TECHNICAL SPECIFICATION

ISO/TS 11137-4

First edition
2020-06

Sterilization of health care products — Radiation —

Part 4: Guidance on process control

Stérilisation des produits de santé — Irradiation —

Partie 4: Recommandations sur le contrôle de processus

Reference number
ISO/TS 11137-4:2020(E)

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

Contents

Page

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).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of 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 www.iso.org/iso/foreword.html.

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

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

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

ISO 11137-1 describes the requirements for the development, validation and routine control of a radiation sterilization process, and ISO 11137-3 gives guidance on dosimetric requirements in all stages of this development, validation and control. The purpose of ISO/TS 11137-4 is to provide additional guidance on the establishment and control of the irradiation process, including setting process target doses and verifying that the process is in a state of control.

This document addresses the establishment of methods to set process target doses and verify the process is in a state of control. Dosimetry is used during the validation of a radiation sterilization process to measure doses, and the interpretation of dosimetry results from operational and performance qualification studies is critical in establishing a process that will meet the requirements specified for minimum and maximum dose as outlined in ISO 11137-1, ISO 11137-2 and ISO/TS 13004.

Routine dosimetry is used to monitor that the process is in a state of control and dose specifications have been met. One purpose of this technical specification is to provide guidance on the application of a dose measurement as a tool used for monitoring an irradiation process using statistical techniques.

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 achieving conformity with the minimum and maximum dose specifications. Methods other than those given in the guidance may be used, if they are effective in achieving conformity with the requirements of ISO 11137-1, ISO 11137-2 and ISO/TS 13004.

Sterilization of health care products — Radiation —

Part 4: Guidance on process control

1 Scope

This document provides additional guidance to that given in ISO 11137-3 on meeting the requirements specified in ISO 11137-1, ISO 11137-2 and ISO/TS 13004 for the establishment and control of a radiation sterilization process using gamma, electron beam, and X-irradiation.

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 11137-1:2006, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

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

3 Terms, definitions and symbols

For the purposes of this document, the terms and definitions given in ISO 11137-1, ISO 11137-3 and the following apply.

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

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

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

3.1 General

3.1.1
acceptance range
range within which the statistic under consideration lies with a specified probability when the process is in a state of control

3.1.2
action level
value from monitoring that necessitates immediate intervention

[SOURCE: ISO 11139:2018, 3.5]

3.1.3
alert level
value from monitoring providing early warning of deviation from specified conditions

Note 1 to entry: An alert level value provides early warning of a potential deviation for a process under control. Although further action is not required, increased supervision of the process is recommended.

[SOURCE: ISO 11139:2018, 3.11, modified — Note 1 to entry has been added.]

3.1.4
cycle time
period of time an irradiation container spends in each dwell position in a gamma process, used as a control parameter for dose

Note 1 to entry: Cycle time can also apply to x-ray and could also include the time required to move between dwell positions.

[SOURCE: ISO 11139:2018, 3.73, modified — Note 1 to entry has been added.]

3.1.5
influence quantity
quantity that, in a direct measurement, does not affect the quantity that is actually measured, but affects the relation between the indication and the measurement result

Note 1 to entry: In radiation processing dosimetry, this term includes temperature, relative humidity, time intervals, light, radiation energy, absorbed-dose rate, and other factors that might affect dosimeter response, as well as quantities associated with the measurement instrument.

[SOURCE: VIM 2012, 2.52, modified — Note 1 to entry added from ISO/ASTM 52701:2013.]

3.1.6
measurement uncertainty
parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand

3.1.7
process control
specific activities to ensure process requirements are achieved

[SOURCE: ISO 11139:2018, 3.209]

3.1.8
process load
volume of material with a specified product loading configuration irradiated as a single entity

Note 1 to entry: The process load consists of one or more irradiation containers.

[SOURCE: ISO/ASTM 52303:2015, 3.1.10]

3.1.9
process target dose
D_{target}
dose, at a specified monitoring location, which the irradiation process parameters are set to deliver

3.1.10
process variability
measure of factors that result in a random distribution of data around the average that provides information on how well the process can perform when all special cause variation is removed

3.1.11
Statistical Process Control
SPC
set of techniques for improving the quality of process output by reducing variability through the use of one or more control charts and a corrective action strategy used to bring the process back into a state of statistical control

[SOURCE: ASTM E2587-16]

3.1.12
targeting buffer
standard factor or factors used to determine process target doses which has been demonstrated to be more conservative calculated values of UF_{lower} and UF_{upper} during historical routine processing

