BS EN ISO 11137-3:2017

BSI Standards Publication

Sterilization of health care products - Radiation

Part 3: Guidance on dosimetric aspects of development, validation and routine control

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National foreword

This British Standard is the UK implementation of EN ISO 11137-3:2017. It is identical to ISO 11137-3:2017. It supersedes BS EN ISO 11137-3:2006, which is withdrawn.

The UK participation in its preparation was entrusted to Technical Committee CH/198, Sterilization and Associated Equipment and Processes.

A list of organizations represented on this committee can be obtained on request to its secretary.

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Published by BSI Standards Limited 2017

ISBN 978 0 580 82896 6

ICS 11.080.01

Compliance with a British Standard cannot confer immunity from legal obligations.

This British Standard was published under the authority of the Standards Policy and Strategy Committee on 31 August 2017.

Amendments/corrigenda issued since publication

Date	Text affected

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 11137-3

July 2017

ICS 11.080.01

Supersedes EN ISO 11137-3:2006

English Version

Sterilization of health care products - Radiation - Part 3: Guidance on dosimetric aspects of development, validation and routine control (ISO 11137-3:2017)

Stérilisation des produits de santé - Irradiation - Partie 3: Directives relatives aux aspects dosimétriques de développement, la validation et le contrôle de routine (ISO 11137-3:2017)

Sterilisation von Produkten für die Gesundheitsfürsorge - Strahlen - Teil 3: Anleitung zu dosimetrischen Aspekten der Entwicklung, Validierung und Lenkung der Anwendung (ISO 11137-3:2017)

This European Standard was approved by CEN on 15 March 2017.

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Ref. No. EN ISO 11137-3:2017: E

European foreword

This document (EN ISO 11137-3:2017) has been prepared by Technical Committee ISO/TC 198 "Sterilization of health care products" in collaboration with Technical Committee CEN/TC 204 "Sterilization of medical devices" the secretariat of which is held by BSI.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by January 2018 and conflicting national standards shall be withdrawn at the latest by January 2018.

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Endorsement notice

The text of ISO 11137-3:2017 has been approved by CEN as EN ISO 11137-3:2017 without any modification.

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Foreword

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

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical committee ISO/TC 198, *Sterilization of health care products*.

This second edition cancels and replaces the first edition (ISO 11137-3:2006), which has been technically revised.

A list of all parts in the ISO 11137 series can be found on the ISO website.

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 an 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 document provides guidance on the use of dose measurements (dosimetry) during all stages in the development, validation and routine control of the radiation sterilization process.

Requirements in regard to dosimetry are given in ISO 11137-1 and ISO 11137-2 and ISO/TS 13004. This document 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 , ISO 11137-2 and ISO/TS 13004 .

INTERNATIONAL STANDARD **ISO 11137-3:2017(E)**

Sterilization of health care products - Radiation —

Part 3:
Guidance on dosimetric aspects of development, validation and routine control

1 Scope

This document gives guidance on meeting the requirements in ISO 11137-1 and ISO 11137-2 and in ISO/TS 13004 relating to dosimetry and its use in development, validation and routine control of a radiation sterilization process.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 11137-1 , *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 , *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

ISO/TS 13004 , *Sterilization of health care products — Radiation — Substantiation of a selected sterilization dose: Method* $VD_{max}{}^{SD}$

ISO 13485 **,** *Medical devices — Quality management systems — Requirements for regulatory purposes*

3 Terms, definitions and symbols

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

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at http://www.electropedia.org/

— ISO Online browsing platform: available at http://www.iso.org/obp

3.1 General

3.1.1
absorbed dose
dose
quantity of ionizing radiation energy imparted per unit mass of a specified material

[SOURCE: ISO 11137-1:2006, 3.1, modified]

Note 1 to entry: For the purposes of this document, the term “dose” is used to mean “absorbed dose”.

3.1.2
combined standard measurement uncertainty
standard measurement uncertainty (3.1.13) that is obtained using the individual standard measurement uncertainties associated with the input quantities in a measurement model

[SOURCE: VIM 2012, 2.31]

3.1.3
coverage factor
number larger than one by which a *combined standard measurement uncertainty* (3.1.2) is multiplied to obtain an *expanded measurement uncertainty* (3.1.7)

Note 1 to entry: A coverage factor is usually symbolized as "*k*" (see also the GUM:1995, 2.3.6).

3.1.4
direct dose measurement
measurement of *absorbed dose* (3.1.1) with a dosimeter at the location of interest

Note 1 to entry: For example, a direct measurement of minimum dose is made with a dosimeter at the minimum dose location in an irradiation container.

3.1.5
dose uniformity ratio
ratio of the maximum to the minimum *absorbed dose* (3.1.1) within the irradiation container

3.1.6
dosimetry system
interrelated elements used for determining *absorbed dose* (3.1.1), including dosimeters, instruments, associated reference standards and procedures for their use

[SOURCE: ISO/TS 11139:2006, 2.15]

3.1.7
expanded measurement uncertainty
product of a *combined standard measurement uncertainty* (3.1.2) and a factor larger than the number one

Note 1 to entry: The factor depends on the type of probability distribution of the output quantity in a measurement model and on the selected coverage probability.

Note 2 to entry: The term "factor" in this definition refers to a coverage factor.

3.1.8
indirect dose measurement
measurement of *absorbed dose* (3.1.1) at a location remote from a directly measured dosimeter, calculated by the application of factors

Note 1 to entry: For example, where the minimum dose in an irradiation container cannot easily be measured directly, a dosimeter placed in a remote location may be measured and factors applied to that measurement to calculate the minimum dose.

3.1.9
scan length
dimension of the irradiation zone, perpendicular to the scan width and direction of the electron beam at a specified distance from the accelerator window

Note 1 to entry: ISO/ASTM standards use "beam length" to mean the same thing that "scan length" means in this document. This document uses "scan length" for consistency with ISO 11137-1 .

3.1.10
scan width
dimension of the irradiation zone in the direction that the beam is scanned, perpendicular to the scan length and direction of the electron beam at a specified distance from the accelerator window

Note 1 to entry: ISO/ASTM standards use "beam width" to mean the same thing that "scan width" means in this document.

3.1.11
simulated product
material with attenuation and scattering properties similar to those of the product, material or substance to be irradiated

Note 1 to entry: Simulated product is used as a substitute for the actual product, material or substance to be irradiated. When used in routine production runs in order to compensate for the absence of product, simulated product is sometimes referred to as compensating dummy. When used for absorbed dose mapping, simulated product is sometimes referred to as "phantom material".

Note 2 to entry: In this document, "dose mapping" is used for "absorbed dose mapping."

3.1.12
spatial resolution
resolution in two dimensions

Note 1 to entry: Ability to detect change in dose in two dimensions.

3.1.13
standard measurement uncertainty
uncertainty of the result of a measurement expressed as a standard deviation

[SOURCE: VIM 2012, 2.30, modified]

3.1.14
uncertainty budget
statement of a measurement uncertainty, of the components of that measurement uncertainty, and of their calculation and combination

Note 1 to entry: An uncertainty budget should include the measurement model, estimates and measurement uncertainties associated with the quantities in the measurement model, covariances, type of applied probability density functions, degrees of freedom, type of evaluation of measurement uncertainty and any coverage factor.

[SOURCE: VIM 2012, 2.33]

3.2 Symbols

Symbol	Meaning
$D_{max,acc}$	maximum acceptable dose determined in accordance with ISO 11137-1:2006 , 8.1
D_{ster}	sterilization dose determined in accordance with ISO 11137-1:2006 , 8.2
D_{max}	direct measurement of maximum dose in a given irradiation container
D_{min}	direct measurement of minimum dose in a given irradiation container
D_{mon}	direct measurement of dose at the routine monitoring position
$R_{max/min}$	ratio of maximum to minimum dose (D_{max}/D_{min}) determined by dose mapping

Symbol	Meaning
$R_{max/mon}$	ratio of maximum to monitor dose (D_{max}/D_{mon}) determined by dose mapping
$R_{min/mon}$	ratio of minimum to monitor dose (D_{min}/D_{mon}) determined by dose mapping
$D_{mon}^{ster} = D_{ster}/R_{min/mon}$	Dose at monitoring positions that correlate to dose specifications
$D_{mon}^{max,acc} = D_{max,acc}/R_{max/mon}$	
D_{target}^{lower}	calculated dose at the routine monitoring position used for establishing process parameters that ensures at a specified level of confidence that D_{ster} is met or exceeded during routine processing
D_{target}^{upper}	calculated dose at the routine monitoring position used for establishing process parameters that ensures at a specified level of confidence that $D_{max,acc}$ is not exceeded during routine processing

4 Measurement of dose

4.1 General

4.1.1 Direct and indirect dose measurements

The term “dose measurement” is used in this document as a general term to indicate the determination of absorbed dose. It can refer both to a direct measurement of dose by a dosimeter at the location of interest or to an indirect measurement of dose which relates to the calculation of the absorbed dose at a location remote from a directly measured dose by the application of factors. The factors associated with an indirect measurement of dose are usually determined during operational qualification (OQ) and performance qualification (PQ) studies and reflect ratios of doses at different locations for a given irradiation process. If the factors and their associated uncertainties have been determined using traceable dose measurements, then the indirect measurement can itself be regarded as traceable and will fulfil the requirements of ISO 11137-1 in terms of measurement traceability and uncertainty.

4.1.2 Dosimetry systems

ISO 10012 or ISO 13485 (see also ISO 11137-1) provide requirements for all aspects of the dosimetry system(s) used. The dosimetry system(s) need to be included in a formal measurement management system, as defined in ISO 10012 , which sets out quality procedures to achieve metrological confirmation and continual control of the measurement processes. An important aspect of this is the competence and training of staff involved, both in the calibration and operation of the dosimetry system(s), and also in the performance and analysis of dose measurements. Activities such as the choice of location of dosimeters for dose mapping and the analysis of the resultant data require specific skills and training.

NOTE Examples of general requirements for dosimetry in radiation processing are given in Reference [19] and further guidance on dose mapping can be found in Reference [18].

Measurements of absorbed dose in connection with the radiation sterilization of health care products are expressed in terms of absorbed dose to water and, therefore, dosimetry systems should be calibrated in terms of absorbed dose to water.

4.1.3 Best estimate of dose

With the completion of the calibration of the dosimetry system and establishment of measurement traceability (see 4.2.3), the result of each dose measurement, direct and indirect, represents the best estimate of dose.

Values from dose measurements should not be corrected by applying associated measurement uncertainty.

4.2 Dosimetry system selection and calibration

4.2.1 General

Dosimetry systems used in the development, validation and routine control of a radiation sterilization process should be capable of providing accurate and precise measurements over the entire dose range of interest and under the conditions of use.

4.2.2 Selection of dosimetry systems

4.2.2.1 Direct dose measurements are required in the development, validation and routine control of radiation sterilization; different dosimetry systems might be needed for these three different tasks. For example, in sterilization dose establishment, the range of doses required for a verification or an incremental dose experiment might be outside the calibrated range of the dosimetry system used for the measurement of dose in routine processing and, in such circumstances, a different system would have to be employed.

