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Sterilization of health care products — Radiation —

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

Stérilisation des produits de santé — Irradiation —
Partie 3: Directives relatives aux aspects dosimétriques de développement, la validation et le contrôle de routine

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Foreword

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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.

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):

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

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

