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Sterilization of health care products — Radiation —

Part 3: Guidance on dosimetric aspects

Stérilisation des produits de santé — Irradiation —

Partie 3: Directives relatives aux aspects dosimétriques

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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 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.

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 11137-3 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care product*.

This first edition, together with ISO 11137-1 and ISO 11137-2, cancels and replaces ISO 11137:1995.

ISO 11137 consists of the following parts, under the general title *Sterilization of health care products — Radiation*:

— *Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

— *Part 2: Establishing the sterilization dose*

— *Part 3: Guidance on dosimetric aspects*

Introduction

An integral part of radiation sterilization is the ability to measure dose. Dose is measured during all stages of development, validation and routine monitoring of the sterilization process. It has to be demonstrated that dose measurement is traceable to a national or International Standard, that the uncertainty of measurement is known, and that the influence of temperature, humidity and other environmental considerations on dosimeter response is known and taken into account. Process parameters are established and applied based on dose measurements. This part of ISO 11137 provides guidance on the application of dose measurements (dosimetry) during all stages of the sterilization process.

ISO 11137-1 describes requirements that, if met, will provide a radiation sterilization process, intended to sterilize medical devices, which has appropriate microbicidal activity. Furthermore, compliance with the requirements helps ensure that this activity is both reliable and reproducible so that predictions can be made, with reasonable confidence, that there is a low level of probability of there being a viable microorganism present on product after sterilization.

Generic requirements of the quality management system for design and development, production, installation and servicing are given in ISO 9001 and particular requirements for quality management systems for medical device production are given in ISO 13485. The standards for quality management systems recognize that, for certain processes used in manufacturing or reprocessing, the effectiveness of the process cannot be fully verified by subsequent inspection and testing of the product. Sterilization is an example of such a process. For this reason, sterilization processes are validated for use, the performance of the sterilization process monitored routinely and the equipment maintained.

Requirements in regard to dosimetry are given in ISO 11137-1 and ISO 11137-2. This part of ISO 11137 gives guidance to these requirements. The guidance given is not normative and is not provided as a checklist for auditors. The guidance provides explanations and methods that are regarded as being suitable means for complying with the requirements. Methods other than those given in the guidance may be used, if they are effective in achieving compliance with the requirements of ISO 11137-1.

Sterilization of health care products — Radiation —

Part 3: Guidance on dosimetric aspects

1 Scope

This part of ISO 11137 gives guidance on the requirements in ISO 11137 parts 1 and 2 relating to dosimetry. Dosimetry procedures related to the development, validation and routine control of a radiation sterilization process are described.

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

ISO 11137-2:2006, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 11137-1, ISO 11137-2 and the following apply.

3.1
dosimetry system
interrelated elements used for determining absorbed dose, including dosimeters, instruments, associated reference standards and procedures for their use

[ISO/TS 11139:2005]

4 Measurement of dose

Measurement of absorbed dose in connection with the radiation sterilization of medical devices is expressed in terms of absorbed dose to water. Dosimetry systems should be calibrated in terms of absorbed dose to water. In this part of ISO 11137, absorbed dose is referred to as dose.

5 Selection and calibration of dosimetry systems

5.1 General

The dosimetry system(s) used to monitor the irradiation of product has to be capable of providing accurate and precise results over the entire dose range of interest.

5.2 Selection of dosimetry systems

5.2.1 Dosimetric measurements are required in sterilization dose establishment, validation and routine control of radiation sterilization; different dosimetry systems might be needed for these different tasks. In dose establishment, for example, the range of doses required for a verification or incremental dose experiment might be outside the recommended (and calibrated) operating range of the dosimetry system used for the measurement of sterilization dose and, in such circumstances, an alternative system would have to be employed.

5.2.2 Guidance on the selection of appropriate dosimetry systems used in radiation sterilization can be found in ISO/ASTM 51261. The properties of individual dosimetry systems and procedures for their use are given in the ISO/ASTM Practices listed in the Bibliography.