4.2.2.2 Guidance on the selection of appropriate dosimetry systems used in the development, validation and routine control of radiation sterilization can be found in ISO/ASTM 52628[19]. The properties of individual dosimetry systems are given in Reference [28]. Procedures for their use are given in the ISO/ASTM Practices listed in the References [5], [7] to [11], [13] and [15].

4.2.3 Calibration of dosimetry systems

4.2.3.1 Calibration of dosimetry systems for use in radiation sterilization is a significant activity. The response of most dosimeters is influenced by one or more of the conditions of irradiation and measurement (e.g. temperature, humidity, exposure to light, 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; see ICRU 80 [28] and ISO/ASTM 52701 [20] for further details. Therefore, calibration should be carried out under conditions that match as closely as possible the actual conditions of use. This means that calibrations or calibration verifications might be needed for each irradiator pathway. It is inappropriate to apply the calibration curve supplied by the dosimeter manufacturer without verification of its validity. However, the supplier's curve might provide useful information about the expected response of the dosimetry system. Where practicable, the calibration should be based on irradiations carried out in the irradiator of intended use, rather than derived from irradiations carried out at a different irradiator.

4.2.3.2 In order to ensure traceability of dose measurements, calibration irradiations and reference standard dosimeters used as part of a calibration should be supplied by a national metrology institute recognized by the International Committee for Weights and Measures (CIPM) or other calibration laboratory in accordance with ISO/IEC 17025 . A calibration certificate provided by a laboratory not having formal recognition or accreditation might not necessarily be proof of traceability to a national or an International Standard and additional documentary evidence will be required (see ISO/ASTM 51261).

4.2.3.3 The ability to make accurate direct dose measurements depends on the calibration and consistency of performance of the entire dosimetry system. This means that all of the equipment associated with the measurement procedure, not just the dosimeters, should be controlled and calibrated or, if equipment cannot be calibrated, its performance should be verified.

4.2.3.4 It is important that the validity of the calibration is maintained throughout the period of use of the calibration results. This might entail performing verification of the calibration using a reference dosimetry system (see ISO/ASTM 52628) at regular intervals and also when a significant change in

irradiation conditions has occurred, for example, following source replenishment. Seasonal variations in temperature and humidity can potentially affect dosimeter response. A periodic assessment to quantify these variations and their effect, if any, on dosimeter response should be carried out and a calibration verification exercise carried out if necessary.

4.2.3.5 The response of some types of dosimeters is known to be influenced by the period of time between termination of irradiation and measurement. The magnitude of this effect can depend on storage conditions during this period and the manufacturer's recommendations on storage should be followed, particularly regarding temperature, humidity and exposure to light. The effect of storage conditions should be taken into account when determining the acceptable time interval between termination of irradiation and measurement of the dosimeters and when interpreting dose measurements. For more information on factors that can influence dosimeter response, see ISO/ASTM 52701.

4.2.3.6 Detailed calibration procedures are given in ISO/ASTM 51261. Information on estimating and reporting uncertainty of dose measurement can be found in ISO/ASTM 51707. Additional guidance is given in Reference [30].

As discussed in ISO/ASTM 51261, the estimate of uncertainty should take into account the differences between calibration and routine processing, e.g. differences in influence quantities such as irradiation temperature or absorbed dose rate, or differences in measurement practices such as use of average versus individual value for dosimeter thickness or background absorbance.

4.3 Dose measurement uncertainty

4.3.1 General concepts

It is a requirement in ISO 11137-1 that dose measurements are traceable to an appropriate national or International Standard and that the level of uncertainty of the measurements is known. Consequently, all potentially significant sources of measurement uncertainty should be identified and their magnitudes assessed. However, depending on the method chosen for quantifying measurement uncertainty, it may be possible to determine the magnitudes of combinations of components of uncertainty, rather than quantifying each component individually.

All measurements, direct and indirect, need to have an estimate of uncertainty that indicates the degree of knowledge associated with the measurement (i.e. the quality of the measurement). When a quantity, such as absorbed dose, is measured, the result depends on multiple factors, such as the dosimetry system, the skill of the operator or the measurement environment. Even if the same dosimeter is measured several times on the same instrument, there will be a spread of results characteristic of the dosimetry system.

4.3.2 The Guide to the expression of uncertainty in measurement (GUM) methodology

4.3.2.1 In the context of measurement uncertainty, this document follows the methodology and terminology described in Reference [26].

4.3.2.2 A dose measurement can be considered to be an estimate of the true value of the absorbed dose. In the case of a well-defined and controlled measurement process, the measurement result will be the best estimate of the value of the absorbed dose (4.1.3). However, the uncertainty inherent in the measurement means that there will be a finite probability that the true value will actually lie above or below the measurement result.

4.3.2.3 In many cases, the probability of the true value being above or below the measurement result will follow a Gaussian, or "normal", distribution. The peak of the distribution represents the measured (best estimate) value, with values above and below this becoming progressively less likely at increasing distances from the measurement result. The width of the Gaussian distribution is characterised by a parameter known as the standard uncertainty (or standard deviation), given the symbol σ (sigma).

NOTE There are many different types of probability distributions that might appropriately characterize individual components of uncertainty. However, in order to mathematically combine these individual components to estimate the total uncertainty in the dose measurement, it is necessary that they be presented in the same form, for example relative standard deviation. Refer to the GUM and ISO/ASTM 51707 for additional information on probability distributions and combining components of uncertainty.

4.3.2.4 A convenient way to express measurement uncertainty is by a confidence interval or coverage interval, which represents the range within which the true value of the quantity is likely to lie. The confidence interval has to be based on a stated level of confidence that the true value will be within the range.

4.3.2.5 A common way to express a measurement result is in the form $x \pm y$, where x is the measured or calculated (best estimate) value and y is the standard measurement uncertainty multiplied by a coverage factor (k). A standard measurement uncertainty multiplied by a coverage factor is known as an "expanded measurement uncertainty". According to the GUM, the value of the coverage factor used must be stated. A coverage factor of 2 is commonly used, corresponding to a level of confidence of approximately 95 %.

NOTE The exact relationship between the level of confidence and expanded measurement uncertainty depends on the number of degrees of freedom associated with the measurement (see the GUM for further information).

4.3.2.6 In order to establish the uncertainty associated with a measurement of dose, it is necessary to first identify all potentially significant sources of uncertainty and then quantify them either individually or in combination. This is most readily done by considering, in turn, each step involved in the calibration and use of a dosimetry system and assessing what uncertainties are likely to be associated with each of these steps. The procedure used in the GUM is to ascribe to each component of uncertainty an effective standard deviation, known as a "standard uncertainty", and to combine these standard uncertainties to produce an estimate of overall uncertainty. This method allows both random and systematic influences to be combined to produce an overall estimate of uncertainty that represents the quality of the measurement. A tabulation of the individual components of uncertainty, along with their values and methods of estimation, is often referred to as an "uncertainty budget". Detailed descriptions of how to carry out this process are given in, for example, ISO/ASTM 51707 [16] and CIRM 29[30].

4.3.3 Radiation sterilization specific aspects of dose measurement uncertainty

4.3.3.1 For dose measurements in radiation sterilization processing, the measurement uncertainty that has to be considered is the uncertainty associated with the direct measurement of dose or with the estimate of the value of dose received by product in an irradiation container through an indirect measurement (4.1.1).

4.3.3.2 Dose received by product in an irradiation container is measured directly during dose mapping exercises, but this is not always the case during routine radiation processing. Radiation processes may be monitored directly by dose measurement at positions of minimum and maximum doses or at positions remote from those locations. When not monitoring at the minimum and maximum locations, direct measurements at the remote monitoring location need to be multiplied by factors to account for dose differences between the dose at the monitoring dosimeter position and those at the position of minimum and maximum dose in an irradiation container. These factors are expressed as dose ratios, e.g. $R_{min/mon}$ and $R_{max/mon}$, and are experimentally determined in dose mapping exercises and are subject to uncertainty. The ratios can directly correlate product specification doses (D_{ster} and $D_{max,acc}$) to specific dose values ($D_{mon}{}^{ster}$ and $D_{mon}{}^{max,acc}$) at the monitoring position (see 3.2):

$$D_{mon}{}^{ster} = D_{ster}/R_{min/mon} \quad (1)$$

$$D_{mon}{}^{max,acc} = D_{max,acc}/R_{max/mon} \quad (2)$$

4.3.3.3 The uncertainty components associated with direct or indirect measurement of dose in an irradiation container can be subdivided as given below:

— the uncertainty reported by the calibration standards laboratory;

— the uncertainty due to mathematical fitting of the calibration function;

— the uncertainty related to the effect of environmental influence quantities on dosimeters during calibration and use;

— the uncertainty related to the reproducibility of the monitoring dosimeter;

— the uncertainty, for indirect measurements, in dose ratios derived from dose mapping;

— the uncertainty, if applicable, for indirect measurements, arising from variations in irradiator dose delivery between the irradiation of the monitoring dosimeter and the irradiation of the container in which it is required to estimate the dose.

The items on this list should be considered in establishing an uncertainty budget but may not be applicable to all processes; they are not intended to be a checklist. Depending on the method chosen for quantifying measurement uncertainty, it may be possible to determine the magnitudes of combinations of components of uncertainty, rather than quantifying each component individually.

Uncertainty values can be used to determine process target dose values (D_{target} ^{lower} and D_{target} ^{upper}) that are higher than D_{ster} (or D_{mon} ^{ster} if the process is not monitored at the minimum dose location) and lower than $D_{max,acc}$ (or D_{mon} ^{max,acc} if the process is not monitored at the maximum acceptable dose location). One method for determining process target values is to use values of the product $k\sigma$ to calculate process target doses, where σ is a standard uncertainty derived from a combination of those components given above that are applicable to the specific situation. The value of k is dependent on the required level of confidence associated with the process. Annex D illustrates the determination of process target doses using $k\sigma$.

5 Establishing the maximum acceptable dose

5.1 Tests to establish the maximum acceptable dose need to be carried out using product that has been irradiated to doses equal to or greater than the highest dose anticipated during sterilization processing.

The value of the actual maximum dose received during sterilization processing can 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. Such considerations should be taken into account when selecting doses for testing.

5.2 Irradiation geometries for the performance of tests on product should be chosen to ensure that the dose is determined accurately and that the dose distribution is as uniform as practicable. Irradiation in irradiation containers used for sterilization processing might produce too wide a dose uniformity ratio to be meaningful for testing purposes. If such irradiation containers are used, the location of test product should be such that the dose uniformity ratio is minimized. Separate dose mapping might be needed to determine the distribution of dose received. These dose mapping exercises do not have to be carried out at the same doses as those used for testing of product (see Note). The use of lower 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. It might be necessary to demonstrate that the use of different doses does not alter dose distribution.

NOTE Such dose mapping exercises are similar to those required for Performance Qualification (PQ) (see Clause 9).

