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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

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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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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.

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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.

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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.

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[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]

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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

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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

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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		✓	✓

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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.

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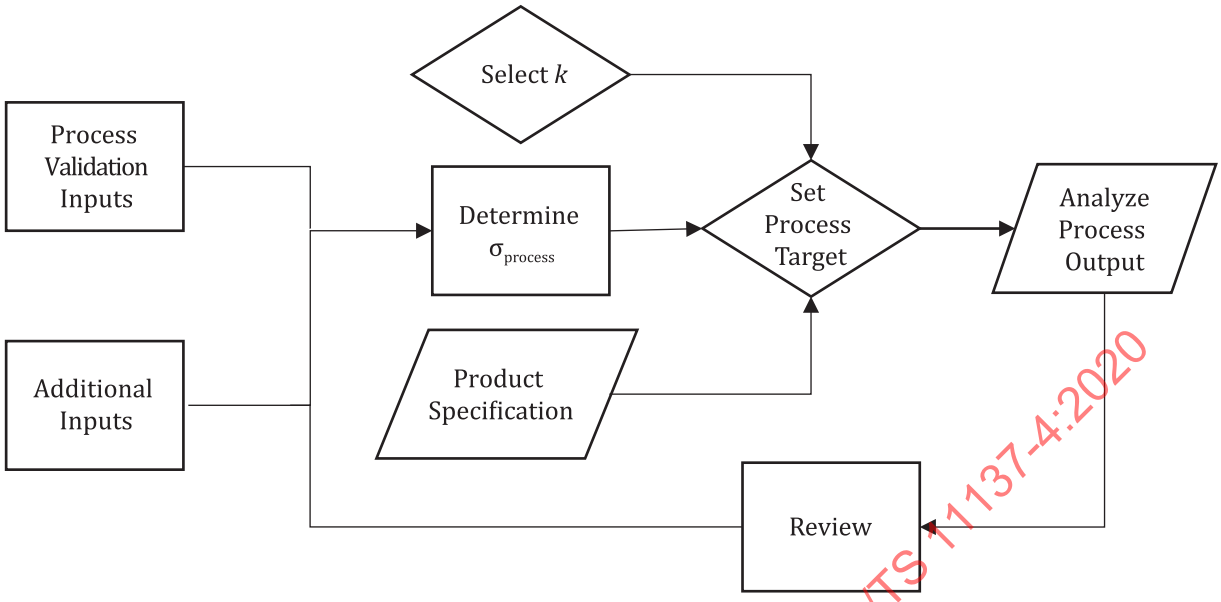

Figure 1 — Inputs and steps in establishing a process target dose

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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.

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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.

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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.

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For gamma and X-ray facilities, rules regarding processing categories can be established during OQ. A key part of establishing processing categories is the evaluation of how density variations in surrounding irradiation containers affect known dose distributions and magnitudes in order to determine allowable density variations within a processing category. A product can be a member of more than one processing category depending on the range of allowable process target doses. Products which can be processed in more than one processing category are often used to transition between densities. See 5.4.3 and 6.3.6 for more information on transitions.

For electron beam irradiation, products are typically irradiated in sequence with gaps introduced to mitigate influences between product groups with different density characteristics or processing requirements. Products can be grouped into processing categories if the dose map results indicate that they can be processed with the same processing parameters and the influence of adjacent irradiation containers, if applicable, has been characterized and taken into account.

5.3 Components of $\sigma_{process}$

5.3.1 General

$\sigma_{process}$ is used in setting process target doses and represents a combination of the variability associated with the process and the inherent uncertainty in the measurement of dose (ISO 11137-3:2017, D.2). In order to establish $\sigma_{process}$, it is necessary to first identify all potentially significant sources of measurement uncertainty (see ISO 11137-3:2017, 4.3.1) and process variability. It is then necessary to consider the relevance of all components to the way the irradiation process is validated, operated and monitored (ISO 11137-3:2017, D.2). The relevance of different components depends on how the irradiation process is designed, validated and managed.

$\sigma_{process}$ can be derived in a number of different ways. These could involve quantifying individual or combined components and can also involve the use of historical data including OQ data.

An important consideration in the estimation of $\sigma_{process}$ is whether or not all of the relevant components are apparent in the measurements made during PQ. Certain components will express themselves all the time, while others can be only apparent over time, or not at all. Figure 2 and the following sections describe the main categories of components of $\sigma_{process}$ and how they can be estimated.