3.2 Symbols

Symbol	Meaning
D_{min}	direct measurement of minimum dose in a given irradiation container
D_{max}	direct measurement of maximum dose in a given irradiation container
D_{mon}	direct measurement of dose at the routine monitoring position
D_{ster}	Sterilization dose determined in accordance with ISO 11137-1:2006, 8.2
$D_{max,acc}$	maximum acceptable dose determined in accordance with ISO 11137-1:2006, 8.1
$D_{min}^{limit} = D_{ster} * UF_{lower}$	calculated dose at the minimum dose position used for establishing process parameters that ensures at a specified level of confidence that D_{ster} is met or exceeded during routine processing
$D_{max}^{limit} = D_{max,acc} * UF_{upper}$	calculated dose at the maximum dose position used for establishing process parameters that ensures at a specified level of confidence that $D_{max,acc}$ is not exceeded during routine processing
$UF_{lower} = 1/(1 - k * \sigma_{process}^{min}/100)$	process factor used to calculate D_{target}^{lower} and D_{min}^{limit} (where $\sigma_{process}^{min}$ is expressed as a percentage)
$UF_{upper} = 1/(1 + k * \sigma_{process}^{max}/100)$	process factor used to calculate D_{target}^{upper} and D_{max}^{limit} (where $\sigma_{process}^{max}$ is expressed as a percentage)
$R_{min/mon} = D_{min} / D_{mon}$	ratio of minimum to monitor dose determined by dose mapping
$R_{max/mon} = D_{max} / D_{mon}$	ratio of maximum to monitor dose determined by dose mapping
$D_{mon}^{ster} = D_{ster}/R_{min/mon}$	dose at the monitoring position that correlates to the sterilization dose specification
$D_{mon}^{max,acc} = D_{max,acc}/R_{max/mon}$	dose at the monitoring position that correlates to maximum acceptable dose specification
$D_{target}^{lower} = D_{min}^{limit} / R_{min/mon}$	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
$D_{target}^{upper} = D_{max}^{limit} / R_{max/mon}$	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
σ_{cal}	component of uncertainty related to the calibration of the dosimetry system including the uncertainty reported by the calibration laboratory, uncertainty in the mathematical fit of the calibration function, and uncertainties due to influence quantities, but excluding components due to the reproducibility of the dosimeter measurement (see σ_{rep})
σ_{mach}	component of variability related to the radiation source and conveyor system
σ_{map}	component of variability measured during a dose mapping exercise
$\sigma_{process}$	standard deviation associated with the irradiation process used for setting process target doses $\sigma_{process}^{max}$ — The standard deviation associated with the process maximum dose $\sigma_{process}^{min}$ — The standard deviation associated with the process minimum dose
σ_{rep}	component of variability associated with the reproducibility of the dosimeter measurement

4 Principles applied in validating and controlling an irradiation process

4.1 General

Many dose measurements are made in the validation of an irradiation process as described in ISO 11137-1 and ISO 11137-3. These measurements are used to establish a relationship between processing parameters, monitoring dose, and the range of doses to a product, and to characterize the variability associated with the process itself. These measurements are made with calibrated dosimetry systems traceable to internationally recognized standards with a known level of uncertainty.

It is a requirement to monitor that the validated radiation sterilization process is in a state of control. ISO 11137-1:2006, 10.6 requires the use of dosimeters in routine monitoring and control and provides guidance on the additional review of monitoring of process parameters when determining that product has been processed according to specification.

The combination of dose measurements, monitoring of the associated processing parameters used to achieve those doses, and procedural controls are critical in establishing a process and determining whether or not it is in a state of control.

4.2 Use of the dose measurement at the monitoring location

4.2.1 General

Analysis of measurements from routine monitoring dosimeters is used to determine whether or not process specifications have been met. There are two methods of analysis that can be considered:

1) interpretation of dose measurements as a direct or indirect measure of dose delivered to product; and

2) interpretation of dose measurements to monitor that a process is in a state of control.

In all cases, a validated process provides an expectation of the monitored dose based on derived process target doses and associated processing parameters. The interpretation of the monitoring dose should be documented in the process specification.

The ability to detect changes in the process is limited by the intrinsic variability of dose at the routine monitoring location i.e. the variability measured when the process is in control. If σ_{rep} of the monitoring dosimetry system is large or dosimeter placement imprecise, this variability might be significantly higher than the true variability of the process. In such circumstances, significant changes in the process could go undetected, because they are masked by the high intrinsic variability at the monitoring location. Steps should be taken to minimise variability arising from the monitoring dosimetry system and dosimeter placement. See 6.5.4 and Annex A, Example 3.