5.3 Where irradiation containers cannot be used to achieve doses with the required dose uniformity ratio or dose magnitude, alternatives include use of non-standard processing where irradiations are performed outside the normal process flow. For example, gamma irradiators that routinely process

irradiation containers through a specified conveyor path may also irradiate product "off-carrier" or by using special conveyor systems. "Off-carrier" processing of product may involve the manual placement of product at fixed locations within the irradiator. Rotation of product on turntables or manual manipulation of product on processing tables at these fixed locations may be used to improve dose uniformity.

5.4 Caution should be exercised in the interpretation of test results and in the assignment of the maximum acceptable dose. Product items for testing are not usually irradiated to the same dose, but rather to a range of doses. In these circumstances, the maximum acceptable dose is the lowest dose received by the product items for which the properties were found to be acceptable.

5.5 The doses required in establishing the maximum acceptable dose might be outside the calibrated range of available dosimetry systems. In such cases it might 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.

NOTE Delivering doses in increments might not incorporate influences of, for example, irradiation temperature that product could experience in routine processing and which might affect product performance.

6 Establishing the sterilization dose

6.1 The methods of establishing the sterilization dose (see ISO 11137-2 and ISO/TS 13004) require product, or portions thereof [Sample Item Portion (SIP)], to be irradiated with a dose or doses within specified tolerances. To avoid compromising the outcome of the dose establishment method, the dosimetry system should be sufficiently accurate and precise to ensure dose measurements are within the tolerances specified in the method.

NOTE This clause addresses dosimetry for sterilization dose establishment, but the principles for delivery of dose within the required tolerances also apply to irradiations for sterilization dose audits.

6.2 The achievement of doses within the tolerances specified in sterilization dose establishment methods is based on measurements used to derive minimum and maximum doses to any point on/in a given product item or SIP. Detailed dose mapping of individual product items might be required, particularly in the case of electron beam irradiation. Such dose mapping exercises are similar to those required for PQ (see Clause 9).

6.3 Configuration of product during irradiation should be chosen to achieve minimum variation in dose, both within individual product items and between product 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 distribution of doses on the product item. Dismantling and repackaging of product might affect product bioburden. In this context, see ISO 11137-2:2013 , 5.4.1.

6.4 To determine the range of doses to product, or portions thereof, dose mapping exercises are performed. These dose mapping exercises do not have to be carried out at the same doses as those used for sterilization dose establishment (see Note). The use of different 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. It might be necessary to demonstrate that the use of different doses does not alter dose distribution.

NOTE Such dose mapping exercises are similar to those required for PQ (see Clause 9).

6.5 Replicate dose mapping exercises should be performed on product in order to quantify and potentially reduce measurement uncertainties of dose to product. Without data from a replicate dose mapping exercise for a product, sufficient dosimeters should be placed in each irradiation container to identify the locations of and measure the minimum and maximum doses.

6.6 The measurement uncertainty associated with dose mapping data should be taken into account in performing irradiations in establishing the sterilization dose in order to ensure that the specified dose

tolerances are met. The approach taken will depend on the conditions of irradiation and dose monitoring, but the general principles given in Clause 9 (PQ) and Annex D involving calculation of target doses are relevant and should be applied as appropriate.

6.7 Irradiation for dose establishment purposes using gamma rays is normally carried out using a special irradiator that is designed for irradiation at doses lower than the sterilization dose or a defined location outside the normal product path in an irradiator, such as on a turntable, or a special irradiation pathway designed for low dose irradiation.

6.8 Irradiation for dose establishment purposes using electrons or X-rays can normally be carried out at the irradiator used for sterilization, as low doses can be achieved by reducing irradiator beam current, increasing conveyor speed, or otherwise reducing the product residence time in the beam.

Care should be exercised when selecting beam parameters at electron beam or X-ray facilities in order to obtain low doses. In some electron accelerators, for example, the electron energy might change if the beam current is changed, thereby affecting dose distribution.

6.9 Irradiation using electrons can be carried out with the product surrounded by the material to scatter the electrons and to produce a more uniform dose distribution. The nature of the surrounding material used should be recorded. Similar techniques might also be applicable for X-ray irradiation because the unidirectional beam produced by some designs of X-ray irradiators might otherwise lead to unacceptable large dose uniformity ratios.

6.10 For each of the methods of sterilization dose establishment given in ISO 11137-2 and ISO/TS 13004 , tolerances are specified for doses delivered. These are summarized in Annex C. The actions to be taken in the event of the tolerances not being met vary according to the sterilization dose establishment method and are described in ISO 11137-2 and in ISO/TS 13004 .

NOTE The dose tolerances in ISO 11137-2:2013 and ISO/TS 13004 and the actions to be taken if those tolerances are not met are different from those given in ISO 11137-2:2006 .

7 Installation qualification

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

NOTE Information on the various dosimetry-related activities required in IQ is given below in this document and also in a number of clauses in ISO 11137-1 . For convenience, Table B.1 shows the location of applicable clauses in this document and ISO 11137-1 .

7.2 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 7.4 to 7.7, but these should not be considered exhaustive.

7.3 Most methods of determining the electron beam characteristics involve dose measurements traceable to an appropriate national or International Standard. The determination of some characteristics (for example, scan width) might not involve traceable dose measurements.

7.4 For X-ray irradiators, it is required to measure either the electron beam energy or X-ray energy during IQ. No published standard methods are yet available for energy measurement for industrial X-ray beams. Where the design of the X-ray irradiator permits, it is acceptable to measure the electron beam energy incident on the X-ray target in accordance with standard methods (see ISO/ASTM 51649).

NOTE Methods for energy measurement for industrial X-ray beams have been published[25], but these are not standard methods.

7.5 For electron accelerators where the beam is scanned and pulsed, it is important that there is sufficient overlap between beam pulses and scans to provide the required degree of dose uniformity at the product surface. This involves consideration of the relationship between scan frequency, scan width, pulse repetition rate (for pulsed accelerators) and conveyor speed relative to the cross-sectional distribution of the unscanned electron beam at the product surface (see ISO/ASTM 51649).

7.6 Characterization of dose uniformity involves, in many cases, measurement of the dose uniformity both in the direction of product travel and in the directions perpendicular to product travel.

7.7 Details of the methods for electron beam characterization can be found in ISO/ASTM 51649 and ISO/ASTM 51818 and those for X-ray characterization in ISO/ASTM 51608.

7.8 There are no specific dosimetric requirements for IQ of gamma irradiators. Depending on how the irradiator was specified, it might be necessary to carry out dose measurements and/or dose mapping in IQ to verify that operation is within specifications. Examples include specifications of dose rate and dose uniformity. Dose measurements similar to those used in Operational Qualification (OQ) might be utilized.

8 Operational qualification

8.1 General

8.1.1 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 and dose magnitude through dose mapping exercises and relating these dose attributes to process parameters.

8.1.2 Repeat measurements to show consistent and stable operation are an important part of OQ and should be performed at defined intervals and following any change which might affect dose or dose distribution, such as source replenishment in gamma facilities or modifications to conveyor systems. The overall strategy for OQ should be based on the anticipated methods of operation of the irradiator.

NOTE Information on the various dosimetry-related activities required in OQ is given below in this document and also in a number of clauses in ISO 11137-1 . For convenience, Table B.2 shows the location of applicable clauses in this document and ISO 11137-1 .

8.2 Gamma irradiators

8.2.1 Dose mapping for OQ is carried out to characterize the irradiator with respect to the distribution and reproducibility of dose in defined loading configurations and to establish the effect of process interruption on dose throughout the irradiation container.

8.2.2 Dose mapping should be performed by placing dosimeters in irradiation containers filled to their design limits with a material of homogeneous density. At least two dose mapping exercises should be carried out, one with material at the lower limit of the density range for which the irradiator is intended to be used and another with material at the upper limit of this range. OQ measurements are required for each pathway through the irradiator (ISO 11137-1:2006 , 9.2.6).

In many gamma irradiator designs, the relationship between irradiation time and minimum dose is not linear over the density range to be qualified. In such instances, more than two dose mapping

exercises with different densities might be carried out to determine the performance characteristics of the irradiator.

NOTE Material of homogeneous density might be, for example, sheets or plates of expanded polyethylene foam, cardboard or wood.

8.2.3 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 within and 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 carried out on the same or similar irradiators. This means that a greater number of replicate exercises might be required for a new irradiator than for requalification dose mapping exercises.

During dose mapping for OQ, the irradiator should have in place a sufficient number of irradiation containers to mimic effectively an irradiator filled with containers holding material of the specified density that is being dose mapped. The number of containers required to achieve this depends on the irradiator design. As a minimum, any irradiation container adjacent to or between the source and a container being mapped should contain material of the same density.

8.2.4 Individual dosimeters, dosimeter strips or dosimeter sheets should be placed within the irradiation container in sufficient quantity to determine the dose distribution. The number of dosimeters will depend upon the size of the irradiation container and the design of the irradiator. For example, with a 1,0 m × 1,0 m × 0,5 m container, dosimeters might be placed in a three-dimensional 10 cm grid (i.e. at 10 cm intervals) on at least the exterior planes facing the source and on the mid-plane of the container.

For requalification dose mapping where there are no anticipated changes to the distribution of dose, data from previous exercises can be used to optimize the positioning of the dosimeters, so that dosimeters can be concentrated in areas of potential minimum and maximum dose and of high dose gradient.

Mathematical modelling techniques, under an appropriate QA program including benchmarking, might be useful in optimizing the positioning of dosimeters and potentially reducing the number of dosimeters to be used in the dose mapping exercise. See Annex A.

8.2.5 Data from OQ dose mapping exercises can be used to establish

— the relationships between timer setting and/or conveyor speed and the magnitude of dose at a defined location within the irradiation container for material of different densities, and

— the relationship between dose uniformity within the irradiation container and the material density.

Approximate 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.

8.2.6 Specific dose measurements should be carried out in order to assess the effect of process interruption on dose throughout the irradiation container. One approach to carrying out these measurements is to irradiate a container having dosimeters located as described in 8.2.4 and in areas of the container which are expected to be most influenced by source transit and interrupting the process when the container is close to the source. 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.

NOTE Using mathematical modelling to calculate effects of process interruption might supplement measurements.

The effect of process interruption may not have to be determined for each OQ. For example, after source replenishment, dose distribution within the irradiation container might be similar to that when the previous process interruption study was performed. In this case, a process interruption study may not be required. Justification for not including a process interruption study in OQ should be documented.

8.2.7 Process interruption can cause changes in magnitudes of the minimum and maximum doses and also in the locations at which these extremes occur. In routine processing, consideration should be given to the allowable number of interruptions that can occur without doses to product falling outside specification. This will depend on how close doses are to specified limits during normal, uninterrupted processing.

NOTE Additional guidance on performing process interruption dose mapping exercises is available in ISO/ASTM 52303 and AAMI TIR29.

8.2.8 Dose mapping exercises should be performed for special conveyor systems or fixed locations in the irradiator designated for manual placement of products. Dose distribution in products in these locations might be influenced by products present in the main irradiator pathway. Consideration should be given to the effect on dosimetry calibration and uncertainty (see ISO/ASTM 51261) of the conditions associated with the use of such conveyors and locations, e.g. dose rate and temperature. Therefore, a dosimetry system calibration curve might need to be established for each irradiator pathway and fixed location. This might entail generating a new calibration curve or verifying an existing one.

