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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

Reference number
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Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
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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*

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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.

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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.

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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.

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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.

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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.

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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 $\times$ 1,0 m $\times$ 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.

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9.2.9 A separate dose mapping exercise should be performed for special conveyor systems (research loops) or fixed locations in the irradiation cell (turntables) designated for manual placement of products. Consideration should be given to the effect on dosimetry of the conditions associated with the use of such conveyors and locations, e.g. dose rate and temperature.

9.2.10 Additional dose mapping studies can be performed that will provide data to reduce or eliminate dose mapping studies in PQ. Examples of such studies include a) the effects of partially-filled irradiation containers that can occur at the end of an irradiation batch, and b) the loading of test materials in the centre of the irradiation container, which might be used to reduce the product width within the irradiation container in order to achieve the desired maximum to minimum dose ratio.

Partially-filled irradiation containers can receive higher doses than full containers; therefore, dosimeters should be placed at potential maximum dose zones in the partially filled containers as well as adjacent full containers during the dose mapping exercise.

Loading of product in the centre of the irradiation container can result in a change in the magnitude and distribution of dose as compared to full containers. In such circumstances, dosimeters should be placed at potential minimum and maximum dose zones.

9.2.11 Data from OQ dose mapping exercises will often provide useful indication of the probable locations of maximum and minimum doses in actual product loads.

9.3 Electron beam irradiators

9.3.1 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 a process interruption on the dose. Dose mapping should be carried out over a range of selected operating parameters which covers the operational limits to be used in the irradiation of products. Dose mapping should be performed by placing dosimeters in the 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. Generally, it is necessary to use one density only for OQ dose mapping but more detailed information can be obtained by using more than one density, e.g. materials of density close to the limits of density range for which the irradiator is intended to be used.

9.3.2 A sufficient number of irradiation containers (at least three) should be dose mapped at each chosen set of operating parameters in order 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. This means that a greater number of replicate exercises can be required for a new installation than for requalification at defined intervals.

9.3.3 The dose distribution in the irradiation container being mapped can be affected by material in the preceding or following containers. This effect should be assessed and its magnitude determined. Depending on the irradiator design, it might be necessary to precede or follow the containers being dose mapped with containers filled with a material of similar density.

9.3.4 Dosimeters should be placed in a three dimensional array, including the surface, of the test material to be irradiated. The dosimeters should be sufficient in number to measure the dose distribution throughout the entire volume of the irradiation container. The number of dosimeters will depend upon the size of the irradiation container, the design of the irradiator and the energy of the electron accelerator.

The dosimeters may be sheets, continuous dosimeter strips, discrete dosimeters or discrete dosimeters placed adjacent to each other to form strips.

Data from previous exercises can be used to optimize the location of the dosimeters. Mathematical modelling techniques, such as Monte Carlo calculations, can be used in optimizing the positioning of dosimeters. See Annex A.

9.3.5 Data from the dose mapping exercises can be used to determine the relationships between characteristics of the beam, the conveyor speed and the magnitude of dose at a defined location within, or on, an irradiation container filled with a homogeneous material of known density. An alternative approach is to

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define a location with a fixed geometry for a dosimeter that is travelling with, but separate from, the irradiation container and determine the relationships between characteristics of the beam, the conveyor speed and the magnitude of dose at that location. This position can be used as a defined monitoring position during routine processing.

9.3.6 Specific dose measurements should be carried out in order to assess the effect of process interruption on dose. This effect can be determined by placing dosimeters or dosimeter strips at the position where the effect of a process interruption is expected to be greatest. This location is often on the surface of the irradiation container facing the electron beam. The irradiation container is irradiated under normal process conditions and the process is interrupted when the irradiation container is in the beam. The process is restarted and the effect of the process interruption is determined by comparison of dose measured with process interruption with dose measured without process interruption.

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

9.3.8 Depending on the irradiator design, dose mapping should be carried out to determine the effects on dose and dose distribution that can occur in irradiation containers as a result of changing to product of different density. The acceptable range of densities that may 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 test materials in order to determine the additional dose variation when the two material densities are irradiated sequentially.

9.3.9 Data from OQ dose mapping can provide an indication of the locations of maximum and minimum doses in product loads.

9.4 X-ray irradiators

9.4.1 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 a process interruption on the dose. Dose mapping should be performed by placing dosimeters in an irradiation container filled to its design limits with a material of homogeneous density. This density should be within the density range for which the irradiator is to be used. Dose mapping should be carried out over a range of selected operating parameters and material densities that cover the operational limits encountered in the irradiation of products. At least two material densities should be used – one close to the lower limit of the density range for which the irradiator is intended to be used and another close to the upper limit of this range.

