max}^{SD} and corresponding SIP dose reduction factor. Use Formula (1) (see 6.2.5.3) to calculate the SIP VD_{max}^{SD} (see Kowalski and Tallentire[11]).

NOTE Use of an SIP less than 1,0 is not permitted for product with an average bioburden less than 1,0 (see 6.3.2.1).

6.3.7 Stage 5: Perform verification dose experiment

6.3.7.1 Select 10 product items from the single batch of product.

6.3.7.2 Irradiate these product items at VD_{max}^{SD} obtained from the identified table in Clause 8 or derived using Formula (1), whichever is appropriate.

The highest dose to product items shall not exceed VD_{max}^{SD} by more than 10 % or 0,1 kGy, whichever is greater.

A tolerance of 0,1 kGy is allowed in order to accommodate the ability and practicality of irradiation facilities to deliver and measure VD_{max}^{SD} doses below 1,0 kGy.

The arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of VD_{max}^{SD}.

Determine the dose delivered (see 5.5).

If the highest dose to product items exceeds VD_{max}^{SD} by more than 10 % or 0,1 kGy, whichever is greater, the verification dose experiment shall be repeated.

If the arithmetic mean of the highest and lowest doses to product items is less than 90 % of VD_{max}^{SD}, the verification dose experiment may be repeated. If this mean dose is less than 90 % of VD_{max}^{SD} and, on performance of tests of sterility, acceptable results are observed (see 6.3.8), the verification dose experiment need not be repeated.

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

6.3.8 Stage 6: Interpretation of results

6.3.8.1 If no more than one positive test of sterility is obtained from the 10 tests carried out, accept verification and thereby substantiate the selected sterilization dose.

6.3.8.2 If two positive tests of sterility are obtained, perform a confirmatory verification dose experiment (see 6.3.9).

6.3.8.3 If three or more positive tests of sterility are obtained, do not accept verification as the selected sterilization dose can be inadequate.

If the occurrence of these positive tests of sterility can be ascribed to incorrect performance of the determination of bioburden, incorrect performance of tests of sterility or incorrect delivery of VD_{max}^{SD} or a specific bioburden-related cause, implement corrective action and repeat the verification dose experiment using a further 10 product items. If, as a result of corrective action, the estimate of average bioburden changes, use the VD_{max}^{SD} (6.3.6) that corresponds to the changed average bioburden. If the estimate of average bioburden is unchanged, use the same VD_{max}^{SD} as that used in the verification dose experiment that was not accepted. Interpret the results of the repeat verification dose experiment in accordance with 6.3.8.

If the occurrence of these positive tests of sterility cannot be ascribed to incorrect performance of the determination of bioburden, incorrect performance of tests of sterility or incorrect delivery of VD_{max}^{SD} or a specific bioburden-related cause, the selected sterilization dose is not substantiated and another approach for establishing a sterilization dose shall be used. Other approaches are:

a) selection and substantiation of a higher sterilization dose than that for which verification was not accepted using Method VD_{max}^{SD}, starting at Stage 3 (6.3.5);

b) Method 1;

c) Method 2; and

d) a method providing assurance, in regard to achieving maximally an SAL of 10^{-6}, equivalent to that of other methods of dose establishment.

6.3.9 Confirmatory verification dose experiment

6.3.9.1 General

If a confirmatory verification dose experiment is to be carried out (see 6.3.8.2), the three stages below shall be followed.

6.3.9.2 Stage 1: Obtain samples of product

Select 10 product items from the single production batch of product.

6.3.9.3 Stage 2: Perform confirmatory verification dose experiment

6.3.9.3.1 Irradiate these product items at VD_{max}^{SD} obtained in 6.3.6.

The highest dose to product items shall not exceed VD_{max}^{SD} by more than 10 % or 0,1 kGy, whichever is greater.

A tolerance of 0,1 kGy is allowed in order to accommodate the ability and practicality of irradiation facilities to deliver and measure VD_{max}^{SD} doses below 1,0 kGy.

The arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of VD_{max}^{SD}.

Determine the dose delivered (see 5.5).

If the highest dose to product items exceeds VD_{max}^{SD} by more than 10 % or 0,1 kGy, whichever is greater, the confirmatory verification dose experiment shall be repeated.

If the arithmetic mean of the highest and lowest doses to product items is less than 90 % of VD_{max}^{SD}, the confirmatory verification dose experiment may be repeated. If this mean dose is less than 90 % of VD_{max}^{SD} and, on performance of tests of sterility, acceptable results are observed (see 6.3.9.4), the confirmatory verification dose experiment need not be repeated.

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

6.3.9.4 Stage 3: Interpretation of results

6.3.9.4.1 If there are no positive tests of sterility from the 10 tests carried out, accept confirmatory verification and thereby substantiate the selected sterilization dose.

6.3.9.4.2 If any positive tests of sterility are obtained, do not accept verification as the selected sterilization dose can be inadequate.

If the occurrence of these positive tests of sterility can be ascribed to incorrect performance of tests of sterility or incorrect delivery of VD_{max}^{SD}, or a specific bioburden-related cause, implement corrective action and repeat the confirmatory verification dose experiment using a further 10 product items and the same VD_{max}^{SD} as that used originally. Interpret the results of the repeat confirmatory verification dose experiment in accordance with 6.3.9.4.

If the occurrence of these positive tests of sterility cannot be ascribed to incorrect performance of tests of sterility or incorrect delivery of VD_{max}^{SD}, or a specific bioburden-related cause, the selected sterilization dose is not substantiated and another approach for establishing a sterilization dose shall be used. Other approaches are:

a) selection and substantiation of a higher sterilization dose than that for which verification was not accepted using Method VD_{max}^{SD}, starting at Stage 3 (6.3.5);

b) Method 1;

c) Method 2; and

d) a method providing assurance, in regard to achieving maximally an SAL of 10^{-6}, equivalent to that of other methods of dose establishment.