8.2.9 Additional dose mapping studies can be performed during OQ that will provide data to reduce dose mapping studies in PQ (see Clause 9). Examples of such studies include determining the effects of partially filled irradiation containers and the loading of product in the centre of the irradiation container in order to achieve the desired dose uniformity ratio.

Partially filled irradiation containers can receive higher doses than full containers; therefore, during the dose mapping exercise, dosimeters should be placed at potential maximum dose zones in the partially filled containers as well as in full containers whose dose distribution might be affected by the presence of any partially filled containers.

NOTE Loading of product in the centre of the irradiation container can result in a change in the magnitude and distribution of dose compared with those found for full containers.

8.2.10 Further dose mapping should be carried out to determine the effects on the magnitude and distribution of dose that might occur as a result of processing a product of a particular density before or after processing product of another density. The acceptable range of densities that can be processed together can be determined based on the results from these dose mapping exercises. The effect of density changes on the dose magnitude and distribution will depend on the design of the irradiator and how the density change is introduced into the irradiator. The density of the material in the irradiation containers to be dose mapped should represent the range of density to be processed together routinely. A sufficient number of irradiation containers likely to be affected by the change in surrounding densities should be dose mapped. The dose mapping data should be compared with those obtained from containers where there has been no change in density (see 8.2.3).

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

8.3 Electron beam irradiators

8.3.1 Dose mapping for OQ is carried out to characterize the irradiator with respect to the distribution and reproducibility of dose in defined load configurations and to establish the effect of a process interruption on dose throughout the irradiation container.

Dose mapping should be carried out at the electron beam energy used for product irradiation. If more than one energy is used, then OQ dose mapping should be carried out for each energy. If more than one scan width is used, then OQ dose mapping should be carried out using selected scan widths to cover the operational limits to be used in the irradiation of product.

8.3.2 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 the density range for which the irradiator is intended to be used.

NOTE Material of homogeneous density might be, for example, sheets or plates of expanded polyethylene foam.

It is recommended to use single-sided irradiation for OQ dose mapping in order to obtain maximal information about consistent and stable operation of the irradiator.

8.3.3 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 within and 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 carried out on the same or similar irradiators. This means that a greater number of replicate exercises might be required for a new irradiator than for requalification dose mapping exercises.

Electron beam irradiators are generally designed such that irradiation containers are conveyed through the radiation field which may or may not include separation between containers. Typically, separation between containers can occur

a) by design (i.e. fixed spacing between containers which may result in only one irradiation container in the radiation field at any time),

b) when changing product batches, or

c) when changing irradiation parameters.

The spacing between containers and differences in density or material configuration between containers can influence the dose distribution within each container. Therefore, dose mapping carried out to assess such effects might give information that is useful for PQ dose mapping.

8.3.4 Individual dosimeters, dosimeter strips or dosimeter sheets should be placed in a three-dimensional array, including the surface, within the test material of homogeneous density to be irradiated. The number of dosimeters will depend upon the size of the irradiation container, the design of the irradiator and the energy of the electron beam. Data from previous exercises can be used to optimize the location of the dosimeters.

For requalification dose mapping where there are no anticipated changes to the distribution of dose, data from previous exercises can be used to optimize the positioning of the dosimeters, so that dosimeters can be concentrated in areas of potential minimum and maximum dose and of high dose gradient.

Mathematical modelling techniques, under an appropriate QA program including benchmarking, might be useful in optimizing the positioning of dosimeters and potentially reducing the number of dosimeters to be used in the dose mapping exercise. See Annex A.

8.3.5 Data from the dose mapping exercises carried out with the particular electron beam irradiator can be used to establish 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.

Such a defined location is that of the minimum or maximum dose in the irradiation container or a location with a fixed geometry for a dosimeter travelling with, but separate from, the irradiation container. This latter location can be used as a defined monitoring position during routine processing.

8.3.6 Specific dose measurements should be carried out in order to assess the effect of process interruption on dose throughout the irradiation container. This effect can be determined by placing dosimeters 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 and is likely to be

more pronounced at short distances to the beam window. 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 the dose measured when process interruption occurs with that measured without process interruption.

Depending on the design of the irradiator, it might be necessary to assess the effect of process interruption on dose for different irradiation conditions and different causes of interruption. The effects might be different at, for example, high conveyor speed with high mass product and low conveyor speed with low mass product. Process interruptions arising from the safety system, from the electron beam and from the conveyor might have different effects on dose and these effects should be determined.

8.3.7 Process interruption can cause changes in the magnitudes of minimum and maximum dose and also in the locations at which these extremes occur. In routine processing, consideration should be given to the allowable number of interruptions that can occur without doses to product falling outside specification. This will depend on how close doses are to specified limits during normal, uninterrupted processing.

NOTE Additional guidance on performing process interruption dose mapping exercises is available in ISO/ASTM 52303 and AAMI TIR29.

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

8.4 X-ray irradiators

8.4.1 Dose mapping for OQ is carried out to characterize the irradiator with respect to the distribution and reproducibility of dose in defined loading configurations and to establish the effect of a process interruption on dose throughout the irradiation container.

Dose mapping should be carried out at the electron beam energy used for product irradiation. If more than one energy is used, then OQ dose mapping should be carried out for each energy. If more than one scan width is used, then OQ dose mapping should be carried out using selected scan widths to cover the operational limits to be used in the irradiation of products.

8.4.2 Dose mapping should be performed by placing dosimeters in irradiation containers filled to their design limits with a material of homogeneous density. At least two dose mapping exercises should be carried out, one with material at the lower limit of the density range for which the irradiator is intended to be used and another with material at the upper limit of this range. OQ measurements are required for each pathway through the irradiator.

If the X-ray irradiator design is such that the relationship between irradiation time and minimum dose is not linear over the density range, more than two dose mapping exercises should be carried out to determine the performance characteristics of the irradiator.

NOTE Material of homogeneous density might be, for example, sheets or plates of expanded polyethylene foam, cardboard or wood.

8.4.3 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 within and 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 carried out on the same or similar irradiators. This means that a greater number of replicate exercises might be required for a new irradiator than for requalification dose mapping exercises.

During dose mapping for OQ, the irradiator should have in place a sufficient number of irradiation 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.

8.4.4 Individual dosimeters, dosimeter strips or dosimeter sheets should be placed in a three-dimensional array, including the surface of the test material of homogeneous density to be irradiated. The number of dosimeters will depend upon the size of the irradiation container, the design of the irradiator and on the energy of the X-ray beam. For example, with a 1,0 m × 1,0 m × 0,5 m container, dosimeters might be placed in a three-dimensional 10 cm grid (i.e. at 10 cm intervals) on at least the exterior planes facing the X-ray beam and on the mid-plane of the container.

For requalification dose mapping where there are no anticipated changes to the distribution of dose, data from previous exercises can be used to optimize the positioning of the dosimeters, so that dosimeters can be concentrated in areas of potential minimum and maximum dose and of high dose gradient.

Mathematical modelling techniques, under an appropriate QA program including benchmarking, might be useful in optimizing the positioning of dosimeters and potentially reducing the number of dosimeters to be used in the dose mapping exercise. See Annex A.

8.4.5 Data from dose mapping exercises carried out with the particular X-ray irradiator can be used to establish

— the relationships between characteristics of the beam, distance between product and X-ray target, 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, and

— the relationship between dose uniformity within the irradiation container and the material density.

An alternative approach (off-carrier monitoring) 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.

8.4.6 Specific dose measurements should be carried out in order to assess the effect of process interruption on dose throughout the irradiation container. This effect can be determined by placing dosimeters 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 when process interruption occurs with dose measured without process interruption.

Depending on the design of the irradiator, it might be necessary to assess the effect of process interruption on dose for different irradiation conditions and different causes of interruption. The effects might be different at, for example, high conveyor speed with high mass product and low conveyor speed with low mass product. Process interruptions arising from the safety system, from the electron beam and from the conveyor, might have different effects on dose and these effects should be determined.

8.4.7 Process interruption can cause changes in the magnitudes of minimum and maximum dose and also in the locations at which these extremes occur. In routine processing, consideration should be given to the allowable number of interruptions that can occur without doses to product falling outside specification. This will depend on how close doses are to specified limits during normal, uninterrupted processing.

NOTE Additional guidance on performing process interruption dose mapping exercises is available in ISO/ASTM 52303 and AAMI TIR29.

8.4.8 Dose mapping exercises should be performed for special conveyor systems or fixed locations in the irradiator designated for manual placement of products. Dose distribution in product in these locations might be influenced by product present in the main irradiator pathway. Consideration should be given to the effect on dosimetry calibration and uncertainty (see ISO/ASTM 51261) of the conditions associated with the use of such conveyors and locations, e.g. dose rate and temperature. A dosimetry

system calibration curve might need to be established for each irradiator pathway and fixed location. This might entail generating a new calibration curve or verifying an existing one.

8.4.9 Additional dose mapping studies can be performed during OQ that will provide data to reduce dose mapping studies in PQ (see Clause 9). Examples of such studies include determining the effects of partially filled irradiation containers and the loading of product in the centre of the irradiation container in order to achieve the desired dose uniformity ratio.

Partially filled irradiation containers can receive higher doses than full containers; therefore, during the dose mapping exercise, dosimeters should be placed at potential maximum dose zones in the partially filled containers as well as in full containers whose dose distribution might be affected by the presence of any partially filled containers.

NOTE Loading of product in the centre of the irradiation container can result in a change in the magnitude and distribution of dose compared with those found for full containers.

8.4.10 Further dose mapping should be carried out to determine the effects on the magnitude and distribution of dose that might occur as a result of processing product of a particular density before or after processing product of another density. The acceptable range of densities that can be processed together can be determined based on the results from these dose mapping exercises. The effect of density changes on the dose magnitude and distribution will depend on the design of the irradiator, and how the density change is introduced into the irradiator. The density of the material in the irradiation containers to be dose mapped should represent the range of density to be processed together routinely. A sufficient number of irradiation containers likely to be affected by the change in surrounding densities should be dose mapped. The dose mapping data should be compared with those obtained from containers where there has been no change in density (see 8.4.3).

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

9 Performance qualification

9.1 General

9.1.1 Several factors related to the irradiator and product influence dose distribution in product. The data acquired from a dose mapping exercise in PQ are used to identify locations and magnitudes of minimum and maximum doses to product and to calculate the relationship between these doses and the dose at the routine monitoring position(s). The routine monitoring positions selected may be locations within the irradiation container (e.g. locations of minimum and maximum doses) or may be a location at a separate position adjacent to and moving with the irradiation container.

For PQ dose mapping purposes, it is acceptable to irradiate using doses outside the dose specification for product provided that information is available to demonstrate that the use of these doses does not affect dose distribution.

NOTE Information on the various dosimetry-related activities that are required in PQ is given below in this document and also in a number of clauses in ISO 11137-1 . For convenience, Table B.3 shows the location of applicable clauses in this document and ISO 11137-1 .

9.1.2 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 meet the specified sterilization dose without exceeding the maximum acceptable dose.