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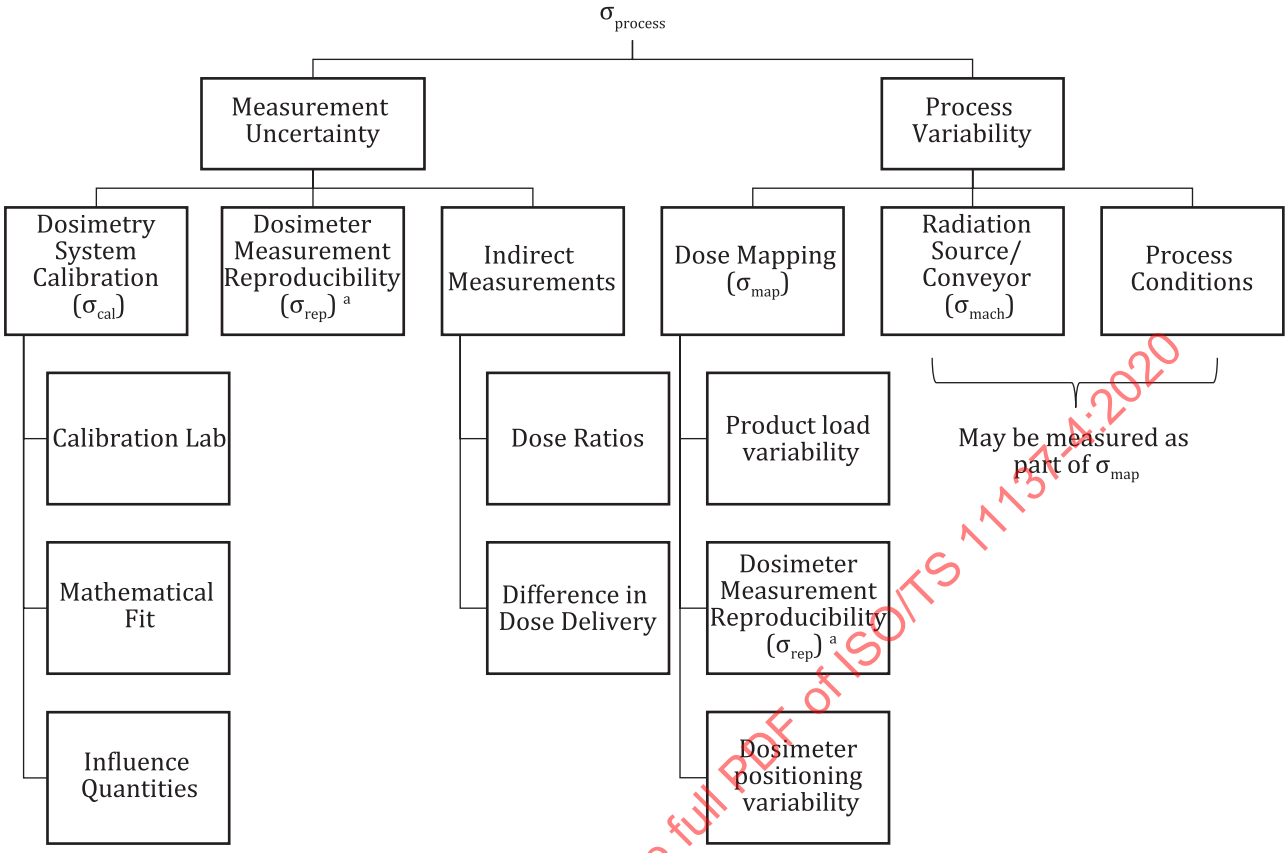

Figure 2 — Components of $\sigma_{process}$

5.3.2 Components related to measurement uncertainty

Uncertainty is inherent in every dosimeter measurement, but the relevance of measurement uncertainty components in processing for inclusion in $\sigma_{process}$ needs to be determined by competent personnel. Some of these components are captured in the dose mapping process and some are not.

Components related to measurement uncertainty can be categorized into three groups: Components related to dosimetry system calibration, components related to dosimeter measurement reproducibility, and components related to indirect measurements.

Components of uncertainty related to dosimetry system calibration, σ_{cal}, include:

a) the uncertainty reported by the calibration standards laboratory;

b) the uncertainty due to the mathematical fitting of the calibration function;

c) the uncertainty related to the effect of environmental influence quantities on dosimeters during calibration and use.