7 Maintaining process effectiveness

7.1 General

For product produced as multiple production batches, periodic determinations of bioburden and sterilization dose audits are carried out to confirm the continued effectiveness of the established sterilization dose. Requirements for maintaining process effectiveness given in ISO 11137-1:2006, Clause 12 apply to a selected sterilization dose substantiated using Method VD_{max}^{SD}. None of these requirements apply to product produced as a single production batch.

7.2 Frequency of determination of bioburden

Follow requirements in ISO 11137-1.

7.3 Sterilization dose audit

7.3.1 Frequency

The frequency at which sterilization dose audits are carried out shall be in accordance with ISO 11137-1:2006, 12.1. Sterilization dose audits are not required during periods in which product is not produced. A review of environmental and manufacturing controls, together with determinations of bioburden, should be conducted in conjunction with sterilization dose audits. If the review indicates lack of control, appropriate action shall be taken.

7.3.2 Outcome

Actions resulting from the outcome of a sterilization dose audit shall apply to all product comprising the product family (see Clause 4).

7.3.3 Procedure for auditing a sterilization dose substantiated using Method VD_{max}^{SD}

7.3.3.1 General

7.3.3.1.1 For the performance of a sterilization dose audit for a selected sterilization dose, substantiated using Method VD_{max}^{SD}, use an SIP equivalent to that used originally in substantiating the sterilization dose.

7.3.3.1.2 In applying the sterilization dose audit, the four stages below shall be followed.

NOTE For a worked example, see 9.3.

7.3.3.2 Stage 1: Obtain samples of product

Select 20 product items from a single batch of product, in accordance with 5.1, 5.2 (if applicable) and 5.3.

7.3.3.3 Stage 2: Determine average bioburden

7.3.3.3.1 Apply the correction factor found from the most recent validation of the method of bioburden determination.

7.3.3.3.2 Determine the bioburden of each of 10 product items and calculate the average bioburden.

Bioburden is generally determined on individual product items, but when the bioburden is low (e.g. less than 10), it is permissible to pool the 10 product items for the determination of average bioburden. This guidance does not apply to SIP; SIPs should not be pooled, rather a larger SIP should be chosen (see 5.2.5).

NOTE 1 An observation of no colonies in the determination of bioburden is sometimes expressed as less than the limit of detection. Use of the limit of detection as a bioburden value in calculating average bioburden can lead to overestimation of the average. The use of an approach for bioburden determination having a low limit of detection can reduce such overestimation.

NOTE 2 These bioburden data are not intended to be used in obtaining the value of SIP equal to 1,0 VD_{max}^{SD} for the sterilization dose audit. They are used for process monitoring and control (e.g. trend analysis), investigation of sterilization dose audit failure and obtaining the dose augmentation value. The adjustment of the verification dose is not appropriate with each bioburden study; however, for a sustained shift in magnitude of the bioburden, dose re-establishment can substantiate the sterilization dose (see ISO 11137-1).

7.3.3.4 Stage 3: Perform verification dose experiment

7.3.3.4.1 Irradiate 10 product items at VD_{max}^{SD} used in the most recent successful substantiation of the selected sterilization dose.

The highest dose to product items shall not exceed VD_{max}^{SD} by more than 10 % or 0,1 kGy, whichever is greater.

A tolerance of 0,1 kGy is allowed in order to accommodate the ability and practicality of irradiation facilities to deliver and measure VD_{max}^{SD} doses below 1,0 kGy.

The arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of VD_{max}^{SD}.

Determine the dose delivered (see 5.5).

If the highest dose to product items exceeds VD_{max}^{SD} by more than 10 % or 0,1 kGy, whichever is greater, the verification dose experiment shall be repeated.

If the arithmetic mean of the highest and lowest doses to product items is less than 90 % of VD_{max}^{SD}, the verification dose experiment may be repeated. If this mean dose is less than 90 % of VD_{max}^{SD} and, on performance of tests of sterility, acceptable results are observed (see 7.3.3.5), the verification dose experiment need not be repeated.

7.3.3.4.2 Subject each irradiated product item individually to a test of sterility (see 5.4.1) using the media and incubation conditions used in the original dose substantiation. Record the number of positive tests of sterility.

7.3.3.5 Stage 4: Interpretation of results

7.3.3.5.1 If no more than one positive test of sterility is obtained from the 10 tests carried out, accept the sterilization dose audit.

7.3.3.5.2 If two positive tests of sterility are obtained, perform a confirmatory sterilization dose audit (see 7.3.3.6).

7.3.3.5.3 If three or more positive tests of sterility are obtained, do not accept the sterilization dose audit as the selected sterilization dose can be inadequate.

If the occurrence of these positive tests of sterility can be ascribed to incorrect performance of tests of sterility or incorrect delivery of VD_{max}^{SD}, or a specific bioburden-related cause, implement corrective action and repeat the verification dose experiment as soon as practicable using a further 10 product items from a batch manufactured under conditions that are representative of normal production and the same VD_{max}^{SD} as that used in the sterilization dose audit that was not accepted. Interpret the results of the repeat verification dose experiment in accordance with 7.3.3.5.

If the occurrence of these positive tests of sterility cannot be ascribed to incorrect performance of tests of sterility or incorrect delivery of VD_{max}^{SD}, or a specific bioburden-related cause, the following shall apply.

a) If three to six positive tests of sterility are obtained, augment the selected sterilization dose immediately (see 7.3.3.7) and re-establish the sterilization dose as soon as practicable using another approach. Other approaches are:

   1) selection and substantiation of a higher sterilization dose than that for which verification was not accepted using Method VD_{max}^{SD}, starting at Stage 1 (6.2.2 or 6.3.3, as appropriate);

   2) Method 1;

   3) Method 2; and

   4) a method providing assurance, in regard to achieving maximally an SAL of 10^{-6}, equivalent to that of other methods of dose establishment.