9.1.3 Data from the OQ dose mapping can provide initial information on the placement of dosimeters for PQ dose mapping. Particular attention should be paid to regions of potential minimum and maximum doses that should be more closely mapped than regions of intermediate dose.

9.1.4 Dose mapping should be carried out in sufficient detail to identify the magnitudes and locations of the minimum and maximum doses 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 and in ISO/ASTM 52303. Mathematical modelling techniques, under an appropriate QA program including benchmarking, can be useful in optimizing the positioning of dosimeters and potentially reducing the number of dosimeters. See Annex A.

NOTE Additional information on dose mapping aspects can be found in AAMI TIR29 and ISO/ASTM 52303.

9.1.5 PQ should be repeated if OQ measurements show that the irradiator has changed to an extent where one or more of the conclusions from PQ are no longer valid or if there is a change in product that might affect dose or dose distribution. However, there is no requirement to repeat PQ on a regular basis.

9.2 Gamma irradiators

9.2.1 Loading pattern

9.2.1.1 For dose mapping, individual product cartons should be arranged within an irradiation container in a way that defines the intended routine loading pattern. Consideration should be given to key product characteristics, including individual product carton dimensions and weight, and allowable variations in these parameters, the dose specification for the product and insights gained from OQ dose mapping. Samples of product cartons to be processed during the PQ should be measured and weighed to ensure product cartons conform to defined product characteristics.

Product cartons are generally oriented to utilize the volume of the irradiation container optimally. However, in some instances, the available space cannot be utilized due to product constraints such as narrow dose range specification, product high density or heterogeneity or carton dimensions.

The defined product loading configuration within an irradiation container may consist of more than one type of product and include a range of carton sizes and weights. The effects on dose distribution of loading products with different densities at different locations within the container should be investigated. The effect on dose distribution might be examined by performing dose mapping exercises on various load configurations where the extremes in product density are configured in various locations in the irradiation container. The results of the dose mapping exercise might result in one or more locations of potential minimum or maximum dose (see ISO/ASTM 52303).

9.2.1.2 In some situations, product cartons can move within the irradiation container or product units can move within the product carton, both possibly affecting dose distribution.

If product cartons can move within the irradiation container and in so doing affect dose distribution, the product should be secured to prevent such movement. Materials used to secure product during PQ should also be used during routine processing and defined in the process specification. In the event the product cartons cannot be sufficiently secured, this should be taken into account during dose mapping, for example, by mapping a worst case configuration.

If product can move within a product carton, and in so doing affect dose distribution, this should be taken into account during dose mapping, for example, by mapping several possible orientations of product within the product carton to establish a worst case scenario with respect to dose distribution.

9.2.1.3 Low-density products tend to be fairly homogeneous such that the orientation of individual products within the irradiation container is unlikely to have a significant effect on dose distribution when irradiating with gamma rays. However, product orientation for non-uniform products, such as those containing high-density components and void spaces (e.g. metal and metal/polymer implants) might make it difficult to achieve an acceptable dose distribution and, in some instances, specific orientation of products might be required within each irradiation container.

9.2.1.4 A sufficient number of fully loaded irradiation containers should be dose mapped at the designated set of process parameters in order to allow determination of variability of dose and dose distribution between containers. A minimum of three containers should be dose mapped in order to obtain statistically valid data. Confidence in the measured values is, however, increased by performing a larger number of dose mapping exercises. For replicate dose mapping exercises, it could be sufficient to place dosimeters only in regions of dose extremes, rather than carry out a full dose mapping exercise.

The number of irradiation containers containing product or simulated product to precede and follow the dose mapped product will depend on the specific irradiator design. The design of the dose mapping exercise will influence the information that can be obtained about the sources of variability (see Annex D). Further guidance can be found in ISO/ASTM 52303.

9.2.1.5 Partially filled irradiation containers should also be mapped to ensure the dose specification is met. Given that a partially loaded container might contain anywhere from one carton to one carton less than a fully loaded container, the dose distribution might vary based on the number of cartons within the partially filled container. Therefore, evaluation of the dose distribution in partially filled irradiation containers should include assessment of the dose distribution based on varying amounts of product within the irradiation container. Testing of partially filled containers during OQ can provide valuable information that can facilitate exercise design for PQ. Alternatively, adding simulated product to the partially filled irradiation container to simulate a fully loaded container might reduce effects on dose distribution caused by partially filled containers.

If partially filled irradiation containers lead to unacceptable dose distributions, this might be addressed by adding an appropriate amount of simulated product. Details of such an addition should be part of the process specification.

9.2.2 Dosimetry

9.2.2.1 Dosimeter placement

9.2.2.1.1 Dosimeters should be placed throughout each fully loaded irradiation container to be mapped in sufficient numbers to determine the minimum and maximum dose locations. Data from the OQ dose mapping might be used to guide dosimeter placement, focusing dosimeter placement on expected regions of minimum and maximum doses.

9.2.2.1.2 Dosimeters should be placed in regions of expected minimum and maximum doses in partially filled irradiation containers as well as surrounding irradiation containers whose dose distributions can be influenced by the partially filled irradiation containers.

9.2.2.1.3 The location to be used for routine process monitoring should be included in the dosimeter placement plan for PQ. This monitoring location should be a location of convenience in, on or near the irradiation container, but always a location that travels with the irradiation container. While not required, it might be convenient to use either the minimum or maximum dose location as the monitoring location.

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

9.2.2.1.5 For a product that causes localized shielding or scattering, it might be necessary to use thin film dosimeters to obtain the required spatial resolution. If thin film dosimeters with no protective sachet are used, these dosimeters can be extremely susceptible to changes in environmental conditions, such as humidity, which can cause significant measurement errors. These errors can be reduced by irradiating thin film dosimeters with no protective sachet in close proximity to reference dosimeters or thin film dosimeters in their protective sachets during the dose mapping exercise. The positioning of the unprotected dosimeters with the reference dosimeter should ensure that the two types of dosimeters are irradiated to the same dose. Differences between the dose measurements of the two types of dosimeters can be used to correct the dose mapping results.

9.2.2.1.6 For a low-density product being irradiated by gamma rays, it might be appropriate to place dosimeters outside the sterile barrier system of product, as significant dose gradients might not occur on/in individual product items. Typical examples are products made up of elements of low atomic number (e.g. non-metallic product) which, in addition, do not contain material with densities or masses great enough to cause local shielding or scattering to adjacent areas.

NOTE In some irradiator designs, significant dose gradients might occur in low-density product due to the design of the irradiator and location of structural materials of the irradiation container.

9.2.2.1.7 For a product that contains materials with densities or masses great enough to cause local shielding or scattering when being irradiated, it might be necessary to place dosimeters inside the sterile barrier system of product in order to determine the minimum and maximum doses. For example, an implant made of titanium has a significantly greater density than that of the packing materials and therefore might require placement of dosimeters inside the sterile barrier system.

9.2.2.2 Replicate dose mapping exercises

Replicate dose mapping exercises are carried out in order to obtain information on variability of measured doses caused by irradiator variation, product variation and dosimeter measurement reproducibility. A minimum of three dose mapping exercises — each carried out using a separate irradiation container — is recommended in order to obtain statistically valid data. Confidence in the measured values is increased by performing 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. Further guidance can be found in ISO/ASTM 52303.

There may be specialized cases, such as irradiation for sterilization dose establishment, where only one or two irradiation containers are used. In these cases, sufficient dosimeters should be placed in each irradiation container to identify the locations of and to measure the minimum and maximum doses.

9.2.3 Analysis of dose mapping data

Dose mapping data are analysed to

a) define a routine monitoring position related to the locations of minimum and maximum doses to product, and

b) define components of uncertainty, related to the use of a routine monitoring position to make indirect measurements of minimum and maximum dose to product, where applicable.

NOTE For guidance on selection of routine monitoring positions, see AAMI TIR29 and ISO/ASTM 52303. For guidance on how to use the data to define components of uncertainty, see Annex D.

9.3 Electron beam irradiators

9.3.1 Loading pattern

9.3.1.1 For dose mapping, individual product cartons should be arranged within an irradiation container in a way that defines the intended routine loading pattern. Consideration should be given to the key product characteristics, including individual product carton dimensions and weight, and allowable variations in these parameters, product composition, orientation of the product cartons and units within the product carton relative to the beam direction, the dose specification for the product and insights gained from OQ dose mapping. Samples of product cartons to be irradiated during the PQ should be measured and weighed to ensure product cartons conform to defined product characteristics.

Product orientation within the product carton might influence dose distribution and should therefore be considered when preparing product for electron beam sterilization. Product cartons are generally oriented to utilize the volume of the irradiation container optimally. However, in some instances, the

available space cannot be utilized due to product constraints such as narrow dose range specification, product high density or heterogeneity or carton dimensions.

9.3.1.2 In some situations, product cartons can move within the irradiation container or product units can move within the product carton, both possibly affecting dose distribution.

If product cartons can move within the irradiation container and in so doing affect dose distribution, the product should be secured to prevent such movement. Materials used to secure product during PQ should also be used during routine process and defined in the process specification. In the event the product cartons cannot be sufficiently secured, this should be taken into account during dose mapping, for example, by mapping a worst case configuration.

If the product can move within a product carton, and in so doing affect dose distribution, this should be taken into account during dose mapping, for example, by mapping several possible orientations of product within the product carton to establish the worst case scenario with respect to dose distribution.

9.3.1.3 A sufficient number of fully loaded irradiation containers should be dose mapped at the designated set of process parameters in order to allow determination of variability of dose and dose distribution between containers. A minimum of three containers should be dose mapped in order to obtain statistically valid data. Confidence in the measured values is, however, increased by performing a larger number of dose mapping exercises. For replicate dose mapping exercises, it could be sufficient to place dosimeters only in regions of dose extremes, rather than carry out a full dose mapping exercise.

Depending on the irradiator design, at least one irradiation container fully loaded with product might precede and follow the dose mapped irradiation containers to minimize the effect other dissimilar products in the irradiator might have on the dose distribution in the PQ product. The design of the dose mapping experiment will influence the information about the sources of variability that can be obtained (see Annex D). Additional guidance can be found in ISO/ASTM 52303.

Results from the dose mapping exercise might indicate how modification of certain process parameters can provide doses within specifications for routine sterilization processing. Modification of parameters without repeating the dose mapping would only be acceptable if prior studies demonstrated how changing these parameters affect dose delivery. This would generally occur in situations where parameters (e.g. conveyor speed, beam current, etc.) have been shown to have a direct relationship to dose delivered.

A mathematical model that has been suitably benchmarked might be used to determine the effect of change in parameters on dose delivery.

9.3.1.4 Partially filled irradiation containers should also be mapped to ensure the dose specification is met. Given that a partially loaded container might contain anywhere from one carton to one carton less than a fully loaded container, the dose distribution might vary significantly based on the number of cartons within the partially filled container. Therefore, evaluation of the dose distribution in partially filled irradiation containers should include assessment of the dose distribution based on varying amounts of product within the irradiation container. Alternatively, adding simulated product to the partially filled irradiation container to simulate a fully loaded container might reduce effects on dose distribution caused by partially filled containers.