NOTE σ_{cal} does not include the reproducibility of the dosimeter measurement as determined during the calibration exercise as this component of uncertainty will be expressed in components related to process variability, see 5.3.3.

The uncertainty due to the calibration standards laboratory and mathematical fit of the calibration function will not be apparent in measured variability but can display a noticeable change after a new calibration is performed and implemented. The effect of influence quantities can be unapparent over a short time period but noticeable over longer time periods as, for example, seasonal shifts can change environmental conditions.

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The inherent variability associated with a dosimeter measurement is designated as σ_{rep}. In an irradiation process, it might not be practical to measure this component in isolation as the variability due to all other aspects of process delivery will contribute to observed variability in repeated dose measurements. In some applications of dose measurements, this variability can be included in a statement of uncertainty associated with a measurement (see References [3] and [4]). However, this component should not be treated as an additional component of $\sigma_{process}$ as it will be captured in other observed variability.

Additional components of uncertainty will need to be considered in the case of indirect dose measurements. These are described in detail in ISO 11137-3.

More information on components of uncertainty and influence quantities can be found in ISO/ASTM 51261[3], ISO/ASTM 51707[4], and ISO/ASTM 52701[6].

5.3.3 Components related to process variability

A PQ dose mapping exercise (ISO 11137-1:2006, 9.3) is designed to capture components of $\sigma_{process}$. However, depending on the design of the PQ dose mapping experiment (5.2.2), different components of $\sigma_{process}$ will be captured.

The components of process variability captured in the dose mapping exercise are designated σ_{map}, and components that can contribute to σ_{map} include:

a) the product loading variability;

b) the radiation source and conveyor system variability (σ_{mach});

c) the reproducibility of the dosimetry system (σ_{rep});

d) the variability of process conditions (e.g. density transitions in the case of gamma irradiation);

e) the variability in dosimeter positioning.

These components of variability are measured in combination in some form during dose mapping, but the extent to which the full variability of the process is captured will depend on the design of the dose mapping exercise. See 5.2.2.

Some of the variability measured in σ_{map} relates not only to the variability of the product, but also to the variability in placement of dosimeters in replicate maps. If dosimeter placement is not performed consistently, this can inflate the measurement of σ_{map} in a way that does not truly reflect the product dose variability. More information on PQ dose mapping can be found in ISO/ASTM 52303[5].

The component of σ_{mach} measured in σ_{map} will capture the variability over the period of time that the dose mapping exercise took place. In some cases, σ_{mach} can be estimated if the processing parameters for the irradiator are well understood and characterized.

A combination of σ_{mach} and σ_{rep} can be measured over time using a routine monitoring location which is independent of other influences such as product (Annex A, Example 5). An example of estimation of σ_{mach} based on processing parameters can be found in Annex A, Example 4.

Dose maps are often performed in a “quiet system”, which means that the variability of process conditions is not always captured as part of PQ. Operational qualification studies can provide additional components of $\sigma_{process}$ where applicable, such as process interruptions, transitions between different densities, effects of partially filled irradiation containers and variability over time. Components related to these studies can be combined as part of $\sigma_{process}$ if these effects are anticipated as part of normal processing. Annex A, Examples 1 through 5 consider additional components of $\sigma_{process}$ which were not captured in PQ.

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5.3.4 Combining components of uncertainty

The relevant components of $\sigma_{process}$, when combined in quadrature, i.e. the square root of the sum of the squares, contribute toward its total value.

For example calculations of $\sigma_{process}$, see Annex A. Multiple examples are provided to give a sense of the different components that are relevant depending on the design of the qualification studies, the irradiation process and how the irradiation process is managed.

Regardless of the approach taken in estimating $\sigma_{process}$, ongoing process monitoring should be used to verify and possibly refine the initial estimate of $\sigma_{process}$.

5.3.5 Reducing $\sigma_{process}$

If $\sigma_{process}$ is overestimated, it can reduce the ability or flexibility to process product. Overestimation can occur if uncertainty or variability components are double counted, or if these components are estimated overly conservative. These issues can be avoided by a properly established budget containing all significant components of uncertainty and variability. Concepts to reduce the value of certain components are provided in Table 2.

NOTE The identification and quantification of the components of $\sigma_{process}$ provides information on which components are the greatest contributors to $\sigma_{process}$ and, therefore, will have the greatest effect on how the overall variability associated with the process can be reduced. This can include, but is not limited to, the categories of components that can contribute to $\sigma_{process}$ listed in Table 2.

