TECHNICAL REPORT

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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*

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 main task of technical committees is to prepare International Standards, but in exceptional circumstances a technical committee may propose the publication of a Technical Report of one of the following types:

— type 1, when the required support cannot be obtained for the publication of an International Standard, despite repeated efforts;

— type 2, when the subject is still under technical development or where for any other reason there is the future but not immediate possibility of an agreement on an International Standard;

— type 3, when a technical committee has collected data of a different kind from that which is normally published as an International Standard ("state of the art", for example).

Technical Reports of types 1 and 2 are subject to review within three years of publication, to decide whether they can be transformed into International Standards. Technical Reports of type 3 do not necessarily have to be reviewed until the data they provide are considered to be no longer valid or useful.

ISO/TR 13409, which is a Technical Report of type 2, was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products.*

This document is being issued in the Technical Report (type 2) series of publications (according to subclause G.3.2.2 of part 1 of the ISO/IEC Directives, 1995) as a "prospective standard for provisional application" in the field of radiation sterilization because there is an urgent need for guidance on how standards in this field should be used to meet an identified need.

This document is not to be regarded as an "International Standard". It is proposed for provisional application so that information and experience of its use in practice may be gathered. Comments on the content of this document should be sent to the ISO Central Secretariat.

A review of this Technical Report (type 2) will be carried out not later than three years after its publication with the options of: extension for another three years; conversion into an International Standard; or withdrawal.

Annex A of this Technical Report is for information only.

Introduction

The International Standard ISO 11137, *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 the 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 specifies that one of two approaches is to be used to select the sterilization dose; either i) the selection of a product specific sterilization dose, or, ii) the application of a minimum dose of 25 kGy following substantiation of the appropriateness of this dose.

An informative annex to ISO 11137 (Annex B) 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 (Tallentire, 1973; Tallentire, Dwyer and Ley, 1971; Tallentire and Khan, 1978). Subsequently, standardized methods were developed (Davis, *et al*, 1981; Davis, Strawderman and Whitby, 1984; Whitby and Gelda, 1979) which formed the basis of the dose substantiation procedures put forward in the Association for the Advancement of Medical Instrumentation (AAMI) recommended practice for sterilization by gamma irradiation, *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 various microbial species, assumes that each species has its own unique 'D_{10}' value. 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 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 report 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, Annex B, paragraphs B.3.4.1 - 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 one 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 Report Type 2 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 document so that this experience can be taken into account when ISO 11137 is next revised.

Manufacturers of health care products who intend to use the protocols contained in this Technical Report are reminded that the requirements for all users of Radiation Sterilization contained in ISO 11137 equally apply 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 requirements for proper control of the quality of raw materials, for the manufacturing environment, and for the establishment of the basic properties of the packaging material are all essential.

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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

1 Scope

This technical report 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.

NOTE 1 Information collected in applying the method of dose substantiation described in this technical report may be used in meeting the product qualification requirements for sterilization dose selection of ISO 11137 (see 6.2.2).

NOTE 2 This technical report is considered "informative," and use of the terms "shall," "should," etc. should be considered within the context of this technical report only. That is, if the decision is made to use this method of dose substantiation, then the method should be followed in adherence with the requirements ("shall") and recommendations ("should") as set forth in this technical report.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this International Technical Report, Type 2. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this Technical Report are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO 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 the population of microorganisms on products*

ISO 11737-2:—[1], *Sterilization of medical devices — Microbiological methods — Part 2: Tests of sterility performed in the validation of a sterilization process*

[1] In preparation

3 Definitions, symbols and abbreviations

For the purposes of this Technical Report, the following definitions apply and are presented in the order in which they occur in the text.

3.1 sterilization dose: Minimum absorbed dose required to achieve the specified sterility assurance level.

3.2 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.

3.3 bioburden: Population of viable microorganisms on a product unit.

NOTE 3 In the context of radiation sterilization, bioburden is determined immediately prior to sterilization.

3.4 fraction positive: Quotient derived from the number of positive tests of sterility divided by the total number of tests of sterility performed (number of positive tests of sterility plus number of negative tests of sterility).

3.5 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 (SAL).

NOTE 4 For this Method, the verification dose is selected to achieve a predetermined SAL 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.

3.6 product unit: Health care product, collection of products, or components within a primary package.

3.7 sterility assurance level (SAL): The probability of a viable microorganism being present on a product unit after sterilization.

NOTE 5 SAL is normally expressed as 10^{-n}.

NOTE 6 In the context of validation, the SAL may take levels other than that achieved by sterilization.

3.8 sample item portion (SIP): Defined portion of a health care product unit that is tested.

3.9 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.

3.10 false positive: Result of a test of sterility in which a true negative is interpreted as a positive.

3.11 sterilization dose audit: Action taken to detect whether or not a change in sterilization dose is needed.

3.12 D_{10}: Radiation dose required to kill 90 percent of a homogeneous microbial population where it is assumed that the death of microbes follows first order kinetics.

NOTE 7 In this context, the unit of D_{10} is kGy.

3.13 false negative: Result of a test of sterility in which a true positive is interpreted as a negative.

3.14 negative test of sterility: A test of sterility which does not exhibit detectable microbial growth after incubation.

3.15 positive test of sterility: A test of sterility which exhibits detectable microbial growth after incubation.

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, weight, volume, or surface area of the product unit to be 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 8 The occurrence of 17 positives out of 20 tests of sterility indicates that there is an average of 2 cfu/SIP.

NOTE 9 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;