TECHNICAL SPECIFICATION

ISO/TS 13409

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Sterilization of health care products — Radiation sterilization — Substantiation of 25 kGy as a sterilization dose for small or infrequent production batches

Stérilisation des produits de santé — Stérilisation par irradiation — Justification d'une dose de stérilisation de 25 kGy pour des lots de fabrication de faible volume ou intermittents

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 3.

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 with a view to deciding whether it should be confirmed for a further three years, revised to become an International Standard, or withdrawn. In the case of a confirmed ISO/PAS or ISO/TS, it is reviewed again after six years at which time it has to be either transformed into an International Standard or withdrawn.

Attention is drawn to the possibility that some of the elements of ISO/TS 13409 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO/TS 13409 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

Introduction

ISO 11137:1995, *Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization*, specifies the requirements for assuring that the activities associated with the process of radiation sterilization are performed properly. One of the activities encompassed within that International Standard is the selection of the dose of radiation to be applied to health care products to render them sterile (the sterilization dose). ISO 11137:1995 specifies that one of two approaches be used to select the sterilization dose ; either

a) the selection of a product specific sterilization dose, or

b) the application of a minimum dose of 25 kGy following substantiation of the appropriateness of this dose.

Annex B to ISO 11137:1995 describes two methods of selecting a sterilization dose. These methods are designated Method 1 and Method 2. The basis for these methods owes much to the ideas first propounded by Tallentire [8], [9], [10]. Subsequently, standardized methods were developed [4], [5], [11] which formed the basis of the dose substantiation procedures put forward in the Association for the Advancement of Medical Instrumentation *Guideline for gamma radiation sterilization* (AAMI, 1984).

These methods of selection of sterilization dose use data derived from the inactivation of the microbial population in its natural state, and are based on a probability model for the inactivation of microbial populations. The probability model, as applied to bioburden made up of a mixture of microbial species, assumes that each species has its own unique D_{10} values. In the model, the probability that a particular item will be sterile after exposure to a given dose of radiation is defined in terms of the initial number of organisms on the item prior to irradiation, and their D_{10} values.

The application of Methods 1 and 2 as described in annex B of ISO 11137:1995 requires that a relatively large number of product items, drawn from a number of separate production batches, be used to establish the sterilization dose. This is not always practicable. Health care manufacturers regularly produce new products and they are also, on occasion, required to manufacture a single batch of a product for a special order, field trial or clinical investigation. In addition, batches of many health care products are small and might be produced infrequently (that is, less than once every three months). For products manufactured in all these situations, determination and maintenance of a validated sterilization dose is as important as for large production batches. The method described in this Technical Specification provides guidance on how to allow substantiation of 25 kGy as an appropriate sterilization dose within the limitations stipulated in the method.

The present method is based on Method 1, described in ISO 11137:1995, B.3.4.1 to B.3.4.1.3. Method 1 depends upon experimental verification that the response to radiation of bioburden is greater than that of a microbial population having a standard distribution of resistances. In practice, an estimate is made of the average bioburden prior to irradiation. For this bioburden, the dose that gives an SAL of 10^{-2} for the standard distribution of resistances is obtained. This dose is designated the verification dose, and it represents the dose that will reduce a microbial population with a standard distribution of resistances to a level that gives on average a 1 in 100 probability of a non-sterile product unit. A sample of 100 product units or portion thereof (SIP) is then exposed to the verification dose and each product unit is tested individually for sterility. If there are not more than two positive tests out of the 100 tests, the sterilization dose is selected for any desired SAL at the estimated level of bioburden.

With the present method, if the verification dose experiment is passed, the product is sterilized using a sterilization dose of 25 kGy on the assumption that microorganisms having a standard distribution of resistances represent a more severe challenge to the sterilizing dose than organisms occurring on products.

It was decided to publish the present method as a Technical Specification because, unlike Methods 1 and 2 which had been used extensively since 1984, there was little practical experience in the application of this method. Users of this method are urged to submit any comments on the application and content of this Technical Specification so that this experience can be taken into account during the current revision of ISO 11137.

Manufacturers of health care products who intend to use the protocols contained in this Technical Specification are reminded that the requirements contained in ISO 11137:1995 for all users of radiation sterilization apply equally to the manufacture and control of products for which a sterilization dose of 25 kGy is to be substantiated by this method. In particular, there is a requirement that products be manufactured in circumstances such that the bioburden is controlled. Compliance with the requirement, and for the establishment of the basic properties of the packaging material are all essential.

Sterilization of health care products — Radiation sterilization — Substantiation of 25 kGy as a sterilization dose for small or infrequent production batches

1 Scope

This Technical Specification describes a method of substantiating the suitability of 25 kGy as a sterilization dose for radiation sterilization of products with an average bioburden of less than 1 000 colony-forming units (cfu) that are manufactured in small quantities (less than 1 000 product units).