   Continue to use the augmented sterilization dose until re-establishment of the sterilization dose is completed.

b) If seven or more positive tests of sterility are obtained, discontinue sterilization at the selected sterilization dose. Do not augment the selected sterilization dose and do not resume sterilization until the sterilization dose is re-established using another approach. Other approaches are:

   1) selection and substantiation of a higher sterilization dose than that for which verification was not accepted using Method VD_{max}^{SD}, starting at Stage 1 (6.2.2 or 6.3.3, as appropriate);

2) Method 1;

3) Method 2; and

4) a method providing assurance, in regard to achieving maximally an SAL of 10^{-6}, equivalent to that of other methods of dose establishment.

7.3.3.6 Confirmatory sterilization dose audit

7.3.3.6.1 General

7.3.3.6.1.1 For the performance of a confirmatory sterilization dose audit for a selected sterilization dose, substantiated using Method VD_{max}^{SD}, use an SIP equivalent to that used originally in substantiating the sterilization dose.

7.3.3.6.1.2 In applying the confirmatory sterilization dose audit, the three stages below shall be followed.

7.3.3.6.2 Stage 1: Obtain samples of product

Select 10 product items from a single batch of product, in accordance with 5.1, 5.2 (if applicable) and 5.3. The 10 product items for the performance of confirmatory sterilization dose audit may be selected from either the batch used for the verification dose experiment carried out in the original sterilization dose audit (see 7.3.3) or a second batch manufactured under conditions that are representative of normal production (see 5.3).

7.3.3.6.3 Stage 2: Perform confirmatory verification dose experiment

7.3.3.6.3.1 Irradiate 10 product items at VD_{max}^{SD} used in the most recent successful substantiation of the selected sterilization dose.

The highest dose to product items shall not exceed VD_{max}^{SD} by more than 10 % or 0,1 kGy, whichever is greater.

A tolerance of 0,1 kGy is allowed in order to accommodate the ability and practicality of irradiation facilities to deliver and measure VD_{max}^{SD} doses below 1,0 kGy.

The arithmetic mean of the highest and lowest doses to product items should not be less than 90 % of VD_{max}^{SD}.

Determine the dose delivered (see 5.5).

If the highest dose to product items exceeds VD_{max}^{SD} by more than 10 % or 0,1 kGy, whichever is greater, the confirmatory verification dose experiment shall be repeated.

If the arithmetic mean of the highest and lowest doses to product items is less than 90 % of VD_{max}^{SD}, the confirmatory verification dose experiment may be repeated. If this mean dose is less than 90 % of VD_{max}^{SD} and, on performance of tests of sterility, acceptable results are observed (see 7.3.3.6.4), the confirmatory verification dose experiment need not be repeated.

7.3.3.6.3.2 Subject each irradiated product item individually to a test of sterility (see 5.4.1) using the media and incubation conditions used originally in the substantiation of the selected sterilization dose and record the number of positive tests of sterility.

7.3.3.6.4 Stage 3: Interpretation of results

Interpret the results of the confirmatory verification dose audit performed in accordance with 7.3.3.6, as follows:

a) If there are no positive tests of sterility from the 10 tests carried out, accept the sterilization dose audit.

b) If one to four positive tests of sterility are obtained, do not accept the sterilization dose audit. Augment the selected sterilization dose immediately (see 7.3.3.7) and re-establish the sterilization dose as soon as practicable using another approach. Other approaches are:

   1) selection and substantiation of a higher sterilization dose than that for which the sterilization dose audit was not accepted, starting at Stage 1 (6.2.2 or 6.3.3, as appropriate);

   2) Method 1;

   3) Method 2; and

   4) a method providing assurance, in regard to achieving maximally an SAL of 10^{-6}, equivalent to that of other methods of dose establishment.

   Continue to use the augmented sterilization dose until re-establishment of the sterilization dose is completed.

c) If five or more positive tests of sterility are obtained, do not accept the sterilization dose audit. Discontinue sterilization at the selected sterilization dose. Do not augment the selected sterilization dose and do not resume sterilization until the sterilization dose is re-established using another approach. Other approaches are:

   1) selection and substantiation of a higher sterilization dose than that for which the sterilization dose audit was not accepted, starting at Stage 1 (6.2.2 or 6.3.3, as appropriate);

   2) Method 1;

   3) Method 2; and

   4) a method providing assurance, in regard to achieving maximally an SAL of 10^{-6}, equivalent to that of other methods of dose establishment.

If the occurrence of one or more positive tests of sterility can be ascribed to incorrect performance of tests of sterility or incorrect delivery of VD_{max}^{SD}, or a specific bioburden-related cause, implement corrective action and repeat the confirmatory sterilization dose audit (see 7.3.3.6) using a further 10 product items from a batch manufactured under conditions that are representative of normal production and the same VD_{max}^{SD} as that used in the original sterilization dose substantiation. Interpret the results, in accordance with a) to c) above.

7.3.3.7 Augmentation of a sterilization dose substantiated using Method VD_{max}^{SD}

From the previously identified table in Clause 8 (see Table 4) for the selected sterilization dose, obtain the dose augmentation value corresponding to the average bioburden (SIP equal to 1,0) as determined in accordance with 7.3.3.3. If the average bioburden is not given in the table, use the closest tabulated value greater than the average bioburden to obtain the dose augmentation value. The augmented sterilization dose is the sum of the selected sterilization dose and the dose augmentation value.

7.3.4 Failure of a sterilization dose audit

Following failure of a sterilization dose audit requiring the re-establishment of the sterilization dose, the cause of failure shall be investigated and either correction or corrective action, or both, taken in accordance with ISO 11137-1:2006, 4.4. As part of the investigation, the effect of irradiating product at the sterilization dose that has failed sterilization dose audit on the achievement of the specified SAL

for previously irradiated batches of product shall be considered and a risk assessment undertaken on their suitability for use. The investigation and subsequent actions shall be recorded in accordance with ISO 11137-1:2006, 4.1.2.