Table 2 — Potential components of $\sigma_{process}$ and actions to reduce them

Component	Detail	Notes	Action to reduce
σ_{cal} Components related to dosimetry system uncertainty	Uncertainty reported by the calibration standards laboratory	This component will not manifest itself in observed variability for a given dosimeter batch/calibration, but should be included for measurements that require traceability. σ_{cal} can become apparent in the form of a step change in routine monitoring results when a new dosimeter batch or calibration is used.	Use an accredited calibration lab with a lower reported uncertainty.
	Uncertainty due to mathematical fitting of the calibration function	Uncertainty can vary dependent on dose level. This component will not manifest itself in observed variability for a given dosimeter batch / calibration and is inherent in every dose measurement.	Increase the number of replicate measurements during calibration; select the calibration curve best fitted to the data using a residual plot to support selection; choose doses most suited to cover the operational range of the irradiator.
	Uncertainty related to the effect of environmental influence quantities on dosimeters during calibration and use	Dependent on the conditions in which dose mapping occurred, these might or might not have been captured, e.g., dose mapping at lower doses might not reflect the influence quantities, namely temperature, seen in routine irradiation.	Ensure calibration conditions and/or verification conditions reflects conditions during mapping exercises and routine irradiation, including temperature and dose rate as applicable. Repeat calibration seasonally if required.
NOTE This table provides possible component groups to provide a framework for readers. It is important to note that components can be grouped differently in practice to avoid double counting, etc.			

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Table 2 *(continued)*

Component	Detail	Notes	Action to reduce
σ_{rep} monitoring Reproducibility	Consistency of dosimeter placement for measurement of monitoring dose	Measured doses depend on both radiation delivery characteristics as well as effects of surrounding products.	Make sure dosimeters are consistently placed, possibly using a template for placement or a fixed holder on the irradiation container.
	Variability due to product influences	In electron beam, scattering from products can affect σ_{rep} seen at the routine monitoring position if placed on or in the irradiation container. In gamma and X-ray, voids in product packages or shifts in process loads within the irradiation container can lead to inconsistent doses at the routine monitoring position.	Use routine dosimetry at a location remote from product. Well defined product packaging procedures to ensure consistent presentation of the product to the beam are important when using dosimetry locations remote from product. Since the dosimeter is not on the irradiation container it will not be able to detect incorrectly packaged product. Packaging designed to prevent products from moving within the irradiation container will also reduce variability due to product influences.
Measurement — Indirect	Uncertainty, for indirect measurements, in dose ratios derived from dose mapping	The uncertainty associated with ratios is relevant when using a routine monitoring dosimeter to make an indirect measurement of minimum or maximum product dose delivered during the process.	Use a method of process monitoring as opposed to product dose measurement in setting process targets. See 4.2 and 6.5.4. Monitor minimum and/or maximum dose directly. See Annex A, Example 2.
σ_{map} Components related to dose measurements during Qualification studies	Variability of loading configuration	Refers to tolerances on how product boxes are placed inside an irradiation container.	Define a more secure loading configuration to reduce variability due to products shifting, or introduce materials to prevent product from moving within the irradiation container.
	Variability of product	Refers to variations in products, relevant where individual product units inside a product box have inconsistent packing, such as bulk materials, or where products are not produced uniformly.	Administrative or other controls to ensure that individual product carton loads are packed consistently. Define an even distribution of density within the product case orientation to reduce density variability across the load.
NOTE This table provides possible component groups to provide a framework for readers. It is important to note that components can be grouped differently in practice to avoid double counting, etc.			