The spacing between adjacent irradiation containers going through the beam and/or the amount of product within the partially filled irradiation container might also affect the dose delivered to fully loaded irradiation containers adjacent to the partially filled irradiation containers. Therefore, this should be considered when establishing the dosimeter placement plan (see 9.3.9).

If partially-filled irradiation containers lead to unacceptable dose distributions, this might be addressed by adding an appropriate amount of simulated product. Details of such an addition should be part of the process specification.

9.3.2 Dosimetry

9.3.2.1 Dosimeter placement

9.3.2.1.1 Dosimeters should be placed throughout each fully loaded irradiation container to be mapped in sufficient numbers to determine the minimum and maximum dose locations. For a product that is processed using electron beam irradiators, it is usually necessary to place dosimeters inside the sterile barrier system of the product in order to determine the minimum and maximum doses. Unlike gamma or X-ray, data from dose mapping exercises performed with homogeneous materials during OQ are not generally used to guide dosimeter placement during PQ, given the non-homogeneous nature of the product.

9.3.2.1.2 Dosimeters should be placed in regions of expected minimum and maximum doses in partially filled irradiation containers as well as surrounding irradiation containers whose dose distributions may be influenced by the partially filled irradiation containers.

9.3.2.1.3 The location to be used for routine process monitoring should be included in the dosimeter placement plan for the PQ. This monitoring location should be a location of convenience in, on or near the irradiation container, but always a location that travels with the irradiation container. While not required, it can be convenient to use either the minimum or maximum dose location as the monitoring location.

9.3.2.1.4 The dosimetry system should have a spatial resolution high enough to allow measurement of dose gradients that might occur, for example, at material interfaces. For electron beam irradiation, the magnitude of the dose gradients can be several tens of percent over a distance of less than 1 mm, for example, for irradiation of small metal components (see, for example, Reference [29]).

9.3.2.1.5 For a product that causes localized shielding or scattering, it might be necessary to use thin film dosimeters to obtain the required spatial resolution. If thin film dosimeters with no protective sachet are used, these dosimeters can be extremely susceptible to changes in environmental conditions, such as humidity, which can cause significant measurement errors. These errors can be reduced by irradiating thin film dosimeters with no protective sachet in close proximity to reference dosimeters or thin film dosimeters in their protective sachets during the dose mapping exercise. The positioning of the unprotected dosimeters with the reference dosimeter should ensure that the two types of dosimeters are irradiated to the same dose. Differences between the dose measurements of the two types of dosimeters can be used to correct the dose mapping results.

9.3.2.2 Replicate dose mapping exercises

Replicate dose mapping exercises are carried out in order to obtain information on variability of measured doses caused by irradiator variation, product variation and dosimeter measurement reproducibility. A minimum of three dose mapping exercises — each carried out using a separate irradiation container — is recommended in order to obtain statistically valid data. Confidence in the measured values is increased by performing 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. Further guidance can be found in ISO/ASTM 52303.

There may be specialized cases, such as irradiation for sterilization dose establishment, where only one or two irradiation containers are used. In these cases, sufficient dosimeters should be placed in each irradiation container to identify the locations of and to measure the minimum and maximum doses.

9.3.3 Analysis of dose mapping data

Dose mapping data are analysed to

a) define a routine monitoring position related to the locations of minimum and maximum dose to product, and

b) define components of uncertainty related to the use of routine monitoring position to make indirect measurements of minimum and maximum doses to product, where applicable.

NOTE For guidance on selection of routine monitoring positions, see AAMI TIR29 and ISO/ASTM 52303. For guidance on how to use the data to define components of uncertainty, see Annex D.

9.4 X-ray irradiators

9.4.1 Loading pattern

9.4.1.1 For dose mapping, individual product cartons should be arranged within an irradiation container in a way that defines the intended routine loading pattern. Consideration should be given to the key product characteristics, including individual product carton dimensions and weight and allowable variations in these parameters, the dose specification for the product and insights gained from OQ dose mapping. Samples of product cartons to be processed during the PQ should be measured and weighed to ensure product cartons conform to defined product characteristics.

Product cartons are generally oriented to utilize the volume of the irradiation container optimally. However, in some instances, the available space cannot be utilized due to product constraints such as narrow dose range specification, product high density or heterogeneity, or carton dimensions.

The defined product loading configuration within an irradiation container may consist of more than one type of product and include a range of carton sizes and weights. The effects on dose distribution of loading products with different densities at different locations within the container should be investigated. The effect on dose distribution might be examined by performing dose mapping exercises on various load configurations where the extremes in product density are configured in various locations in the irradiation container. The results of the dose mapping exercise might result in one or more locations of potential minimum or maximum dose (see ISO/ASTM 52303).

9.4.1.2 In some situations, product cartons can move within the irradiation container or product units can move within the product carton, both possibly affecting dose distribution.

If product cartons can move within the irradiation container and in so doing affect dose distribution, the product should be secured to prevent such movement. Materials used to secure product during PQ should also be used during routine processing and defined in the process specification. In the event the product cartons cannot be sufficiently secured, this should be taken into account during dose mapping, for example, by mapping a worst case configuration.

If product can move within a product carton, and in so doing affect dose distribution, this should be taken into account during dose mapping, for example, by mapping several possible orientations of product within the product carton to establish the worst case scenario with respect to dose distribution.

9.4.1.3 Low-density products tend to be fairly homogeneous such that the orientation of individual products within the irradiation container is unlikely to have a significant effect on dose distribution when irradiating with X-rays. However, product orientation for non-uniform products, such as those containing high-density components and void spaces (e.g. metal and metal/polymer implants), might make it difficult to achieve an acceptable dose distribution and, in some instances, specific orientation of products might be required within each irradiation container.

9.4.1.4 A sufficient number of fully loaded irradiation containers should be dose mapped at the designated set of operating parameters in order to allow determination of variability of dose and dose distribution between containers. A minimum of three containers should be dose mapped in order to obtain statistically valid data. Confidence in the measured values is, however, increased by performing a larger number of dose mapping exercises. For replicate dose mapping exercises, it could be sufficient to place dosimeters only in regions of dose extremes, rather than carry out a full dose mapping exercise.

The number of irradiation containers containing product or simulated product to precede and follow the dose mapped product will depend on the specific irradiator design. The design of the dose mapping

exercise will influence the information about the sources of variability that can be obtained, see Annex D. Further guidance can be found in ISO/ASTM 52303.

9.4.1.5 Partially filled irradiation containers should also be mapped to ensure the dose specification is met. Given that a partially loaded container might contain anywhere from one carton to one carton less than a fully loaded container, the dose distribution might vary based on the number of cartons within the partially filled container. Therefore, evaluation of the dose distribution in partially filled irradiation containers should include assessment of the dose distribution based on varying amounts of product within the irradiation container. Testing of partially filled containers during OQ can provide valuable information that can facilitate exercise design for PQ. Alternatively, adding simulated product to the partially filled irradiation container to simulate a fully loaded container might reduce effects on dose distribution caused by partially filled containers.

If partially filled irradiation containers lead to unacceptable dose distributions, this might be addressed by adding an appropriate amount of simulated product. Details of such an addition should be part of the process specification.

9.4.2 Dosimetry

9.4.2.1 Dosimeter placement

9.4.2.1.1 Dosimeters should be placed throughout each fully loaded irradiation container to be mapped in sufficient numbers to determine the minimum and maximum dose locations. Data from the OQ dose mapping might be used to guide dosimeter placement, focusing dosimeter placement on expected regions of minimum and maximum doses.

9.4.2.1.2 Dosimeters should be placed in regions of expected minimum and maximum doses in partially filled irradiation containers as well as surrounding irradiation containers whose dose distributions can be influenced by the partially filled irradiation containers.

9.4.2.1.3 The monitoring location to be used for routine process monitoring should be included in the dosimeter placement plan for PQ. This monitoring location should be a location of convenience in, on or near the irradiation container, but always a location that travels with the irradiation container. While not required, it might be convenient to use either the minimum or maximum dose location as the monitoring location.

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

9.4.2.1.5 For products that cause localized shielding or scattering, it might be necessary to use thin film dosimeters to obtain the required spatial resolution. If thin film dosimeters with no protective sachet are used, these dosimeters can be extremely susceptible to changes in environmental conditions, such as humidity, which can cause significant measurement errors. These errors can be reduced by irradiating thin film dosimeters with no protective sachet in close proximity to reference dosimeters or thin film dosimeters in their protective sachets during the dose mapping exercise. The positioning of the unprotected dosimeters with the reference dosimeter should ensure that the two types of dosimeters are irradiated to the same dose. Differences between the dose measurements of the two types of dosimeters can be used to correct the dose mapping results.

9.4.2.1.6 For a low-density product being irradiated by X-ray, it might be appropriate to place dosimeters outside the sterile barrier system of product, as significant dose gradients might not occur on/in individual product items. Typical examples are products made up of elements of low atomic number (e.g. non-metallic product) which, in addition, do not contain material with densities or masses great enough to cause local shielding or scattering to adjacent areas.

NOTE In some irradiator designs, significant dose gradients might occur in low-density products due to the design of the irradiator and location of structural materials of the irradiation container.

9.4.2.1.7 For a product that contains materials with densities or masses great enough to cause local shielding or scattering when being irradiated, it might be necessary to place dosimeters inside the sterile barrier system of product in order to determine the minimum and maximum doses. For example, an implant made of titanium has a significantly greater density than that of the packing materials and therefore might require placement of dosimeters inside the sterile barrier system.

9.4.2.2 Replicate dose mapping exercises

Replicate dose mapping exercises are carried out in order to obtain information on variability of measured doses caused by irradiator variation, product variation and dosimeter measurement reproducibility. A minimum of three dose mapping exercises — each carried out using a separate irradiation container — is recommended in order to obtain statistically valid data. Confidence in the measured values is increased by performing 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. Further guidance can be found in ISO/ASTM 52303.

There may be specialized cases, such as irradiation for sterilization dose establishment, where only one or two irradiation containers are used. In these cases, sufficient dosimeters should be placed in each irradiation container to identify the location of and to measure the minimum and maximum doses.

9.4.3 Analysis of dose mapping data

Dose mapping data are analysed to

a) define a routine monitoring position related to the locations of minimum and maximum doses to product, and

b) define components of uncertainty related to the use of routine monitoring position to make indirect measurements of minimum and maximum doses to product, where applicable.

NOTE For guidance on selection of routine monitoring positions, see AAMI TIR29 and ISO/ASTM 52303. For guidance on how to use the data to define components of uncertainty, see Annex D.

10 Routine monitoring and control

10.1 General

The measurement of dose at the routine monitoring position during processing is used to verify that the minimum dose meets or exceeds the sterilization dose and that the maximum dose does not exceed the maximum acceptable dose.

It is a requirement in ISO 11137-1:2006 , 11.2 that procedure(s) shall define the requirements for designating a sterilization process as conforming, taking into account the uncertainty of the measurement. Measurement uncertainty therefore needs to be considered when selecting an acceptable range(s) of dose at the routine monitoring location(s) for routine processing (see Annex D). A number of approaches for selection are possible — many being based on user-defined decision rules (see References [3] and [24]).