4.2.2 D_{mon} as an indirect measurement of dose to product

In an indirect measurement, the maximum and minimum doses to product are calculated from the monitoring dose measurement. The calculated doses have uncertainties associated with the dose at the monitoring location as well as the uncertainty associated with the dose at maximum or minimum locations and associated ratios, plus any other applicable components of uncertainty. A combination of these components can be used to determine the maximum and minimum targets for the routine monitoring dose. See 6.5.2, 6.5.3 and Annex A, Examples 1, 2 and 5.

4.2.3 D_{mon} as a process monitor

It is acceptable to monitor a process where the maximum or minimum dose to product are not measured routinely (directly or indirectly), but rather where a range of monitoring doses are established that indicate that the process meets specification. In this situation, the variability associated with the measurement of minimum and maximum doses from PQ, combined with other relevant components of uncertainty can be used in determining maximum and minimum targets for the routine monitoring

dose. The variability of dose at the monitoring location is then used to determine the acceptable range of doses that indicate that the process is in a state of control and meets process specifications. Because the routine monitoring dosimeter is not used to measure minimum or maximum dose to product, the uncertainty associated with the relationship between the monitored dose and the maximum and minimum doses within a process load has no relevance in determining process target doses and process conformance.

4.2.4 D_{min} or D_{max} as a direct measurement of dose to product

When routine dose is measured at the minimum and/or maximum dose location in the process load, then the dosimeter measurement provides a direct measurement of dose to product. It can also be used as an indicator that the process is in control. In such case, the benefits of both 4.2.2 and 4.2.3 might be achieved. See Annex A, Example 2.

There are circumstances where a limited amount of data is available to predict the outcome of a process. An example of this is an off-carrier process which is based on a single dose map (see 6.4.1). In these cases, enough dosimeters need to be placed on products to provide a direct measurement of minimum and maximum dose.

4.3 Monitoring of critical process parameters

An important consideration in process control is the ability to detect if a processing parameter is changing in a manner that can affect the output of the process. The ability to monitor and/or control process parameters critical to the process output is, therefore, an important factor in ensuring the state of control of the irradiation process.

There are three main classes of processing parameters to be considered: parameters that relate to the radiation field, parameters that relate to the exposure time of the product to the radiation field, and parameters that relate to product influence. Table 1 provides an overview of the effect of critical process parameters and how they could be monitored.

Table 1 — Process parameters critical to radiation sterilization

Parameter	Effect	Monitoring	Gamma	Elec-tron	X-ray
Radiation field					
Radioisotope decay	Over time the radiation intensity is reduced	Source decay occurs based on the half-life of the isotope; date of irradiation is recorded	✓		
Electron energy	Energy affects the penetration depth of electrons, scan width, and also X-ray conversion efficiency	Irradiator parameters associated with input power and beam current are monitored; indirect measurements using beam penetration profiles are made periodically as part of a quality control check		✓	✓
Beam current	A change in beam current will lead to a change in the radiation intensity and possibly of the beam energy	Can be monitored indirectly during operation; indirect monitors can be calibrated		✓	✓
Beam scan width	For scanned system, width will affect the size of the radiation field and a reduction in width will increase the radiation intensity	Monitored indirectly by feedback of scanning system, or directly through interception of the beam, or through periodic dosimetric tests		✓	✓

Table 1 *(continued)*

Parameter	Effect	Monitoring	Gamma	Electron	X-ray
Exposure time					
Cycle time	Dose is directly proportional to cycle time. An increase in cycle time equals an increase in dose.	Cycle time is set by operator, recorded as part of the process and associated timers are calibrated	✓		✓
Conveyor speed	Dose is inversely proportional to speed of product travelling through an irradiation field	Feedback from conveyor speed monitors; direct measurements made during periodic tests	✓	✓	✓
Product influence					
Loading pattern	Changes to loading pattern including product orientation inside a carton and/or carton loading into an irradiation container can affect dose delivery	Defined product loading patterns and procedures to ensure products are loaded according to specification	✓	✓	✓
Density and loading pattern of surrounding materials	Materials surrounding product during irradiation can affect dose delivered through attenuation or scattering of radiation	Appropriate scheduling of process loads; defined criteria resulting from OQ for materials surrounding product during irradiation are documented	✓	✓	✓

5 Establishing process target doses

5.1 Inputs and steps in establishing a process target dose

5.1.1 General

The irradiation process is monitored using processing parameters and dosimeter measurements. Three process target doses at the routine monitoring position can be defined; D_{target}^{lower}, D_{target}^{upper} and D_{target} corresponding, respectively, to the lower and upper set limits for the process target dose and the actual process target dose chosen for processing under given conditions.

