TECHNICAL SPECIFICATION

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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 de stérilisation choisie: méthode VD_{max}^{SD}

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Foreword

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

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

In other circumstances, particularly when there is an urgent market requirement for such documents, a technical committee may decide to publish other types of normative document:

— an ISO Publicly Available Specification (ISO/PAS) represents an agreement between technical experts in an ISO working group and is accepted for publication if it is approved by more than 50 % of the members of the parent committee casting a vote;

— an ISO Technical Specification (ISO/TS) represents an agreement between the members of a technical committee and is accepted for publication if it is approved by 2/3 of the members of the committee casting a vote.

An ISO/PAS or ISO/TS is reviewed after three years in order to decide whether it will be confirmed for a further three years, revised to become an International Standard, or withdrawn. If the ISO/PAS or ISO/TS is confirmed, it is reviewed again after a further three years, at which time it must either be transformed into an International Standard or be withdrawn.

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

ISO/TS 13004 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products.*

Introduction

This Technical Specification is intended to be used in conjunction with ISO 11137-1, *Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*. 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} 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 Technical Specification 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, 20, 22,5, 27,5, 30, 32,5 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 Technical Specification. The seven methods in this Technical Specification 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 Technical Specification 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 Technical Specification 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[6] and, from subsequent evaluations involving computational techniques (Kowalski, Aoshuang and Tallentire[7]) and field evaluations (Kowalski et al[8]), it was concluded that the method is soundly based. An overview of the method and aspects of putting it into practice are provided in Kowalski and Tallentire.[9][10] Application of the Method VD_{max} approach to doses other than 25 kGy is discussed in Kowalski and Tallentire.[11][12]

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 ISO 11137 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. Compliance with the requirements for controlling the quality of raw materials, the manufacturing environment, the health, hygiene and attire of personnel and for establishing the basic properties of packaging material is essential.

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

1 Scope

1.1 Inclusions

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

NOTE 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.

1.2 Exclusions

This method is for the substantiation of a selected sterilization dose of 17,5, 20, 22,5, 27,5, 30, 32,5, or 35 kGy only and is not used to substantiate other sterilization doses. 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 The methods for substantiation of selected sterilization doses of 25 kGy and 15 kGy are not included in this Technical Specification; they are described in ISO 11137-2.

1.3 Application

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

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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

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

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

3 Terms and definitions

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

3.1
batch
defined quantity of product, intended or purported to be uniform in character and quality, that has been produced during a defined cycle of manufacture

[SOURCE: ISO/TS 11139:2006, 2.1]

3.2
bioburden
population of viable microorganisms on or in product and/or sterile barrier system

[SOURCE: ISO/TS 11139:2006, 2.2]

3.3
correction
action to eliminate a detected nonconformity

Note 1 to entry: A correction can be made in conjunction with corrective action (3.4).

[SOURCE: ISO 9000:2005, 3.6.6, modified]

3.4
corrective action
action to eliminate the cause of a detected nonconformity or other undesirable situation

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 and corrective action.

[SOURCE: ISO 9000:2005, 3.6.5]

3.5
dose
absorbed dose
quantity of ionizing radiation energy imparted per unit mass of 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 11137-1:2006, 3.1, modified]

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

[SOURCE: ISO 11137-1:2006, 3.10]

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 portion thereof, and the test medium

[SOURCE: ISO 11137-2:2012, 3.1.3]

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

[SOURCE: ISO/TS 11139:2006, 2.20]

3.9
medical device
instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material, or other related article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific 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 for medical purposes by means of *in vitro* examination of specimens derived from the human body;

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

Note 1 to entry: This definition from ISO 13485 has been developed by the Global Harmonization Task Force (GHTF 2002)

[SOURCE: ISO 13485:2003, 3.7, modified]

3.10
Method VD_{max}
procedure for sterilization dose substantiation that uses the maximal verification dose for a given bioburden, consistent with the attainment of a 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.

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/TS 11139:2006, 2.26]

3.12
packaging system
combination of the sterile barrier system and protective packaging

[SOURCE: ISO/TS 11139:2006, 2.28]

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

[SOURCE: ISO 11137-2:2012, 3.1.8]

3.14
product
result of a process

Note 1 to entry: For the purposes of sterilization standards, product is tangible and can be raw material(s), intermediate(s), sub-assembly(ies) or health care product(s)

[SOURCE: ISO 9000:2005, 3.4.2, modified]

3.15
sample item portion
SIP
defined portion of a health care product that is tested

[SOURCE: ISO 11137-2:2012, 3.1.9]

3.16
sterile barrier system
minimum package that prevents ingress of microorganisms and allows aseptic presentation of product at the point of use

[SOURCE: ISO/TS 11139:2006, 2.44]

3.17
sterility
state of being free from viable microorganisms

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

[SOURCE: ISO/TS 11139:2006, 2.45]

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

Note 1 to entry: The term SAL takes a quantitative value, generally 10^{-6} or 10^{-3}. When applying this quantitative value to assurance of sterility, an SAL of 10^{-6} has a lower value but provides a greater assurance of sterility than an SAL of 10^{-3}.

[SOURCE: ISO/TS 11139:2006, 2.46]

3.19
sterilization
validated process used to render product free from viable microorganisms

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/TS 11139:2006, 2.47]

3.20
sterilization dose
SD
dose selected to achieve the specified requirements for sterility

[SOURCE: ISO 11137-1:2006, 3.40, modified]

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

[SOURCE: ISO 11137-2:2012, 3.2.12]

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

[SOURCE: ISO/TS 11139:2006, 2.54]

3.23
verification dose
dose predicted to give a predetermined SAL greater than or equal to 10^{-2} used in establishing the sterilization dose

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

3.24
VD_{max}^{SD}
maximal verification dose for a particular selected sterilization dose (SD) obtained in using Method VD_{max}^{SD}

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, changes that occur in other members of the product family might 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 might be sourced from more than one location;

b) components;

c) product design and size;

d) manufacturing processes;

e) manufacturing equipment;

f) manufacturing environment;

g) manufacturing location.

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

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

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

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

a) geographic and/or climatic differences between locations;

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

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

4.3 Designation of product to represent a product family

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 could be considered as the master product. In such circumstances, any one of these products may be selected as the master product to represent the family, either

a) at random, or

b) according to a documented procedure to include the different products each of which could 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) according to a documented procedure to include different members of the product family. The manufacturing volume and availability of product should be considered in the selection of the equivalent product to represent the product family.

4.3.4 Simulated product

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

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

A simulated product 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 product and/or processes that might affect membership of product families shall be allocated to competent personnel. Such review shall be performed at least annually. The outcome of the review shall be recorded in accordance with 4.1.2 of ISO 11137-1:2006.

4.4.2 Modification to product and/or manufacturing process

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

4.4.3 Records

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

4.5 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 might be higher.
Kit of procedure-related health care products [a]	Each type of health care product comprising the kit	Each health care product is used independently in clinical practice.

[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 in accordance with Table 1. When the use of an entire product is not practicable, a selected portion of product (SIP) may be substituted. The SIP should be as large a portion of the item as practicable and should be of a size that can be handled during testing.

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

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 or equal to 0,9.

5.2.3 If the bioburden is evenly distributed on and/or in the item, the SIP may be selected from any portion of the item. If the bioburden is not evenly distributed, the SIP shall consist of either

a) portions of product selected at random that proportionally represent each of the materials from which the product is made, or

b) the portion of the product that is considered to be the most severe challenge to the sterilization process.

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