This method may be used to substantiate a sterilization dose of 25 kGy for any of the following situations:

a) a single batch of product units;

b) initial production of a new product while the sterilization dose is being established by another method;

c) routine production of small batches.

Information collected in applying the method of dose substantiation described in this Technical Specification may be applicable in meeting the product qualification requirements for sterilization dose selection of ISO 11137:1995 (see 6.2.2).

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this Technical Specification. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this Technical Specification are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 11137:1995, *Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization*

ISO 11737-1:1995, *Sterilization of medical devices — Microbiological methods — Part 1: Estimation of population of microorganisms on products*

ISO 11737-2:1998, *Sterilization of medical devices — Microbiological methods — Part 2: Tests of sterility performed in the validation of a sterilization process*

3 Terms and definitions

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

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

3.2
bioburden
population of viable microorganisms on a product unit

NOTE In the context of radiation sterilization, bioburden is determined immediately prior to sterilization.

3.3
D_{10}
radiation dose required to kill 90 % of a homogeneous microbial population where it is assumed that the death of microbes follows first-order kinetics

NOTE It is expressed in kilograys (kGy).

3.4
false positive
result of a test of sterility in which a true negative is interpreted as positive

3.5
false negative
result of a test of sterility in which a true positive is interpreted as a negative

3.6
fraction positive
quotient derived from the number of positive tests of sterility divided by the total number of tests of sterility performed

3.7
negative test of sterility
test of sterility which does not exhibit detectable microbial growth after incubation

3.8
positive test of sterility
test of sterility which exhibits detectable microbial growth after incubation

3.9
product unit
health care product, collection of products, or components within a primary package

3.10
sample item portion
SIP
defined portion of a health care product unit that is tested

3.11
sterility assurance level
SAL
probability of a viable microorganism being present on a product unit after sterilization

NOTE 1 SAL is normally expressed as 10^{-n}.

NOTE 2 In the context of validation, the SAL may take levels other than that achieved by sterilization.

3.12
sterilization dose
minimum absorbed dose required to achieve the specified sterility assurance level

3.13
sterilization dose audit
action taken to detect whether or not a change in sterilization dose is needed

3.14
test of sterility
test performed to establish the presence or absence of viable microorganisms on product units, or portions thereof, when subjected to defined culture conditions

3.15
verification dose
dose of radiation to which product units, or portions thereof, are nominally exposed in the verification dose experiment with the intention of achieving a predetermined sterility assurance level.

NOTE For this method, the verification dose is selected to achieve a predetermined sterility assurance level ranging from 10^{-1} to $10^{-1,95}$, the actual value depending upon the number of product units, or portions thereof, used in the verification dose experiment.

4 Selection and testing of product

4.1 Selection

4.1.1 Method of selection

The method of selecting product units for subsequent testing can influence the test result observed. It is preferred to select product units at random. When selecting product units from small batches or from a batch of product which is only manufactured intermittently, it is particularly important that the product units be representative of processing procedures and conditions. Product units for testing may be selected from items rejected during the manufacturing process provided that they have been subjected to the same processing and conditions as the remainder of the batch.

4.1.2 Sample item portion (SIP)

Whenever practicable, an entire product unit should be used for testing, but it is recognized that this is not always possible. In such situations, a selected portion of a product unit (sample item portion, SIP), which is convenient to handle during testing, may be substituted. The SIP should be as large a portion of the product unit as is possible to manipulate readily in the laboratory. SIP can be calculated on the basis of length, mass, volume or surface area of the product unit to tested, as appropriate.

The SIP shall represent validly the microbial challenge presented to the sterilization process and the diverse elements of complex product units. The distribution of viable microorganisms on the product unit shall be considered and, if it can be demonstrated that these microorganisms are evenly distributed, the SIP may be selected from any single location on the product unit. In the absence of such a demonstration, the SIP shall be constituted from several portions of a product unit selected at random.

Twenty SIPs should be prepared and a test of sterility performed in accordance with ISO 11737-2. At least 17 of these tests shall be positive. If this criteria is not achieved, a larger SIP is required.

NOTE 1 The occurrence of 17 positives out of 20 tests of sterility indicates that there is an average of 2 cfu/SIP.

NOTE 2 If the entire product unit is tested, no minimum number of positives is specified for non-irradiated samples.

If a product unit or SIP cannot be tested in available laboratory glassware, it may be divided into two or more containers and these containers scored together as one unit; if in the performance of a test of sterility one container yields a positive result, the entire unit is considered positive.

If the product unit has a label claim of sterility of the fluid path only, testing of the fluid path should be considered as the entire product unit (i.e. SIP = 1,0).

The preparation and packaging of an SIP shall be conducted under conditions chosen to minimize alterations in the bioburden. Environmentally controlled conditions should be used for preparation of SIPs.

Packaging materials should be equivalent to those used for the finished product.