9.4.2 A sufficient number of irradiation containers (at least three) should be dose mapped at each chosen set of operating parameters in order 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. This means that a greater number of replicate exercises can be required for a new installation than for requalification at defined intervals.

9.4.3 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.

9.4.4 Individual dosimeters, dosimeter strips or dosimeter sheets should be placed in a three-dimensional array sufficient to measure the dose distribution throughout the entire volume of the irradiation container. The number of dosimeters will depend upon the size of the irradiation container, the design of the irradiation facility, and on the energy of the X-ray beam. With a 1,0 m $\times$ 1,0 m $\times$ 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 optimize 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.

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9.4.5 Data from dose mapping exercises can be used to determine the relationships between characteristics of the beam, the conveyor speed and the magnitude of dose at a defined location within, or on, an irradiation container filled with a homogeneous material of known density. An alternative approach is to define a location with a fixed geometry for a dosimeter that is travelling with, but separate from, the irradiation container and determine the relationships between characteristics of the beam, the conveyor speed and the magnitude of dose at that location. This position can be used as a defined monitoring position during routine processing.

9.4.6 Specific dose measurements should be carried out in order to assess the effect of process interruption on dose. This effect can be determined by placing dosimeters or dosimeter strips at the position where the effect of a process interruption is expected to be greatest. This location is often on the surface of the irradiation container facing the X-ray beam. The irradiation container is irradiated under normal process conditions and the process is interrupted when the irradiation container is in the beam. The process is restarted and the effect of the process interruption is determined by comparison of dose measured with process interruption with dose measured without process interruption.

9.4.7 The response of some dosimeters is known to be influenced by the period of time 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.

9.4.8 Dose mapping should be carried out to determine the effects on dose and dose distribution that can occur in irradiation containers as a result of changing to product of different density. The acceptable range of densities that may 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 test materials, in order to determine the additional dose variation when the two material densities are irradiated sequentially.

9.4.9 A separate dose mapping exercise should be performed for special conveyor systems (research loops) or fixed locations in the irradiation cell (turntables) designated for manual placement of products. Consideration should be given to the effect on dosimetry of the conditions associated with the use of such conveyors and locations, e.g. dose rate and temperature.

9.4.10 Additional dose mapping studies can be performed that will provide data to reduce or eliminate dose mapping studies in PQ. Examples of such studies include a) the effects of partially-filled irradiation containers that can occur at the end of an irradiation batch and b) loading of test materials in the centre of the irradiation container, which might be used to reduce the product width within the irradiation container in order to achieve the desired maximum to minimum dose ratio.

Partially-filled irradiation containers can receive higher doses than full containers; therefore, dosimeters should be placed at potential maximum dose zones in the partially-filled containers as well as adjacent full containers during the dose mapping exercise.

Loading of product in the centre of the irradiation container can result in a change in the magnitude and distribution of dose as compared to full containers. In such circumstances, dosimeters should be placed at potential minimum and maximum dose zones.

9.4.11 Data from OQ dose mapping can provide an indication of the locations of maximum and minimum doses in product loads.

10 Performance qualification

10.1 General

10.1.1 Several factors related to the irradiator and product influence dose distribution. The data acquired from a dose mapping exercise in PQ are used to identify locations and magnitudes of minimum and maximum

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doses within product and to show the relationship between these doses and the dose at the monitoring position(s). The monitoring positions selected may be locations within the irradiation container (e.g. locations of minimum and maximum dose) or may be locations at a separate position adjacent to and moving with the irradiation containers.

10.1.2 Information from doses measured during dose mapping is used to determine the values for process parameters, such as timer setting or conveyor speed, which are set to obtain the specified sterilization dose without exceeding the maximum acceptable dose.

10.1.3 Data from the OQ dose mapping can provide information on the placement of dosimeters for PQ dose mapping. Attention should be paid to regions of probable minimum and maximum doses that should be more closely mapped than areas of intermediate dose.

10.1.4 In a dose mapping exercise, dosimeters should be placed throughout product according to a defined pattern. The dose mapping should be carried out in sufficient detail to identify the maximum and minimum dose positions on or in product being irradiated. Significant dose gradients can occur on or in individual product items and this should be taken into account when positioning dosimeters. Each case needs to be assessed individually, but some general guidance on dosimeter placement is given below. Mathematical modelling techniques, such as Monte Carlo or Point Kernel calculations, can also be useful in optimizing the positioning of dosimeters. See Annex A.

