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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.

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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.

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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/

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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]

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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]

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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]

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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.

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