NOTE It might not be possible to determine the effect of irradiation at the sterilization dose that has failed the sterilization dose audit on achievement of this SAL until the sterilization dose has been re-established.

8 Tables of values for SIP

Tables 5 to 11 contain values for SIP equal to 1,0 VDmaxSD, SIP dose reduction factor and augmentation dose corresponding to applicable values of average bioburden for selected sterilization doses of 17,5 kGy (Table 5), 20 kGy (Table 6), 22,5 kGy (Table 7), 27,5 kGy (Table 8), 30 kGy (Table 9), 32,5 kGy (Table 10) and 35 kGy (Table 11).

Table 5 — 17,5 kGy selected sterilization dose for which the upper limit of average bioburden is 9,0

SD = 17,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{17,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
Less than or equal to 0,1	0,0	NA[a]	3,5
0,15	0,6	NA[a]	3,4
0,20	1,0	NA[a]	3,3
0,25	1,3	NA[a]	3,2
0,30	1,5	NA[a]	3,2
0,35	1,7	NA[a]	3,2
0,40	1,9	NA[a]	3,1
0,45	2,0	NA[a]	3,1
0,50	2,1	NA[a]	3,1
0,60	2,4	NA[a]	3,0
0,70	2,5	NA[a]	3,0
0,80	2,7	NA[a]	3,0
0,90	2,8	NA[a]	2,9
1,0	2,9	2,92	2,9
1,5	3,3	2,83	2,8
2,0	3,6	2,78	2,8
2,5	3,8	2,74	2,7
3,0	3,7	2,50	2,8
3,5	3,6	2,32	2,8
4,0	3,5	2,17	2,8
4,5	3,4	2,05	2,8
5,0	3,3	1,95	2,8
5,5	3,3	1,87	2,9
6,0	3,2	1,79	2,9
6,5	3,1	1,73	2,9
7,0	3,1	1,67	2,9
7,5	3,0	1,62	2,9
8,0	3,0	1,57	2,9

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 5 *(continued)*

SD = 17,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{17,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
8,5	3,0	1,53	2,9
9,0	2,9	1,49	2,9
[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.			

Table 6 — 20 kGy selected sterilization dose for which the upper limit of average bioburden is 45

SD = 20 kGy			
Average bioburden	**SIP equal to 1,0 VD_{max}^{20}** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
less than or equal to 0,1	0,0	NA[a]	4,0
0,15	0,7	NA[a]	3,9
0,20	1,1	NA[a]	3,8
0,25	1,5	NA[a]	3,7
0,30	1,7	NA[a]	3,7
0,35	2,0	NA[a]	3,6
0,40	2,1	NA[a]	3,6
0,45	2,3	NA[a]	3,5
0,50	2,5	NA[a]	3,5
0,60	2,7	NA[a]	3,5
0,70	2,9	NA[a]	3,4
0,80	3,1	NA[a]	3,4
0,90	3,2	NA[a]	3,4
1,0	3,3	3,33	3,3
1,5	3,8	3,24	3,2
2,0	4,1	3,17	3,2
2,5	4,4	3,13	3,1
3,0	4,6	3,09	3,1
3,5	4,7	3,06	3,1
4,0	4,9	3,03	3,0
4,5	5,0	3,01	3,0
5,0	5,1	2,99	3,0
5,5	5,2	2,97	3,0
6,0	5,2	2,95	3,0
6,5	5,3	2,94	2,9
7,0	5,4	2,92	2,9
7,5	5,5	2,91	2,9
8,0	5,5	2,88	2,9
8,5	5,5	2,82	2,9
9,0	5,4	2,77	2,9
9,5	5,4	2,72	2,9
[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.			

Table 6 *(continued)*

SD = 20 kGy			
Average bioburden	**SIP equal to 1,0 VD_{max}^{20}** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
10	5,3	2,67	2,9
11	5,3	2,58	2,9
12	5,2	2,51	3,0
13	5,2	2,44	3,0
14	5,1	2,39	3,0
15	5,1	2,33	3,0
16	5,0	2,28	3,0
17	5,0	2,24	3,0
18	5,0	2,20	3,0
19	4,9	2,16	3,0
20	4,9	2,13	3,0
21	4,9	2,10	3,0
22	4,8	2,07	3,0
23	4,8	2,04	3,0
24	4,8	2,01	3,0
25	4,8	1,99	3,0
26	4,8	1,97	3,1
27	4,7	1,94	3,1
28	4,7	1,92	3,1
29	4,7	1,90	3,1
30	4,7	1,89	3,1
31	4,7	1,87	3,1
32	4,6	1,85	3,1
33	4,6	1,83	3,1
34	4,6	1,81	3,1
35	4,6	1,80	3,1
36	4,6	1,78	3,1
37	4,6	1,77	3,1
38	4,5	1,76	3,1
39	4,5	1,74	3,1
40	4,5	1,73	3,1
41	4,5	1,72	3,1
42	4,5	1,71	3,1
43	4,5	1,70	3,1
44	4,5	1,68	3,1
45	4,4	1,67	3,1

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 7 — 22,5 kGy selected sterilization dose for which the upper limit of average bioburden is 220