There are a number of factors used in the determination of a range of process target doses.

The inputs and steps in establishing a process target dose are listed in the following sections and depicted in Figure 1.

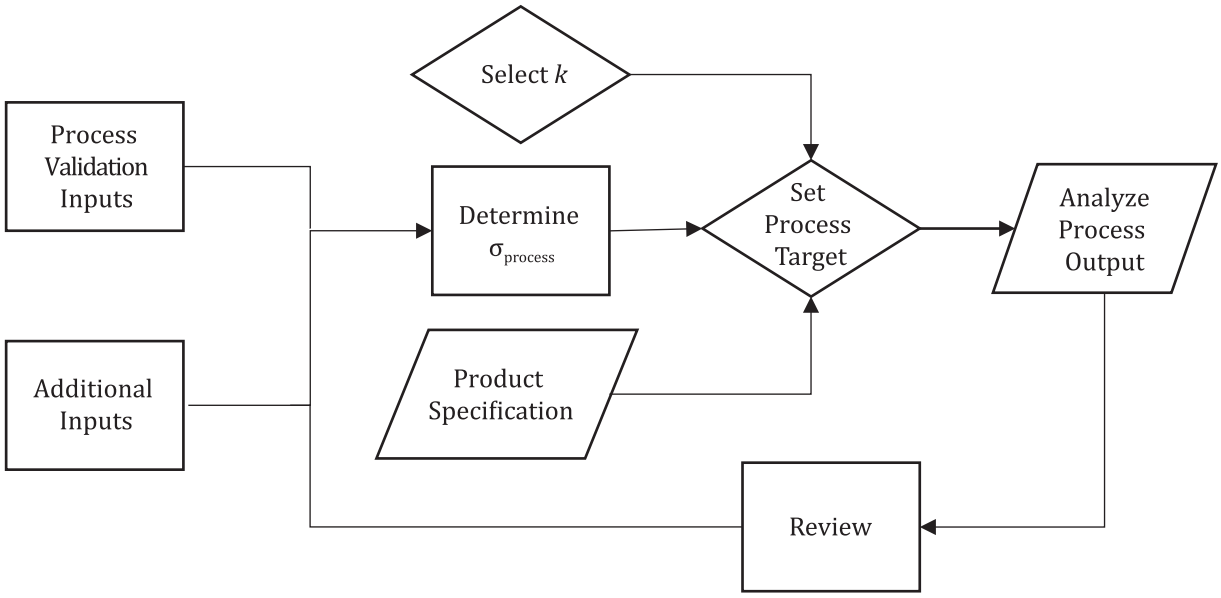

Figure 1 — Inputs and steps in establishing a process target dose

5.1.2 Process validation inputs (installation, operational and performance qualification)

The results of process validation that can be used to provide input into establishing process target doses include the following:

a) the magnitude of minimum dose to product D_{min} for a given loading configuration and set of operating parameters and its relationship to the routine monitoring dose D_{mon};

b) the magnitude of maximum dose to product D_{max} for a given loading configuration and set of operating parameters and its relationship to the routine monitoring dose D_{mon};

c) the variability associated with D_{min}, D_{max} and D_{mon}, and the uncertainty associated with their ratios (if used);

and if applicable the effects of

d) process interruptions;

e) transitions between different product;

f) partially filled irradiation containers.

The application of process validation data in establishing process target doses is discussed further in 5.2.

5.1.3 Additional inputs

Additional inputs may include components that contribute to the uncertainty of the process which are not captured during process validation. These might include, but are not limited to σ_{cal}, and/or targeting buffers defined by the operator as applicable.

5.1.4 Determine $\sigma_{process}$

The standard deviation to be used in setting process target doses is designated $\sigma_{process}$ and can be derived by quantifying individual components of measurement uncertainty and process variability or by quantifying a combination of components obtained during qualification exercises and by the use of historical data for a given irradiator.

Separate determinations of $\sigma_{process}$ used to calculate the upper process target dose ($\sigma_{process}^{max}$) and lower process target dose ($\sigma_{process}^{min}$) can be used to determine the range of process target doses. The estimation of these inputs is discussed further in 5.3.

5.1.5 Product dose specifications

Product dose specifications determined in accordance with ISO 11137-1 are:

a) the sterilization dose D_{ster};

b) the maximum acceptable dose $D_{max,acc}$.