10.2 Gamma and X-ray

10.2.1 For a low density product being irradiated by gamma or X-rays, it is usually appropriate to place dosimeters outside the primary packaging of product, as significant dose gradients might not occur on individual product items. Typical examples are product made up of elements of low atomic number (i.e. non-metallic) which in addition, do not contain masses of material large enough to cause local radiation shielding of adjacent areas.

10.2.2 For product that contains masses of material large enough to cause local shielding when being irradiated by gamma or X-rays, it could be necessary to place dosimeters inside the primary packaging of product in order to determine the maximum and minimum doses.

10.2.3 If product can move within the irradiation container and in so doing affect dose distribution, this should be taken into account during dose mapping, for example, by mapping several possible configurations of product within the irradiation container.

10.2.4 In carrying out dose mapping, attention is given to the size, as well as to the placement, of the dosimeters in order to ensure that the minimum and maximum doses are measured appropriately. To obtain the required spatial resolution, it might be necessary to use thin film dosimeters with no protective sachet. Thin film dosimeters with no protective sachet can be extremely susceptible to changes in humidity, which can cause significant measurement errors. These errors can be reduced by irradiating additional dosimeters in close proximity to reference dosimeters during the dose mapping exercise in a geometry that ensures that the two types of dosimeter are irradiated to the same dose. Any differences between the dose measurements of the two types of dosimeter can be used to correct the dose mapping results.

10.2.5 The dosimetry system should have a high enough spatial resolution to allow measurement of dose gradients that might occur, for example, at material interfaces.

10.2.6 The dose distribution in a partially-filled irradiation container, such as can occur at the end of a batch of product, should be determined. This might require performance of a separate dose mapping exercise for the partially-filled container. The effect that the partially-filled container can have on the dose distribution in other filled containers should be considered. It might be possible to avoid the irradiation of partially-filled containers by filling such containers with material of similar density.

10.2.7 The ratio between the maximum or minimum dose to product and the dose at a monitoring position, if used, is subject to variability and thus to uncertainty. This component of uncertainty contributes to the overall uncertainty in dose to product and should be taken into account when irradiating product for sterilization.

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10.2.8 Replicate dose mapping exercises are carried out in order to obtain information on variability of doses caused by irradiator variation, product variation and dosimeter uncertainty. A minimum of three exercises – each done using a separate irradiation container – is recommended in order to obtain statistically valid data; confidence in the measured values is, however, increased by using a larger number of exercises. For replicate dose mapping exercises, it could be sufficient to place dosimeters only in areas of dose extremes, rather than carry out a full dose mapping exercise.

10.2.9 The data from dose mapping can be analysed to calculate the ratios of minimum dose to dose at the monitoring position and maximum dose to dose at the monitoring position for each exercise. A calculation of the respective mean values, together with their standard deviations, can then be made. The mean minimum to monitor dose ratio and its uncertainty, combined with the uncertainty of the dosimetry system, can be used to select a monitor dose that will ensure that, in subsequent processing, the minimum dose exceeds the sterilization dose with a defined confidence level. See AAMI TIR29 [16].

10.2.10 Information gained from the analysis of dosimetric data is used in preparing the process specification, which includes stipulation of the process parameters and the acceptable limits for the dose at the monitoring position.

10.2.11 Further guidance on the analysis of PQ data and its application to routine processing is provided in AAMI TIR29 [16] and Panel on Gamma & Electron Irradiation [21].

10.3 Electron beam

10.3.1 For product that is processed using electron irradiators, it is usually necessary to place dosimeters inside the primary product packaging of product in order to determine the maximum and minimum doses.

10.3.2 If product could move within the irradiation container and in so doing affect dose distribution, this should be taken into account during dose mapping, for example, by mapping several possible configurations of product within the irradiation container.

10.3.3 In carrying out dose mapping, attention should be given to the size, as well as to the placement, of the dosimeters in order to ensure that the minimum and maximum doses are measured appropriately. To obtain the required spatial resolution, it might be necessary to use thin film dosimeters with no protective sachet. Thin film dosimeters with no protective sachet can be extremely susceptible to changes in humidity, which can cause significant measurement errors. These errors might be reduced by irradiating additional dosimeters in close proximity to reference dosimeters during the dose mapping exercise in a geometry that ensures that the two types of dosimeter are irradiated to the same dose. Any differences between the dose measurements of the two types of dosimeter can be used to correct the dose mapping results.