SD = 22,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{22,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
less than or equal to 0,1	0,0	NA[a]	4,5
0,15	0,8	NA[a]	4,3
0,20	1,3	NA[a]	4,2
0,25	1,7	NA[a]	4,2
0,30	2,0	NA[a]	4,1
0,35	2,2	NA[a]	4,1
0,40	2,4	NA[a]	4,0
0,45	2,6	NA[a]	4,0
0,50	2,8	NA[a]	3,9
0,60	3,0	NA[a]	3,9
0,70	3,3	NA[a]	3,8
0,80	3,4	NA[a]	3,8
0,90	3,6	NA[a]	3,8
1,0	3,8	3,75	3,8
1,5	4,3	3,64	3,6
2,0	4,6	3,57	3,6
2,5	4,9	3,52	3,5
3,0	5,1	3,47	3,5
3,5	5,3	3,44	3,4
4,0	5,5	3,41	3,4
4,5	5,6	3,38	3,4
5,0	5,7	3,36	3,4
5,5	5,8	3,34	3,3
6,0	5,9	3,32	3,3
6,5	6,0	3,30	3,3
7,0	6,1	3,29	3,3
7,5	6,1	3,27	3,3
8,0	6,2	3,26	3,3
8,5	6,3	3,25	3,2
9,0	6,3	3,24	3,2
9,5	6,4	3,22	3,2
10	6,4	3,21	3,2
11	6,5	3,20	3,2
12	6,6	3,18	3,2
13	6,7	3,16	3,2
14	6,8	3,15	3,1
15	6,8	3,14	3,1
16	6,9	3,12	3,1
17	6,9	3,11	3,1

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 7 *(continued)*

SD = 22,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{22,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
18	7,0	3,10	3,1
19	7,0	3,09	3,1
20	7,1	3,08	3,1
21	7,1	3,07	3,1
22	7,2	3,06	3,1
23	7,2	3,06	3,1
24	7,3	3,05	3,0
25	7,3	3,03	3,0
26	7,3	3,00	3,1
27	7,2	2,97	3,1
28	7,2	2,94	3,1
29	7,2	2,92	3,1
30	7,2	2,89	3,1
31	7,2	2,87	3,1
32	7,1	2,85	3,1
33	7,1	2,82	3,1
34	7,1	2,80	3,1
35	7,1	2,78	3,1
36	7,1	2,74	3,1
37	7,1	2,74	3,1
38	7,0	2,73	3,1
39	7,0	2,71	3,1
40	7,0	2,69	3,1
41	7,0	2,68	3,1
42	7,0	2,66	3,1
43	7,0	2,65	3,1
44	7,0	2,63	3,1
45	6,9	2,62	3,1
46	6,9	2,60	3,1
47	6,9	2,59	3,1
48	6,9	2,58	3,1
49	6,9	2,56	3,1
50	6,9	2,55	3,1
55	6,8	2,50	3,1
60	6,8	2,44	3,1
65	6,8	2,40	3,2
70	6,7	2,36	3,2
75	6,7	2,32	3,2
80	6,7	2,29	3,2
85	6,6	2,26	3,2

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 7 *(continued)*

SD = 22,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{22,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
90	6,6	2,23	3,2
95	6,6	2,21	3,2
100	6,5	2,18	3,2
110	6,5	2,14	3,2
120	6,5	2,09	3,2
130	6,4	2,06	3,2
140	6,4	2,03	3,2
150	6,4	2,00	3,2
160	6,3	1,98	3,2
170	6,3	1,95	3,2
180	6,3	1,93	3,2
190	6,2	1,90	3,3
200	6,2	1,88	3,3
220	6,2	1,85	3,3
[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.			

Table 8 — 27,5 kGy selected sterilization dose for which the upper limit of average bioburden is 5 000

SD = 27,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{27,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
less than or equal to 0,10	0,0	NA[a]	5,5
0,15	0,9	NA[a]	5,3
0,20	1,6	NA[a]	5,2
0,25	2,0	NA[a]	5,1
0,30	2,4	NA[a]	5,0
0,35	2,7	NA[a]	5,0
0,40	3,0	NA[a]	4,9
0,45	3,2	NA[a]	4,9
0,50	3,4	NA[a]	4,8
0,60	3,7	NA[a]	4,8
0,70	4,0	NA[a]	4,7
0,80	4,2	NA[a]	4,7
0,90	4,4	NA[a]	4,6
1,0	4,6	4,58	4,6
2,0	5,7	4,36	4,4
3,0	6,3	4,25	4,2
4,0	6,7	4,17	4,2
5,0	7,0	4,11	4,1
6,0	7,2	4,06	4,1
[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.			

Table 8 *(continued)*

SD = 27,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{27,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
7,0	7,4	4,02	4,0
8,0	7,6	3,98	4,0
9,0	7,7	3,95	4,0
10	7,9	3,93	3,9
11	8,0	3,91	3,9
12	8,1	3,88	3,9
13	8,2	3,87	3,9
14	8,3	3,85	3,8
15	8,3	3,83	3,8
16	8,4	3,82	3,8
17	8,5	3,80	3,8
18	8,5	3,79	3,8
19	8,6	3,78	3,8
20	8,7	3,77	3,8
21	8,7	3,76	3,8
22	8,8	3,75	3,7
23	8,8	3,74	3,7
24	8,9	3,73	3,7
25	8,9	3,72	3,7
26	9,0	3,71	3,7
27	9,0	3,70	3,7
28	9,0	3,69	3,7
29	9,1	3,69	3,7
30	9,1	3,68	3,7
31	9,1	3,67	3,7
32	9,2	3,66	3,7
33	9,2	3,66	3,7
34	9,2	3,65	3,7
35	9,3	3,65	3,6
36	9,3	3,64	3,6
37	9,3	3,63	3,6
38	9,4	3,63	3,6
39	9,4	3,62	3,6
40	9,4	3,62	3,6
41	9,4	3,61	3,6
42	9,5	3,61	3,6
43	9,5	3,60	3,6
44	9,5	3,60	3,6
45	9,5	3,59	3,6
46	9,6	3,59	3,6