Acceptable limits for the dose measured at the routine monitoring position are given in the process specification. Dose measurements, direct and indirect, for assessing product conformity represent the best estimate of dose. Therefore, values from dose measurements should not be corrected by associated measurement uncertainty (see 4.1.3).

10.2 Frequency of dose measurements

Dose measurement at the routine monitoring position provides process information that is 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 and/or process. The amount of product that might need to be discarded following an out-of-specification dose measurement could also be an important consideration in setting this frequency.

For processing using gamma rays, dosimeters are typically placed at the beginning and end of each run of a product comprising a particular processing category. Additionally, dosimeters should be placed so that at least one dosimeter is within the irradiator at all times.

For processing using electron beam or X-rays, dosimeters are typically placed at least at the beginning and end of each run of product comprising a processing category that is irradiated using a specific set of processing parameters.

Plotting of successive routine dosimetry measurements on a control chart can provide valuable information on the performance of the irradiation process and enable preventive action to be taken before out-of-specification measurements occur. In certain situations, it may be possible to extend this approach to full statistical process control, as given in Reference [33].

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 and product, taking into account the attenuation and scattering by materials between the radiation 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 capsules in the source rack, irradiation containers, the irradiator support structures and the product. For electron beam and X-ray irradiators, the beam energy, the beam current and the composition and position of the product, the irradiation containers and the adjacent scattering materials should be accurately known. Errors in any input parameter for the calculation can result in errors in the calculated doses, and therefore 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 References [23], [27] and [31].

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 the 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 photon 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 of dose estimation on 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 change of path following different interactions. The probability for each interaction is obtained from published tables. Theoretically, the Monte Carlo method can reliably 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.

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 performance of the irradiator when filled with homogeneous products. Calculations provide information on the expected dose per unit of activity or 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, doses during source transit or shutdown of the electron beam and effects of voids or product heterogeneity.

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 dose mapping exercises. Dosimeters should also be placed in the minimum and maximum dose zones predicted by mathematical modelling as well as other locations to confirm that the irradiator performs as expected.

After dose mapping exercises 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 sequential elements of the following example.

— Use mathematical modelling to calculate the dose distributions in homogeneous products 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.

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 dose mapping exercises. Mathematical modelling also can be used to determine the dose in areas where there can be steep dose gradients, such as near the edges of a product, to ensure that dosimeters provide adequate spatial 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.

Annex B
(informative)

Tables of references for dosimetry-related testing during IQ/OQ/PQ

B.1 Installation qualification

Table B.1 — Electron beam and X-ray (not applicable for gamma)

Qualification activity	Description	Irradiator for sterilization processing	Special irradiator pathways	ISO 11137-1:2006, Clause	ISO 11137-3:2017, Clause
Beam energy	Characterization of beam energy[a]	✓	N/A	9.1.5 and 9.1.6	7.2 to 7.7
Beam current	Characterization of beam current[a]	✓	N/A	9.1.5 and 9.1.6	7.2 to 7.7
Scan width	Characterization of scan width and scan uniformity[1]	✓	N/A	9.1.5 and 9.1.6	7.2 to 7.7

[a] Refer to ISO/ASTM 51649, ISO/ASTM 51818 and/or ISO/ASTM 51608 for detailed guidance for performing these characterizations.

N/A = not applicable.

B.2 Operational qualification

Table B.2 — Gamma, electron beam and X-ray

Qualification activity	Description	Irradiator for sterilization processing	Special irradiator pathways	ISO 11137-1:2006, Clause	ISO 11137-3:2017, Clause
Homogeneous dose mapping	Dose mapping of homogeneous material(s)[a]	✓	N/A	9.2.2 and 9.2.6	8.2.1 to 8.2.6, 8.3.1 to 8.3.4, 8.4.1 to 8.4.6,
Special conveyor systems (research loops) or fixed locations-homogeneous dose mapping	Dose mapping of homogeneous material(s)[a]	N/A	✓	9.2.2 and 9.2.6	8.2.9, 8.4.9
Transition studies	Effect on dose delivery when transitioning between different densities	✓	N/A	9.2.3	8.2.11 8.3.3 8.4.11
Variability	Assessing dose variability between irradiation containers	✓	N/A	9.2.3, 9.2.5	8.2.3, 8.3.3, 8.4.4
Process interruption	Effect on dose delivery due to source transit or beam stop and restart	✓	N/A	9.2.7	8.2.7, 8.2.8, 8.3.6 to 8.3.8, 8.4.8
Partially filled irradiation containers	Effect on dose distribution based on container fill level	✓	N/A		8.2.10, 8.4.10
Special conveyor systems (research loops) or fixed locations container travel dose	Dose contribution resulting from special conveyor systems container transit to/from the irradiation position	N/A	✓		8.2.9, 8.4.9
Parameter inter-relationship[b]	Characterize inter-relationship between beam characteristics, conveyor speed and dose	✓	N/A	9.2.11	8.2.6, 8.3.5, 8.4.7

[a] Refer to ISO/ASTM 52303 for detailed guidance on dose mapping.

[b] Applicable to electron beam and X-ray only.

N/A = not applicable.

B.3 Performance qualification

Table B.3 — Gamma, electron beam and X-ray

Qualification activity	Description	Irradiator for sterilization processing	Special irradiator pathways	ISO 11137-1:2006, Clause	ISO 11137-3:2017, Clause
Product dose mapping	Dose mapping of product(s)[a]	✓	N/A	9.3.1, 9.3.3 and 9.3.6, 9.3.7	9.1.1 to 9.1.5, 9.2.1 to 9.2.3, 9.3.1 to 9.3.3, 9.4.1 to 9.4.3
Special conveyor systems or fixed locations in the irradiator designed for manual placement of products	Dose mapping of product(s)[a,b]	N/A	✓	9.3.2 and 9.3.6	N/A
Transition studies	Effect on dose delivery when transitioning between different densities	✓	N/A	9.3.7	9.2.1.4, 9.4.1.4
Variability	Assessing dose variability between irradiation containers	✓	N/A	9.3.5	9.2.1.4, 9.2.2.2, 9.3.1.4, 9.3.2.2, 9.4.1.4, 9.4.2.2
Partially filled irradiation containers	Effect on dose distribution based on container fill level	✓	N/A	9.3.4	9.2.1.5, 9.2.2.1.2, 9.3.2.1.2, 9.4.1.5, 9.4.2.1.2

[a] Refer to ISO/ASTM 52303 for detailed guidance on dose mapping.

[b] Generally, this involves dose mapping of product configurations for performing sterilization dose establishment, sterilization dose audits, and/or establishment of maximum acceptable dose.

N/A = not applicable.

Annex C
(informative)

Tolerances associated with doses used in sterilization dose setting/substantiation in ISO 11137-2 and ISO/TS 13004

Table C.1 — Tolerances associated with doses used in sterilization dose setting/substantiation in ISO 11137-2 and ISO/TS 13004

	Highest dose to product items	Arithmetic mean of highest and lowest doses to product items
Method 1		
BB ≥ 1,0 (VD range 3,0 to 21,2 kGy)	not > 110 % VD	not < 90 % VD
BB 0,1 to 0,9 (VD range 1,3 to 2,9 kGy)	not > 110 % VD	not < 90 % VD
Method 2A		
IDE	not > ID by 10 % or 1,0 kGy, whichever is greater	not < 90 % ID or ID minus 1,0 kGy, whichever is lesser
VDE	not > D* by 10 % or 1,0 kGy, whichever is greater	not < 90 % D* or D* minus 1,0 kGy, whichever is lesser
Method 2B		
IDE for 1 kGy for other doses	not > 1,2 kGy (20 %) not > ID by 10 % or 0,5 kGy, whichever is greater	not < 0,8 kGy (20 %) not < 90 % ID or ID minus 0,5 kGy, whichever is lesser
VDE	not > D* by 10 % or 1,0 kGy, whichever is greater	not < 90 % D* or D* minus 1,0 kGy, whichever is lesser
Method $VD_{max}25$		
(SIP = 1,0 $VD_{max}25$ range 0,9 to 9,2 kGy)	not > $VD_{max}25$ by 10 %	not < 90 % $VD_{max}25$
Method $VD_{max}15$		
(SIP = 1,0 $VD_{max}15$ range 0,5 to 2,3 kGy)	not > $VD_{max}15$ by 10 % or 0,1 kGy, whichever is greater	not < 90 % $VD_{max}15$

BB = bioburden.

VD = verification dose.

IDE = incremental dose experiment.

VDE = verification dose experiment.

ID = incremental dose.

D* = initial estimate of the dose to provide an SAL of 10^{-2} for test items.

Annex D
(informative)

Application of dose measurement uncertainty in setting process target doses

D.1 General

This annex provides an overview of how dose measurement uncertainty may be used to establish process target doses. Details of establishing process target doses are outside the scope of this document. However, discussion of dosimetry uncertainty in this document is facilitated by a common understanding of how it may be applied in establishing process target doses.

D.2 Standard uncertainty for setting process target doses ($\sigma_{process}$)

In order to establish the components of dose measurement uncertainty relevant to setting process target doses, it is necessary to first identify all potentially significant sources of uncertainty (see 4.3.1) and then consider their relevance to the way the sterilization process is operated and monitored. The standard uncertainty to be used in setting process target doses is designated $\sigma_{process}$ and can be derived by quantifying individual components of uncertainty or by quantifying a combination of components obtained during dose mapping exercises and by the use of historical data for a given irradiator.

See 4.3.3.3 for examples of components of $\sigma_{process}$. The values of $\sigma_{process}$ may be different for the minimum and maximum doses.

A number of the components of uncertainty contributing to $\sigma_{process}$ can be determined through PQ dose mapping exercises. If the PQ dose mapping has been carried out using dose mapping exercises that are designed to capture full process variability, it is possible to analyse the data to obtain a combined value of multiple components of uncertainty. Alternatively, if the PQ dose mapping exercise does not capture the combined effects of these components, additional experiments can be carried out.

In the case of established processing conditions for which there is a history of dose mapping data and where the dose measurement uncertainty at the minimum and maximum dose locations or the ratios $R_{max/mon}$and $R_{min/mon}$are well established; for example, for an established processing category, it might be possible to base the estimate of $\sigma_{process}$ on pooled information from previous dose mapping exercises. The use of pooled data from members of a processing category is likely to result in a more robust determination of $\sigma_{process}$ than values based on a small number of dose mapping exercises.

Some components of uncertainty associated with dosimetry system calibration will not be captured through dose mapping exercises; these should be included in $\sigma_{process}$.

NOTE Examples of approaches for analysing PQ data and determining $\sigma_{process}$ are given in Panel on Gamma & Electron Irradiation[33] and AAMI TIR29 [22].

Regardless of the approach taken, ongoing process monitoring is important in refining the initial estimate of $\sigma_{process}$ and it should be reviewed and adjusted as necessary based on analysis of process monitoring data.