5.3 Calibration of dosimetry system

5.3.1 It is a requirement in ISO 11137-1 that dose measurements be traceable to an appropriate national or International Standard and that their level of uncertainty be known. Consequently, all significant sources of measurement uncertainty should be identified and their magnitudes assessed.

5.3.2 Calibration of dosimetry systems for use in radiation sterilization is a significant activity. The response of most systems is influenced by the conditions of irradiation and measurement (e.g. temperature, humidity, dose rate and interval of time between termination of irradiation and measurement). In addition, the effects of these conditions are often interrelated and they can vary from batch to batch of dosimeters. Therefore, calibration should be carried out under conditions that match as closely as possible the actual conditions of use. This means that calibration is needed for each radiation facility and it is not acceptable to use the outcome of a calibration supplied by the dosimeter manufacturer without additional experimental verification of its validity.

5.3.3 A recognized national metrology institute or other calibration laboratory accredited to ISO/IEC 17025, or its equivalent, should be used in order to ensure traceability to a national or International Standard. A calibration certificate provided by a laboratory not having formal recognition or accreditation will not necessarily be proof of traceability to a national or International Standard and additional documentary evidence will be required.

5.3.4 The ability to make accurate dose measurements depends on the calibration and consistency of performance of the entire dosimetry system. This means that all equipment associated with the measurement procedure, not just the dosimeters, is controlled and its performance verified.

5.3.5 Detailed calibration procedures are given in ISO/ASTM 51261. Information on estimating and reporting uncertainty of measurement can be found in ISO/ASTM 51707. Additional guidance is given in Sharpe and Miller [19].

6 Establishing the maximum acceptable dose

6.1 Testing to establish the maximum acceptable dose must be carried out using product or samples of materials that have been irradiated to doses greater than those anticipated during actual processing. The value of the maximum dose received during sterilization will be influenced by the characteristics of the irradiator and the loading pattern of the product. Thus, transfer of the process to another irradiator, or a change to the loading pattern, might result in a change to the maximum dose to product.

6.2 Irradiation geometries for testing of product or samples of materials should be chosen to ensure that the dose is determined accurately and is as uniform as practicable. Irradiation in containers used for routine sterilization processing will usually produce too wide a range of doses to the product to be meaningful for testing purposes. If routine irradiator containers are used, the location of test product should be such that the range of doses that product receives is minimized.

6.3 The doses required in product or materials testing might be outside calibration range of available dosimeter systems. In such cases it may suffice to deliver the dose in increments, with monitoring of each increment of dose. The total dose is equal to the sum of the incremental doses.

7 Establishing the sterilization dose

7.1 The methods of establishing the sterilization dose (see ISO 11137-2) require product, or portions thereof (Sample Item Portion [SIP]), to be irradiated at doses within specified tolerance levels. The dosimetry system used to monitor such doses shall be capable of providing accurate and precise measurements over the entire dose range of interest. In order to avoid compromising the outcome of the dose setting or dose substantiation methods, the dosimetry system used needs to be sufficiently accurate to ensure measurement within the tolerances specified in the method.

7.2 The dose tolerances specified in the dose setting and substantiation methods refer to the maximum, and in some cases minimum, doses that can be delivered to any point on/in a given product item or SIP. Implicit in this requirement is the fact that the distribution of dose applied to product is known; this can require detailed dose mapping of individual product items, particularly in the case of electron beam irradiation. Such dose mapping is similar to that required for Performance Qualification (PQ, see Clause 10).

7.3 Configuration of product during irradiation should be chosen to achieve minimum variation in dose, both within individual items and between items. This can necessitate the irradiation of product items individually; in exceptional cases, it might be necessary to dismantle and repackage the product in order to achieve an acceptable range of doses applied to the item. In this context, see also 5.4.1 of ISO 11137-2:2006.