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 8 *(continued)*

SD = 27,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{27,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
47	9,6	3,58	3,6
48	9,6	3,58	3,6
49	9,6	3,58	3,6
50	9,6	3,57	3,6
55	9,7	3,55	3,6
60	9,8	3,54	3,5
65	9,9	3,52	3,5
70	10,0	3,51	3,5
75	10,0	3,49	3,5
80	10,1	3,48	3,5
85	10,2	3,47	3,5
90	10,2	3,46	3,5
95	10,3	3,45	3,4
100	10,3	3,44	3,4
110	10,4	3,42	3,4
120	10,5	3,40	3,4
130	10,6	3,39	3,4
140	10,6	3,38	3,4
150	10,7	3,36	3,4
160	10,7	3,35	3,4
170	10,8	3,34	3,3
180	10,8	3,33	3,3
190	10,9	3,32	3,3
200	10,9	3,31	3,3
220	11,0	3,30	3,3
240	11,1	3,28	3,3
260	11,1	3,26	3,3
280	11,1	3,21	3,3
300	11,1	3,18	3,3
325	11,0	3,14	3,3
350	11,0	3,10	3,3
375	11,0	3,07	3,3
400	10,9	3,04	3,3
425	10,9	3,01	3,3
450	10,9	2,98	3,3
475	10,9	2,96	3,3
500	10,9	2,93	3,3
525	10,8	2,91	3,3
550	10,8	2,89	3,3
575	10,8	2,87	3,3

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 8 *(continued)*

SD = 27,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{27,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
600	10,8	2,85	3,3
650	10,8	2,82	3,4
700	10,7	2,79	3,4
750	10,7	2,76	3,4
800	10,7	2,73	3,4
850	10,7	2,71	3,4
900	10,6	2,69	3,4
950	10,6	2,67	3,4
1 000	10,6	2,65	3,4
1 050	10,6	2,63	3,4
1 100	10,6	2,61	3,4
1 150	10,6	2,60	3,4
1 200	10,5	2,58	3,4
1 250	10,5	2,57	3,4
1 300	10,5	2,55	3,4
1 350	10,5	2,54	3,4
1 400	10,5	2,53	3,4
1 450	10,5	2,51	3,4
1 500	10,5	2,50	3,4
1 550	10,4	2,49	3,4
1 600	10,4	2,48	3,4
1 650	10,4	2,47	3,4
1 700	10,4	2,46	3,4
1 750	10,4	2,45	3,4
1 800	10,4	2,44	3,4
1 850	10,4	2,43	3,4
1 900	10,4	2,42	3,4
1 950	10,4	2,41	3,4
2 000	10,4	2,41	3,4
2 100	10,3	2,39	3,4
2 200	10,3	2,37	3,4
2 300	10,3	2,36	3,4
2 400	10,3	2,35	3,4
2 500	10,3	2,34	3,4
2 600	10,3	2,32	3,4
2 700	10,3	2,31	3,5
2 800	10,2	2,30	3,5
2 900	10,2	2,29	3,5
3 000	10,2	2,28	3,5
3 200	10,2	2,26	3,5

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 8 *(continued)*

SD = 27,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{27,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
3 400	10,2	2,24	3,5
3 600	10,2	2,23	3,5
3 800	10,1	2,21	3,5
4 000	10,1	2,20	3,5
4 200	10,1	2,19	3,5
4 400	10,1	2,17	3,5
4 600	10,1	2,16	3,5
4 800	10,1	2,15	3,5
5 000	10,1	2,14	3,5

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 9 — 30 kGy selected sterilization dose for which the upper limit of average bioburden is 23 000

SD = 30 kGy			
Average bioburden	**SIP equal to 1,0 VD_{max}^{30}** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
less than or equal to 0,10	0,0	NA[a]	6,0
0,15	1,0	NA[a]	5,8
0,20	1,7	NA[a]	5,7
0,25	2,2	NA[a]	5,6
0,30	2,6	NA[a]	5,5
0,35	2,9	NA[a]	5,4
0,40	3,2	NA[a]	5,4
0,45	3,5	NA[a]	5,3
0,50	3,7	NA[a]	5,3
0,60	4,0	NA[a]	5,2
0,70	4,3	NA[a]	5,1
0,80	4,6	NA[a]	5,1
0,90	4,8	NA[a]	5,0
1,0	5,0	5,00	5,0
2,0	6,2	4,76	4,8
3,0	6,8	4,63	4,6
4,0	7,3	4,54	4,5
5,0	7,6	4,48	4,5
6,0	7,9	4,43	4,4
7,0	8,1	4,38	4,4
8,0	8,3	4,35	4,3
9,0	8,4	4,31	4,3
10	8,6	4,29	4,3
11	8,7	4,26	4,3

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 9 *(continued)*

SD = 30 kGy			
Average bioburden	**SIP equal to 1,0 VD_{max}^{30}** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
12	8,8	4,24	4,2
13	8,9	4,22	4,2
14	9,0	4,20	4,2
15	9,1	4,18	4,2
16	9,2	4,16	4,2
17	9,3	4,15	4,1
18	9,3	4,13	4,1
19	9,4	4,12	4,1
20	9,5	4,11	4,1
21	9,5	4,10	4,1
22	9,6	4,09	4,1
23	9,6	4,08	4,1
24	9,7	4,06	4,1
25	9,7	4,06	4,1
26	9,8	4,05	4,0
27	9,8	4,04	4,0
28	9,9	4,03	4,0
29	9,9	4,02	4,0
30	9,9	4,01	4,0
31	10,0	4,00	4,0
32	10,0	4,00	4,0
33	10,0	3,99	4,0
34	10,1	3,98	4,0
35	10,1	3,98	4,0
36	10,1	3,97	4,0
37	10,2	3,96	4,0
38	10,2	3,96	4,0
39	10,2	3,95	4,0
40	10,3	3,95	3,9
41	10,3	3,94	3,9
42	10,3	3,94	3,9
43	10,3	3,93	3,9
44	10,4	3,92	3,9
45	10,4	3,92	3,9
46	10,4	3,92	3,9
47	10,4	3,91	3,9
48	10,5	3,91	3,9
49	10,5	3,90	3,9
50	10,5	3,90	3,9
55	10,6	3,88	3,9