Packaging shall be capable of withstanding the radiation doses to be delivered. Packaging for products, or portions thereof, for irradiation shall be chosen in order to minimize contamination during post-irradiation handling.

4.1.3 Selection of items for substantiation of 25 kGy

A sterilization dose of 25 kGy is substantiated for a given product unit. The definition of product unit (see 3.9) covers four situations:

a) an individual health care product within its primary package;

b) a set of components presented in a primary package 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 within a primary package; and

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

In all these situations, the objective of substantiation is to establish that 25 kGy is an adequate sterilization dose for the product unit.

The experimentation carried out for the substantiation of 25 kGy is the determination of the bioburden and the performance of the verification dose experiment. It is the outcome of this experiment that ultimately allows the substantiation of 25 kGy. For the above situations a) through d), the nature of the item(s) employed in the dose substantiation exercise will influence the design and outcome of the substantiation exercise and these, in turn, will affect the decision as to the appropriateness of 25 kGy; thus, a rationalized selection of the item(s) has to be made. As it is the product unit which undergoes sterilization treatment to produce an item that is sterile for use in patient care, it follows that each situation requires consideration of the manner of use of the health care product in clinical practice in order to decide the nature of the item to be employed in the substantiation exercise. Guidance in this regard is given in Table 1.

Table 1 — Selection of items for dose substantiation

Product Unit	Item for bioburden estimation	Item for verification experiment	Rationale
a) Individual healthcare product in its primary package	Individual health care product	Individual health care product	Each health care product is used independently in clinical practice
b) Set of components in primary package	Combination of components	Combination of components	Components are assembled as a product and used together in clinical practice
c) Number of identical health care products in primary package	Single health care product taken from the primary package	Single health care product taken from the primary package	Each health care product is used independently in clinical practice
d) Kit of procedure-related health care products	Each type of health care product	Each type of health care product	Each health care product is used independently in clinical practice

4.2 Microbiological testing

Bioburden determinations and tests of sterility undertaken as part of the method of this Technical Specification shall be conducted using acceptable laboratory practices and in accordance with ISO 11737-1 and ISO 11737-2 respectively.

The method described hereafter uses a single culture medium for the performance of the test of sterility. The use of a single medium assumes that the medium will be optimal for the culture of aerobic and facultative organisms which could survive. When this assumption is not valid, this method shall be conducted using other appropriate media and incubation conditions.

Soybean casein digest broth, with an incubation temperature of (30 ± 2) °C and an incubation period of 14 days, is generally recommended when a single medium is used.

4.3 Product irradiation

The irradiation of product, or SIPs, shall be in compliance with ISO 11137:1995, C.1.5.4.

It is preferred that the product be irradiated in its original form and package. However, to minimize and/or simplify the manipulations during testing and reduce the possibility of false positives in the performance of tests of sterility, the product may be disassembled and repackaged prior to exposure to the verification dose.

NOTE Manipulations prior to irradiation are not always acceptable. In certain instances, such manipulations can change the response of the microorganisms to irradiation. For example, manipulations can alter the chemical environment (typically oxygen pressure) in the vicinity of the microorganisms.

5 Method of substantiation of 25 kGy

5.1 Rationale

This method is an adaptation of Method 1 described in ISO 11137:1995.

Method 1 depends upon experimental verification that the response to radiation of the product bioburden is greater than that of a microbial population having a standard distribution of resistances. This is achieved by performance of a verification dose experiment employing 100 product units, or portions there of, and a requirement to meet defined acceptance criteria that demonstrates an SAL of 10^{-2}.

The present method is intended for products manufactured in batches of less than 1 000 product units. Consequently, the total number of product units taken for bioburden determination is less than the minimum required with Method 1 and the number taken for the verification dose experiment is less than the 100 required when using Method 1.

As fewer product units are tested in the verification dose experiment, an SAL of 10^{-2} cannot be the basis of acceptance, but rather a higher SAL value has to be employed. This higher SAL value is derived from the reciprocal of the number of product units tested in the verification dose experiment. Inevitably, the use of a higher SAL value means that the ability of the method to detect bioburden with a higher resistance to radiation than that corresponding to the standard distribution of resistances is diminished. Consequently, an SAL upper limit of 10^{-1}, corresponding to a minimum of 10 product units for the verification dose experiment, is imposed for the present method of dose substantiation.

Test sample sizes for the performance of bioburden determination and verification dose experiment are given in Table 2. These sample sizes are based on Tables 1 and 2-A of ISO 2859-1:1999, Inspection Level II, using the relationship between the production batch size and sample size. This relationship is approximated by a straight line on log-log scales (that is, plotting log of sample size versus log of geometric mean of the limits of each batch size interval) [7]. This relationship is fit by the following equation:

$$\text{Sample size} = 0{,}58 \times (\text{production batch size})^{0{,}74} \quad (1)$$