7.4 To determine the range of doses applied to product, or portions thereof, dose mapping exercises are performed. These dose mapping exercises do not have to be carried out at the same dose as used for dose setting irradiations. The use of higher doses can enable the dosimetry system to be used in a more accurate part of its operating range, thereby improving the overall accuracy of the dose mapping.

7.5 Consideration should be given to the performance of replicate dose mapping exercises. Performance of replicates will reduce measurement uncertainties.

7.6 Irradiation for dose-setting or substantiation purposes using gamma rays is normally carried out using either a special facility that is designed for irradiation with doses lower than the sterilization dose or a defined location outside the normal product path in a sterilization facility, such as on a turntable or research carrier.

7.7 Irradiation for dose setting or substantiation purposes using electrons or X-rays can normally be carried out at the facility used for sterilization, as low doses can be achieved by reducing irradiator output power and/or increasing conveyor speed.

7.8 Irradiation using electrons can be carried out with the product surrounded by material to scatter the electrons and produce a more uniform dose distribution.

7.9 In the performance of a verification dose experiment, it is required that the highest dose does not exceed the verification dose by more than 10 %. The highest dose is either measured directly during the irradiation or calculated from dose mapping data. If dose mapping data are used, account should be taken of the statistical variability of the data. One approach to achieving this is given in Panel on Gamma & Electron Irradiation [20].

7.10 A repeat of the verification dose experiment is allowed if the arithmetic mean of the highest and lowest doses is less than 90 % of the intended verification dose. The highest and the lowest doses can either be measured directly during irradiation or calculated from dose mapping data.

7.11 Methods 2A and 2B (see ISO 11137-2:2006) each require performance of an incremental dose experiment in which product is irradiated at a series of nominal doses, with the additional requirement that the dose for each increment is measured independently. The highest dose within each dose increment is required to be within a specified dose range and is either measured directly during the irradiation or calculated from dose mapping data. If dose mapping data are used, account should be taken of the statistical variability of the data. One approach to achieving this is given in Panel on Gamma & Electron Irradiation [20].

7.12 Methods 2A and 2B allow a repeat of an incremental dose irradiation using a further set of product, or SIPs, if the arithmetic mean of the highest and lowest doses at that increment is less than the lower limit of the specified range. The highest and the lowest doses are either measured directly during the irradiation or calculated from dose mapping data.

8 Installation qualification

8.1 The purpose of Installation Qualification (IQ) is to demonstrate that the irradiator has been supplied and installed in accordance with its specifications.

8.2 There is a requirement in ISO 11137-1 to determine the characteristics of the beam for an electron or an X-ray irradiator. These characteristics include electron or X-ray energy, average beam current and, if applicable, scan width and scan uniformity. The details of characterization depend on the design and construction of the irradiator. Some examples are given in 8.4 and 8.5, but these should not be considered exhaustive.

8.3 Most methods of determining the electron beam characteristics involve dosimetry, although in many cases only relative measurements (for example, measurement of scan width) are required. In instances where relative measurements are made, measurement traceability might not be required.

8.4 For X-ray irradiators, it is required to measure either the electron beam energy or X-ray energy during IQ. Where the design of the X-ray irradiator permits, it is usual to measure the electron beam energy.

8.5 For electron accelerators, consideration should be given to the relationship between the scan frequency, the scan width, pulse repetition rate (for pulse accelerators) and the conveyor speed relative to the cross-sectional distribution of the electron beam at the product surface in order to ensure that there is sufficient overlap to provide the required degree of dose uniformity.

8.6 Characterization of scan uniformity involves, in many cases, measurement of the uniformity both in the direction of the scan and in the direction of the product travel.

8.7 Details of the methods for electron beam characterization can be found in ISO/ASTM 51649, and those for X-ray characterization in ISO/ASTM 51608.