10.3.4 The dosimetry system should have a high enough spatial resolution to allow measurement of dose gradients that could occur, for example, at material interfaces. For electron beam irradiation, the magnitude of the dose gradients can be several tens of percent over less than 1 mm.

10.3.5 The dose distribution in a partially-filled irradiation container, such as can occur at the end of a batch of product, should be determined. This might require a separate dose mapping exercise for the partially-filled container. The effect that the partially-filled container can have on the dose distribution in other filled containers should be considered. It might be possible to avoid irradiation of partially-filled irradiation containers by filling such containers with material of similar density.

10.3.6 The ratio between the maximum or minimum dose to product and the dose at a monitoring position, if used, is subject to variability and thus to uncertainty. This component of uncertainty contributes to the overall uncertainty in dose to product and should be taken into account when irradiating product for sterilization.

10.3.7 Replicate dose mapping exercises are carried out in order to obtain information on variability of doses caused by irradiator variation, product variation and dosimeter uncertainty. A minimum of three exercises – each done using a separate irradiation container – is recommended in order to obtain statistically-valid data; confidence in the measured values is, however, increased by using a larger number of exercises. For replicate dose mapping exercises, it could be sufficient to place dosimeters only in areas of dose extremes, rather than carry out a full dose mapping exercise.

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10.3.8 The data from dose mapping can be analysed to calculate the ratios of minimum dose to dose at the monitoring position and the maximum dose to dose at the monitoring position for each exercise. The respective mean values, together with their standard deviations, can then be calculated. The mean minimum to monitor dose ratio and its uncertainty, combined with the uncertainty of the dosimetry system, can be used to select a monitor dose that will ensure that in subsequent processing, the minimum dose exceeds the sterilization dose with a defined confidence level. See AAMI TIR29 [16].

10.3.9 Information gained from the analysis of dosimetric data is used in preparing the process specification, which includes stipulation of the process parameters and the acceptable limits for the dose at the monitoring position.

10.3.10 Further guidance on the analysis of PQ data and its application to routine processing is provided in AAMI TIR29 [16] and Panel on Gamma & Electron Irradiation [21].

11 Routine monitoring and control

11.1 General

The relationships between the minimum and maximum doses and the dose at the monitoring position are determined from the results of dose mapping exercise(s). The measurement of dose at the monitoring position during processing is used to verify that the minimum dose exceeds the sterilization dose, and that the maximum dose does not exceed the maximum acceptable dose. Permitted variation limits for the dose measured at the monitoring position are given in the process specification.

11.2 Frequency of dose measurements

Dose measurement at the routine monitoring position provides process parameters that are independent of any other control or measurement system of the irradiator. The minimum frequency of dose measurement should be chosen based on the particular characteristics of the irradiator or process. For processing using gamma rays, dosimeters are typically placed at the beginning and end of each run of product comprising a particular processing category. Additionally, dosimeters can be placed so that at least one dosimeter is within the irradiator cell at all times. For processing using electron beam or X-rays, dosimeters are typically placed at the beginning and end of each run of product comprising a processing category that is irradiated using a specific set of processing parameters.

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Annex A
(informative)

Mathematical modelling

A.1 General

Mathematical models may be used to estimate doses in certain applications. Results of calculations should be verified with dose measurements. Mathematical models can also be useful in optimizing the applications of dose measurements.

Mathematical models can closely simulate the transport of photons or electrons through the irradiator, taking into account the attenuation and scattering by materials between the source and product. Mathematical modelling of dose distribution for gamma irradiators requires accurate knowledge of the source activity distribution and the composition and position of the source, source rack, product carriers, irradiator support structures and product. For electron beam and X-ray irradiators, the beam energy, current and pulse distribution (for pulsed accelerators), and the composition and position of product, product carriers and adjacent scattering materials should be accurately known. Errors in any input parameter for the calculation can result in errors in the calculated doses, so calculated dose distributions should be verified by dose mapping studies.

A brief description of types of models and their uses is given in A.2 and A.3. Further guidance on the use and application of mathematical modelling can be found in ASTM E2232-02.

A.2 Types of model

A.2.1 General

There are a number of methods for mathematical modelling of radiation transport. However, most modelling is performed using either the Point Kernel method or the Monte Carlo method. The Point Kernel method is used for calculating the dose distribution in gamma and X-ray irradiators. It is not used for electron beam irradiators. The Monte Carlo method can be used for gamma, X-ray and electron beam irradiators.