$\sigma_{process}$ includes the uncertainty associated with the direct measurement of dose at the dosimeter location and, depending on the process, additional components associated with dose mapping ratios and random process variability. $\sigma_{process}$ values can be used to determine process target dose values that are higher than D_{ster} (or D_{mon}^{ster} if the process is not monitored at the minimum dose location) and equal to or lower than $D_{max,acc}$ (or $D_{mon}^{max,acc}$if the process is not monitored at the maximum dose location). One method for determining process target values is to use $k\sigma_{process}$ values to calculate

process target values, where the value of *k* is dependent on the required level of confidence associated with the process (see D.3).

D.3 Selection of *k* values

The factor *k* is generally taken to be two, approximating a one-sided 98 % level of confidence. One-sided distributions are selected because the requirement is to exceed the sterilization dose and not to exceed the maximum acceptable dose.

NOTE 1 The actual level of confidence will depend on the number of repeat measurements (degrees of freedom) that are involved in the calculation of uncertainty.

Other values of *k* (see Note 2) might be applicable in specific situations based on the risk assessment of the product and process (see ISO 14971).

NOTE 2 For normal (Gaussian) distributions, the approximate one-sided confidence levels obtained by different selections of *k* are

k = 1 84 % confidence level,

k = 2 98 % confidence level, and

k = 3 99,5 % confidence level.

NOTE 3 See Reference [26] for further information about the relationship between confidence levels and degrees of freedom (number of measurements).

D.4 Radiation sterilization target dose values

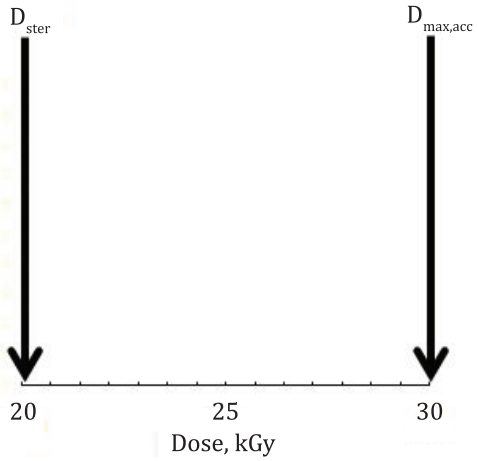
Figures D.1 through D.3 are pictorial representations of key terms for defining radiation sterilization target dose values. All figures are for the same product with D_{ster} and $D_{max,acc}$values of 20 and 30 kGy, respectively, with the same loading configuration in the same irradiator. The only difference is the routine monitoring position.

Figure D.1 a) is a pictorial representation of process specifications for the product.

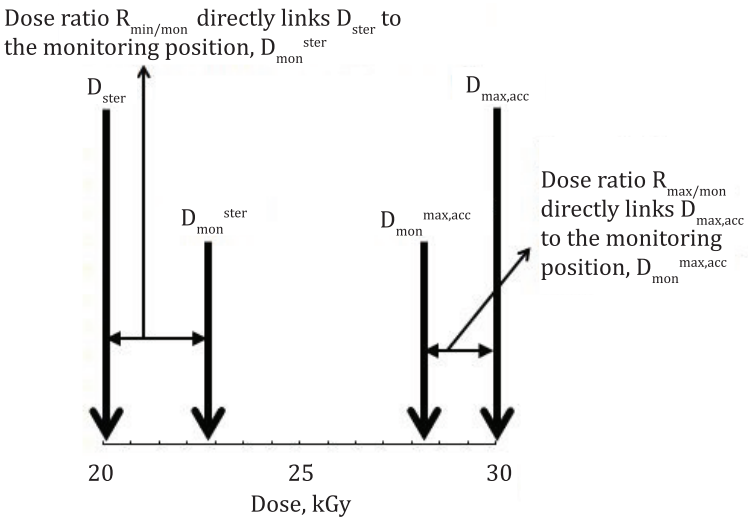
Figure D.1 b) represents the related monitoring dose range that would be associated with using a monitoring dosimeter remote from the positions of minimum and maximum doses.

Figure D.2 a) and Figure D.2 b) are a pictorial representation of process target values for the particular case when the process is monitored at the locations of minimum and maximum doses, respectively.

Figure D.3 a) and Figure D.3 b) are a pictorial representations of process target values in the particular case when the process is monitored at a routine monitoring location remote from the positions of minimum and maximum doses but traveling with the product, respectively.



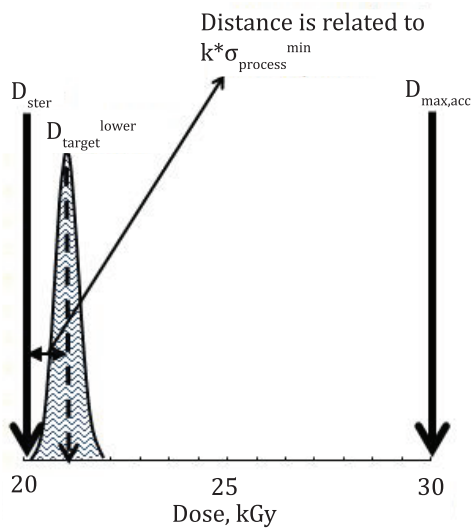
a) Pictorial representation of product specifications, D_{ster} and $D_{max,acc}$, 20 and 30 kGy, respectively



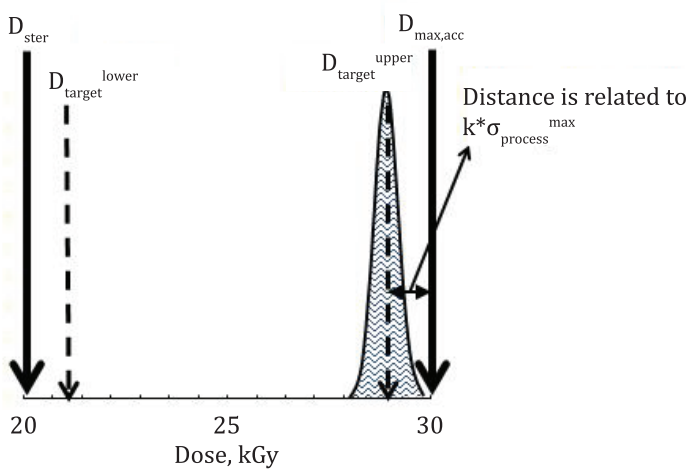
b) Pictorial representation of doses, D_{mon} ^{ster} and D_{mon} ^{max,acc}, at a remote monitoring position that correspond directly through dose ratios to product specifications, D_{ster} and $D_{max,acc}$

NOTE D_{mon} ^{ster} and D_{mon} ^{max,acc} apply when dose is monitored at a routine monitoring location remote from the positions of minimum and maximum doses but traveling with the product.

Figure D.1 — Process specifications



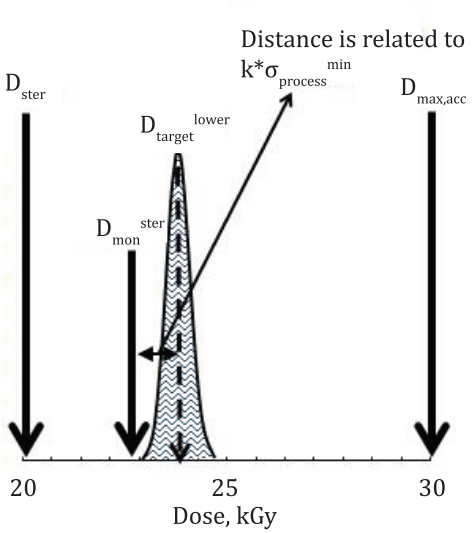
a) Pictorial representation of key terms for defining a radiation sterilization minimum target value for D_{ster} = 20 kGy



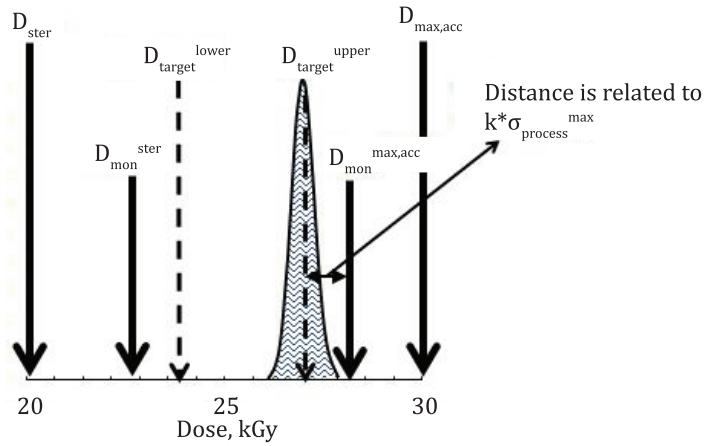
b) Pictorial representation of key terms for defining a radiation sterilization maximum target value for $D_{max,acc}$= 30 kGy

NOTE The normal distribution around D_{target}^{upper} is the distribution associated with the process uncertainty (see D.2).

Figure D.2 — Routine dose monitoring at minimum and maximum dose locations



a) Pictorial representation of key terms for defining a minimum target value for D_{ster} = 20 kGy



b) Pictorial representation of key terms for defining a maximum target value for $D_{max,acc}$ = 30 kGy

NOTE 1 D_{target}^{upper} is correlated with $D_{max,acc}$ through the ratio $R_{max/mon}$.

NOTE 2 The normal distribution around D_{target}^{upper} is the distribution associated the process uncertainty (D.2).

Figure D.3 — Routine dose monitoring at a location remote from position of minimum and maximum dose but travelling with the product

D.5 Calculating process target dose values that take uncertainty into account

$\sigma_{process}$ can be used in the calculation of target doses at the monitoring location that correspond to doses to product in irradiation containers that are within specifications at a given level of confidence.

This can be achieved by the calculation of factors designated UF_{lower} and UF_{upper} as given in Formulae (D.1) and (D.2), respectively:

$$UF_{lower} = 1/(1 - k\sigma_{\text{process}}^{\text{min}}/100) \quad \text{(D.1)}$$

$$UF_{upper} = 1/(1 + k\sigma_{\text{process}}^{\text{max}}/100) \quad \text{(D.2)}$$

where $\sigma_{\text{process}}^{\text{min}}$ and $\sigma_{\text{process}}^{\text{max}}$ are the uncertainty values associated with the minimum and maximum doses, respectively.

Using the values of UF obtained above, two statistically based values of dose at the routine monitoring position D_{mon} can be defined for use in process control. These are designated $D_{\text{target}}^{\text{upper}}$ and $D_{\text{target}}^{\text{lower}}$ as given in Formulae (D.3) and (D.4), respectively:

$$D_{\text{target}}^{\text{upper}} = D_{max,acc}/R_{max/mon} \cdot UF_{upper} \quad \text{(D.3)}$$

$$D_{\text{target}}^{\text{lower}} = D_{ster}/R_{min/mon} \cdot UF_{lower} \quad \text{(D.4)}$$

The monitoring locations may be at the location of minimum and maximum doses or may be at a separate monitoring location.

The D_{target} doses form the basis for process control during routine sterilization, but the manner of interpretation will depend on the method of process control adopted. Details of the method of process control used are outside the scope of this document. The approach chosen will depend on several factors, such as the type of irradiator, the product and other local operating requirements.

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