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 9 *(continued)*

SD = 30 kGy			
Average bioburden	**SIP equal to 1,0 VD_{max}^{30}** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
60	10,7	3,86	3,9
65	10,8	3,84	3,8
70	10,9	3,82	3,8
75	11,0	3,81	3,8
80	11,0	3,80	3,8
85	11,1	3,78	3,8
90	11,1	3,77	3,8
95	11,2	3,76	3,8
100	11,3	3,75	3,8
110	11,3	3,73	3,7
120	11,4	3,71	3,7
130	11,5	3,70	3,7
140	11,6	3,68	3,7
150	11,7	3,67	3,7
160	11,7	3,66	3,7
170	11,8	3,65	3,6
180	11,8	3,63	3,6
190	11,9	3,62	3,6
200	11,9	3,61	3,6
220	12,0	3,60	3,6
240	12,1	3,58	3,6
260	12,2	3,57	3,6
280	12,2	3,55	3,6
300	12,3	3,54	3,5
325	12,4	3,52	3,5
350	12,4	3,51	3,5
375	12,5	3,50	3,5
400	12,6	3,49	3,5
425	12,6	3,48	3,5
450	12,7	3,47	3,5
475	12,7	3,46	3,5
500	12,8	3,45	3,4
525	12,8	3,44	3,4
550	12,8	3,43	3,4
575	12,9	3,42	3,4
600	12,9	3,42	3,4
650	13,0	3,40	3,4
700	13,0	3,39	3,4
750	13,1	3,38	3,4
800	13,2	3,37	3,4

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 9 *(continued)*

SD = 30 kGy			
Average bioburden	**SIP equal to 1,0 VD_{max}^{30}** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
850	13,2	3,35	3,4
900	13,1	3,32	3,4
950	13,1	3,30	3,4
1 000	13,1	3,27	3,4
1 050	13,1	3,25	3,4
1 100	13,1	3,23	3,4
1 150	13,0	3,21	3,4
1 200	13,0	3,19	3,4
1 250	13,0	3,18	3,4
1 300	13,0	3,16	3,4
1 350	13,0	3,14	3,4
1 400	13,0	3,13	3,4
1 450	13,0	3,11	3,4
1 500	13,0	3,10	3,4
1 550	12,9	3,09	3,4
1 600	12,9	3,07	3,4
1 650	12,9	3,06	3,4
1 700	12,9	3,05	3,4
1 750	12,9	3,04	3,4
1 800	12,9	3,03	3,4
1 850	12,9	3,02	3,4
1 900	12,9	3,01	3,4
1 950	12,9	3,00	3,4
2 000	12,9	2,99	3,4
2 100	12,8	2,97	3,4
2 200	12,8	2,95	3,4
2 300	12,8	2,93	3,4
2 400	12,8	2,92	3,4
2 500	12,8	2,90	3,4
2 600	12,8	2,89	3,4
2 700	12,8	2,88	3,5
2 800	12,7	2,86	3,5
2 900	12,7	2,85	3,5
3 000	12,7	2,84	3,5
3 200	12,7	2,82	3,5
3 400	12,7	2,80	3,5
3 600	12,7	2,78	3,5
3 800	12,6	2,76	3,5
4 000	12,6	2,74	3,5
4 200	12,6	2,73	3,5

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 9 *(continued)*

SD = 30 kGy			
Average bioburden	**SIP equal to 1,0 VD_{max}^{30}** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
4 400	12,6	2,71	3,5
4 600	12,6	2,70	3,5
4 800	12,6	2,69	3,5
5 000	12,6	2,67	3,5
5 300	12,5	2,65	3,5
5 600	12,5	2,63	3,5
5 900	12,5	2,62	3,5
6 200	12,5	2,61	3,5
6 500	12,5	2,59	3,5
6 800	12,5	2,58	3,5
7 100	12,4	2,56	3,5
7 400	12,4	2,55	3,5
7 700	12,4	2,54	3,5
8 000	12,4	2,53	3,5
8 500	12,4	2,52	3,5
9 000	12,4	2,50	3,5
9 500	12,4	2,48	3,5
10 000	12,4	2,47	3,5
10 500	12,3	2,46	3,5
11 000	12,3	2,44	3,5
11 500	12,3	2,43	3,5
12 000	12,3	2,42	3,5
13 000	12,3	2,40	3,5
14 000	12,3	2,38	3,6
15 000	12,2	2,36	3,6
16 000	12,2	2,35	3,6
17 000	12,2	2,33	3,6
18 000	12,2	2,32	3,6
19 000	12,2	2,31	3,6
20 000	12,2	2,29	3,6
21 000	12,1	2,28	3,6
22 000	12,1	2,27	3,6
23 000	12,1	2,26	3,6

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 10 — 32,5 kGy selected sterilization dose for which the upper limit of average bioburden is 100 000