A.2.2 Point Kernel

In the Point Kernel method, a gamma or X-ray source (e.g. a gamma source consisting of a number of source capsules distributed over a rectangular plaque or a cylinder) is approximated by a number of point sources. The intervening material between each point source and each point where the dose is to be calculated is determined from the coordinates of the source, irradiator and product volumes. The effect of this intervening material on the dose rate is estimated by assuming that the photons reaching the dose point are reduced by the inverse square relationship with distance and by exponential reduction based on the mass of material. Contributions from degraded scattered photons are approximated by use of a factor called the build-up factor. Build-up factors have been calculated for different materials and energies for different source to product geometries. However, the published values apply only for simple homogeneous geometries (e.g. a point source in an infinite medium). In actual gamma and X-ray irradiators, the source to product geometries are not that simple, and effects of boundaries and mixtures of materials limit the accuracy in the application of build-up factors.

A.2.3 Monte Carlo

In the Monte Carlo method, the transport of each photon or electron from the source through the product and irradiator materials is simulated by the use of random numbers to determine the energy deposition and

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change of path following different interactions. The probability for each interaction is obtained from published tables. Theoretically, the Monte Carlo method can accurately simulate the actual transport of the photons and electrons. However, since each photon or electron follows a unique path, determined by the probabilities for each individual interaction, the dose contribution from a large number of photons or electrons can only be determined from a large number of photon or electron histories. The uncertainty associated with the random statistical fluctuations is estimated and the calculations are continued until an acceptable statistical uncertainty in the calculated dose is reached. Even with modern fast computers, however, exact calculations can require large amounts of computer time, so approximations are usually used. These approximations include biasing the calculations to provide additional histories for rare events.

A.3 Use of models

A.3.1 Design of irradiators

Mathematical modelling is used extensively in the design of irradiators. Calculations are performed to optimize the irradiation geometry to achieve the desired throughputs and dose homogeneity. Data from mathematical modelling are then used to determine the radiation performance of the irradiator when filled with homogeneous product. Calculations provide information on the expected dose per kilocurie of activity or kilowatt of beam power, variation of dose with product density, dose uniformity ratios and locations of the minimum and maximum doses. Some mathematical models can also provide information on the doses received during the transition between different density products, transit doses during movement of the source or shutdown of the electron beam, and effects of voids or product heterogeneity. Some mathematical models can also provide information on the energy spectrum at the different irradiation positions in a gamma or X-ray irradiator.

A.3.2 Operation of gamma and X-ray irradiators

For gamma and X-ray irradiators, information on the expected dose distribution provided by mathematical modelling can be used to ensure that a sufficient number of dosimeters are distributed in the expected zones for minimum and maximum doses in the irradiator dose mapping studies. Dosimeters should also be placed in the minimum and maximum dose zones predicted by the mathematical modelling as well as other locations to confirm that the irradiator performs as expected. Since the mathematical modelling usually assumes that all source, irradiator, and product characteristics are exactly those in the input, the effects of any deviation from these parameters can only be determined from dosimetry.

After the dose mapping studies have confirmed the reliability of the results from the mathematical modelling data, mathematical modelling provides an effective tool for interpolating between the measured results to determine the dose distribution for other intermediate product densities and for determining general trends such as the effects of product density changes or dose variations caused by non-homogeneous products. The use of a combination of mathematical modelling and dose mapping can significantly reduce the amount of dose mapping required, as illustrated in the following example.

— Use mathematical modelling to calculate the dose distributions in homogeneous product of several densities.

— Normalize calculated results to obtain agreement with the dose mapping data and determine normalization factors applicable for the range of product densities measured.

— Calculate the dose distribution for intermediate product densities and apply the required normalization factors.

— Calculate the dose distributions for the first and last product containers when products of different densities are irradiated sequentially.

— Compare calculated data with dose mapping data for several different product densities irradiated sequentially to confirm the reliability of results from mathematical modelling.

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The resultant data can also be used to confirm that dose specifications can be met when specific products are processed together and to determine the optimum timer settings to be used during transition between products of different densities.

A.3.3 Operation of electron beam irradiators

For electron beam irradiators, information on the expected dose distribution provided by mathematical modelling can be used to ensure that a sufficient number of dosimeters are distributed in the expected zones for minimum and maximum doses in the irradiator dose mapping studies. Mathematical modelling also can be used to determine the dose in areas where there may be steep dose gradients, such as near the edges of product, to ensure that dosimeters provide adequate resolution. Results of mathematical modelling could indicate the need to map areas with strips or sheets of dosimetric film to determine doses near product edges.

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