8.8 There are no specific dosimetric requirements for IQ of gamma irradiators. However, depending on irradiator specification, it might be necessary to carry out dose measurements and/or dose mapping in IQ to verify operation within the specification. Dose measurements similar to those used in Operational Qualification (OQ) could be utilized.

9 Operational qualification

9.1 General

The purpose of OQ is to demonstrate that the irradiator, as installed, is capable of operating and delivering appropriate doses within defined acceptance criteria. This is achieved by determining dose distributions through dose mapping exercises and relating these distributions to process parameters.

9.2 Gamma irradiators

9.2.1 Dose mapping for OQ is carried out to characterize the irradiator with respect to the distribution and reproducibility of dose and to establish the effect of process interruption on dose. Dose mapping should be performed by placing dosimeters in an irradiation container filled to its design limits with material of homogeneous density. This density should be within the density range for which the irradiator is to be used. At least two dose mapping exercises should be carried out, one with material close to the lower limit of the density range for which the irradiator is intended to be used and another with material close to the upper limit of this range.

9.2.2 A sufficient number of irradiation containers (at least three) should be dose mapped at each chosen density to allow determination of variability of dose and dose distribution between containers. The detail and number of replicate dose mapping exercises required will be influenced by the amount of knowledge gained from previous OQ dose mapping exercises on the same or similar irradiators. This means that a greater number of replicate exercises might be required for a new installation than for qualification dose mapping exercises after replenishment of sources.

9.2.3 During dose mapping for OQ, the irradiator should have in place a sufficient number of containers to mimic effectively an irradiator filled with containers holding material of the same density as that being dose mapped. The number of containers required to achieve this depends on the irradiator design.

9.2.4 Individual dosimeters, dosimeter strips or dosimeter sheets should be placed in a three-dimensional array sufficient to determine and resolve the dose distribution throughout the entire volume of the irradiation container. The number of dosimeters will depend upon the size of the irradiation container and the design of the irradiation facility. With a 1,0 m × 1,0 m × 0,5 m container, for example, dosimeters might be placed in a three-dimensional 20 cm grid (i.e. at 20 cm intervals) throughout the container. For requalification dose mapping, data from previous exercises can be used to optimise the positioning of the dosimeters. Mathematical modelling techniques, such as Monte Carlo or Point Kernel calculations, can also be useful in optimizing the positioning of dosimeters. See Annex A.

9.2.5 Data from dose mapping exercises can be used to establish the relationships between timer setting and the magnitude of dose at a defined location within the irradiation container for material of different densities. Approximate values for these relationships could be supplied by the irradiator manufacturer or obtained from calculations using mathematical models. Dose mapping data can then be used to refine these approximate relationships for the particular irradiator. See Annex A.

9.2.6 A separate dose mapping exercise should be carried out or a calculation of transit dose performed in order to assess the effect of process interruption. The appropriateness of calculations of transit dose should be verified by dosimetry. This exercise can be done through irradiating a container having dosimeters or dosimeter strips located as described above, and interrupting the process when the container is close to the source where dose is expected to be most influenced by source transit. The effect of process interruption is evaluated by comparing the results with those of dose mapping exercises carried out under normal process conditions. It might be necessary to interrupt the process multiple times in order to evaluate accurately the effect.

9.2.7 The response of some dosimeters is known to be influenced by the period of time that lapses between irradiation and measurement; the magnitude of this effect can depend on temperature during this period. These factors should be taken into account when interpreting measurements from dosimeters that have been subjected to process interruption.

9.2.8 Dose mapping should be carried out to determine the effects on dose and dose distribution that may occur in irradiation containers as a result of changing to product of different density. The acceptable range of densities that can be processed together can be determined based on these measurements. The effect of density changes on dose and dose distribution can be determined by sequentially processing two materials with different densities and dose mapping the last container of the first material density and the first container of the second material density. The data for these containers should be compared to the homogeneous dose mapping data for these materials to determine the additional dose variation when the two material densities are irradiated sequentially.