SD = 32,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{32,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
less than or equal to 0,10	0,0	NA[a]	6,5
0,15	1,1	NA[a]	6,3
0,20	1,8	NA[a]	6,1
0,25	2,4	NA[a]	6,0
0,30	2,8	NA[a]	5,9
0,35	3,2	NA[a]	5,9
0,40	3,5	NA[a]	5,8
0,45	3,8	NA[a]	5,7
0,50	4,0	NA[a]	5,7
0,60	4,4	NA[a]	5,6
0,70	4,7	NA[a]	5,6
0,80	5,0	NA[a]	5,5
0,90	5,2	NA[a]	5,5
1,0	5,4	5,42	5,4
2,0	6,7	5,16	5,2
3,0	7,4	5,02	5,0
4,0	7,9	4,92	4,9
5,0	8,2	4,85	4,9
6,0	8,5	4,79	4,8
7,0	8,8	4,75	4,7
8,0	9,0	4,71	4,7
9,0	9,1	4,67	4,7
10	9,3	4,64	4,6
11	9,4	4,62	4,6
12	9,5	4,59	4,6
13	9,7	4,57	4,6
14	9,8	4,55	4,5
15	9,9	4,53	4,5
16	9,9	4,51	4,5
17	10,0	4,49	4,5
18	10,1	4,48	4,5
19	10,2	4,47	4,5
20	10,2	4,45	4,5
21	10,3	4,44	4,4
22	10,4	4,43	4,4
23	10,4	4,41	4,4
24	10,5	4,40	4,4
25	10,5	4,39	4,4
26	10,6	4,38	4,4

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 10 *(continued)*

SD = 32,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{32,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
27	10,6	4,37	4,4
28	10,7	4,36	4,4
29	10,7	4,36	4,4
30	10,8	4,35	4,3
31	10,8	4,34	4,3
32	10,8	4,33	4,3
33	10,9	4,32	4,3
34	10,9	4,32	4,3
35	11,0	4,31	4,3
36	11,0	4,30	4,3
37	11,0	4,29	4,3
38	11,1	4,29	4,3
39	11,1	4,28	4,3
40	11,1	4,28	4,3
41	11,2	4,27	4,3
42	11,2	4,26	4,3
43	11,2	4,26	4,3
44	11,2	4,25	4,3
45	11,3	4,25	4,2
46	11,3	4,24	4,2
47	11,3	4,24	4,2
48	11,3	4,23	4,2
49	11,4	4,23	4,2
50	11,4	4,22	4,2
55	11,5	4,20	4,2
60	11,6	4,18	4,2
65	11,7	4,16	4,2
70	11,8	4,14	4,1
75	11,9	4,13	4,1
80	11,9	4,11	4,1
85	12,0	4,10	4,1
90	12,1	4,09	4,1
95	12,1	4,07	4,1
100	12,2	4,06	4,1
110	12,3	4,04	4,0
120	12,4	4,02	4,0
130	12,5	4,01	4,0
140	12,6	3,99	4,0
150	12,6	3,98	4,0
160	12,7	3,96	4,0

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 10 *(continued)*

SD = 32,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{32,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
170	12,8	3,95	3,9
180	12,8	3,94	3,9
190	12,9	3,93	3,9
200	12,9	3,92	3,9
220	13,0	3,90	3,9
240	13,1	3,88	3,9
260	13,2	3,86	3,9
280	13,3	3,85	3,8
300	13,3	3,83	3,8
325	13,4	3,82	3,8
350	13,5	3,80	3,8
375	13,5	3,79	3,8
400	13,6	3,78	3,8
425	13,7	3,77	3,8
450	13,7	3,76	3,8
475	13,8	3,75	3,7
500	13,8	3,74	3,7
525	13,9	3,73	3,7
550	13,9	3,72	3,7
575	13,9	3,71	3,7
600	14,0	3,70	3,7
650	14,1	3,69	3,7
700	14,1	3,67	3,7
750	14,2	3,66	3,7
800	14,2	3,65	3,7
850	14,3	3,64	3,6
900	14,4	3,63	3,6
950	14,4	3,62	3,6
1 000	14,4	3,61	3,6
1 050	14,5	3,60	3,6
1 100	14,5	3,59	3,6
1 150	14,6	3,59	3,6
1 200	14,6	3,58	3,6
1 250	14,6	3,57	3,6
1 300	14,7	3,57	3,6
1 350	14,7	3,56	3,6
1 400	14,7	3,55	3,6
1 450	14,8	3,55	3,5
1 500	14,8	3,54	3,5
1 550	14,8	3,54	3,5

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.

Table 10 *(continued)*

SD = 32,5 kGy			
Average bioburden	**SIP equal to 1,0 $VD_{max}^{32,5}$** (kGy)	**SIP dose reduction factor**	**Dose augmentation value** (kGy)
1 600	14,8	3,53	3,5
1 650	14,9	3,53	3,5
1 700	14,9	3,52	3,5
1 750	14,9	3,52	3,5
1 800	14,9	3,51	3,5
1 850	15,0	3,51	3,5
1 900	15,0	3,50	3,5
1 950	15,0	3,50	3,5
2 000	15,0	3,49	3,5
2 100	15,1	3,49	3,5
2 200	15,1	3,48	3,5
2 300	15,1	3,47	3,5
2 400	15,2	3,46	3,5
2 500	15,2	3,46	3,5
2 600	15,2	3,45	3,5
2 700	15,3	3,44	3,5
2 800	15,2	3,43	3,5
2 900	15,2	3,41	3,5
3 000	15,2	3,40	3,5
3 200	15,2	3,37	3,5
3 400	15,2	3,35	3,5
3 600	15,2	3,33	3,5
3 800	15,1	3,31	3,5
4 000	15,1	3,29	3,5
4 200	15,1	3,27	3,5
4 400	15,1	3,25	3,5
4 600	15,1	3,23	3,5
4 800	15,1	3,22	3,5
5 000	15,1	3,20	3,5
5 300	15,0	3,18	3,5
5 600	15,0	3,16	3,5
5 900	15,0	3,14	3,5
6 200	15,0	3,13	3,5
6 500	15,0	3,11	3,5
6 800	15,0	3,09	3,5
7 100	14,9	3,08	3,5
7 400	14,9	3,07	3,5
7 700	14,9	3,05	3,5
8 000	14,9	3,04	3,5
8 500	14,9	3,02	3,5

[a] Not applicable: SIP equal to 1,0 required; see 6.2.1.1 and 6.3.2.1.