5.1.6 Select coverage factor *k*

A coverage factor *k* is selected, representing the level of confidence required or selected for the process (see 5.4.1).

5.1.7 Setting process target doses

The combination of these inputs is used to calculate a range of process target doses at the routine monitoring location defined between:

a) the lowest process target dose that will achieve a minimum dose to product equal to or greater than D_{ster} at a defined level of confidence;

b) the highest process target dose that will achieve a maximum dose to product equal to or less than $D_{max,acc}$ at a defined level of confidence.

The calculation of these targets is discussed in 5.4.

5.1.8 Analyse process output

Analyses of routine dose measurements and monitored processing parameters are used to determine if the process is operating in a state of control (see 6.5 and 6.6).

5.1.9 Review

Ongoing review of data should be used to refine the initial information used to determine $\sigma_{process}$, see 6.6 and Clause 8.

5.2 Performance qualification outputs

5.2.1 General

The purpose of performance qualification (PQ) dose mapping is to provide information about the dose distribution in a process load and the variability associated with the process. Zones of minimum and maximum dose to product for a given process load and set of operating parameters are identified and a location for the routine monitoring position is established.

The minimum or maximum dose zone can be chosen as the monitoring location(s). Alternatively, a measurement of dose in the product can be made indirectly by establishing relationships between the doses at the minimum dose location, maximum dose location and at a routine monitoring position.

Although the minimum number of replicate irradiation containers dose mapped is typically three, a higher number of replicates increases the confidence in the derived average minimum and maximum doses to product and, if applicable, the relationship of these doses to the routine monitoring dose and associated standard deviations for a given process.

D_{ster} and $D_{max,acc}$ are established according to the requirements of ISO 11137-1. Performance Qualification establishes the relationship between D_{ster}, $D_{max,acc}$ and the routine monitoring dose for a given process. This relationship, combined with information on dose measurement uncertainty and process variability, can generate a range of process target doses at the monitoring location(s) (see Figure 5 for an example process).

5.2.2 Experimental design for PQ

There are a number of factors that go into the design of a PQ study which will provide enough information to set up a process that when in a state of control renders product that is irradiated within its dose specifications D_{ster} and $D_{max,acc}$. This can include the determination of the relationship between maximum, minimum and monitoring doses as well as information on the variability of the process.

Factors which can influence the number of dosimeters used and the number of replicate dose maps include, but are not limited to, the following considerations:

a) radiation type (gamma, electron beam, or X-ray);

b) complexity of the product;

c) historic dose mapping data from similar products;

d) information gained from OQ;

e) output of mathematical models.

Information on the use of mathematical models can be found in ASTM E2232[8].

If PQ has been carried out using dose mapping exercises that are planned in such a way as to capture relevant sources of process variability, it is possible to analyse the data to obtain a combined value of multiple components of variability. For example, a PQ dose map study in gamma can be designed to include the expected range of processing conditions including surrounding products, and a PQ dose map study in electron beam can be designed to include combinations of irradiation parameter variations including variations apparent over long time intervals. See Annex A, Example 3 for a PQ designed to provide a combined value of multiple components of variability.

Alternatively, if the PQ dose mapping does not capture the combined effects of these components, such as dose mapping carried out with no variation of the facility parameters or is designed to reduce the variability associated with normal processing (sometimes referred to as a quiet system), additional components of variability should be included to obtain $\sigma_{process}$ where appropriate. This might, for example, be variability associated with the irradiation parameters or surrounding products that would have been determined during OQ. See Annex A, Example 4 for an example calculation of σ_{mach} derived from OQ data.

The calculation of $\sigma_{process}$ can be different when running a quiet system versus running with frequent transitions, partially filled containers, and interruptions. See Annex A, Example 1 for an example where the calculation of $\sigma_{process}$ is adjusted when changing from a quiet system process to a transition.

In the case of established processing conditions for which there is a history of dose mapping and routine monitoring data, it might be possible to base the estimate of $\sigma_{process}$ on pooled information from such data. The use of pooled data, for instance from irradiation of members of the same processing category, is likely to result in a more confident determination of $\sigma_{process}$ than values based on fewer dose maps. See Annex A, Example 2 for a process using historical data.

More examples of approaches for analysing PQ data and determining $\sigma_{process}$ are given in Annex A.

5.2.3 Processing categories

The establishment of processing categories allows the operator to group together products which can be irradiated using the same processing parameters. The choice of parameters might not be optimal for any one product but rather provide a common process that will work for all products in the group.