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Table 2 *(continued)*

Component	Detail	Notes	Action to reduce
	Consistency of dosimeter placement in dose map product	Can unnecessarily inflate the value of σ_{map}	Make sure dosimeters are consistently placed for replicate maps (properly defining location in or on product). Implement appropriate quality control and training to assure consistent placement of dosimeters.
	Uncertainty related to the reproducibility of the dosimetry system used in dose mapping	Will be measured inherently along with contributions of σ_{mach}. Reproducibility of the dose mapping dosimeters should not be included in σ_{cal} as it will appear as part of σ_{map}. This is an example of a component that can be double counted without careful analysis.	Multiple dosimeters at some dose mapping locations can be a way to reduce this contribution, such as the routine monitoring location and expected areas of maximum and minimum dose Measure multiple positions considered equivalent based on symmetry within an irradiation container.
σ_{mach} Components related to machine variability	Variability in output power and energy for electron beam and X-irradiation	Power and energy changes can affect the dose delivery to the product. This variability is measured during OQ.	Improve control of parameters. Assess parameter effect and adjust related tolerances as necessary for given operating conditions. Run process at most stable process parameters if possible.
	Variability in low dose processes at fast conveyor speeds or short cycle times	Product movement at fast conveyor speeds can affect the dose delivery to the product. This is especially apparent at lower doses.	For electron beam, qualify the process with reduced power output. For gamma, qualify the process with fewer source racks for greater speed control (if possible).
Components related to processing conditions	Dose effects due to transitioning between different product densities	For gamma irradiators, the effect on dose to product of different densities present in the irradiator is determined as part of process qualification (ISO 11137-1:2006, 9.3.7). For electron beam, the effect of empty or absent irradiation containers preceding and following the product is captured in the PQ dose mapping exercise.	Transition by going up and down the density range where product dose windows are wide enough. Use phantom material at a similar density to transition between products. Schedule products with similar density characteristics in sequence.
NOTE This table provides possible component groups to provide a framework for readers. It is important to note that components can be grouped differently in practice to avoid double counting, etc.			

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Table 2 *(continued)*

Component	Detail	Notes	Action to reduce
	Dose effects due to process interruptions	In gamma, process interruptions can lead to a small increase in dose and will depend on activity level and the speed at which the source rack returns to the storage location and to the irradiation position as the result of an interruption. In electron beam, the effect of process interruptions can depend on the cause of the interruption, and its magnitude relates to the geometry and power of the beam, the speed/position of the conveyor during the shut-down and restart of the process and the size and weight of the irradiation container. It can be necessary to discard product that has undergone a process interruption.	The effect of process interruptions is not always able to be reduced by modifications to the equipment.
	Dose effects due to partially filled irradiation containers	This is applicable in gamma, and X-ray where partially filled containers can affect dose to product.	The effect of partially filled irradiation containers can be mitigated by filling the remainder of a partially filled container with phantom material to simulate a full container.
NOTE This table provides possible component groups to provide a framework for readers. It is important to note that components can be grouped differently in practice to avoid double counting, etc.			

5.4 Establishing process target doses

5.4.1 Coverage factors

One method for determining the range of process target doses is to apply a coverage factor k to the estimate of $\sigma_{process}$ which is dependent on the required level of confidence that the minimum dose to product exceeds D_{ster} and the maximum does not exceed $D_{max,acc}$.

The coverage factor k is generally taken as $k = 2$, approximating a 95 % level of confidence for a two-sided Gaussian distribution, or a 97,5 % level of confidence for a one-sided Gaussian distribution. Two-sided distributions are used when the requirement is to determine the range of doses around the process target dose such that doses higher and lower than the process target dose are expected. A one-sided distribution is selected when the requirement is to either stay above the required minimum dose, or to stay below an allowed maximum dose. Therefore, processing at D_{target}^{lower} which was established with $k = 2$ means that there is 2,5 % chance (risk) that the minimum dose might fall below D_{ster}.

NOTE The actual confidence level depends on the degrees of freedom (related to the number of measurements). Refer to the Guide to the expression of uncertainty in measurement (GUM)[11] [12] for further information on the relationship between confidence levels and number of measurements.

Different values of k are applicable based on the risk assessment for the product and process (see ISO 14971[2]).

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In some situations, a product with a restrictive dose specification (i.e. small difference between D_{ster} and $D_{max,acc}$) can only be processed using a target dose calculated with a low value of k, in which case the increased risk that $D_{min} < D_{ster}$ and $D_{max} > D_{max,acc}$ should be evaluated, and taken into account as part of the business decision and risk management. A record of process parameters for the batch can provide useful information to assess process conformity.

5.4.2 Process factors

$\sigma_{process}$ can be used in the calculation of the range of doses at the monitoring location(s) that correspond to doses to product in irradiation containers that are within specifications at a defined level of confidence. This can be achieved by the calculation of process factors designated UF_{upper} and UF_{lower}:

$$UF_{upper} = 1 / (1 + k\,\sigma_{process}{}^{max} / 100) \tag{5.1}$$

$$UF_{lower} = 1 / (1 - k\,\sigma_{process}{}^{min} / 100) \tag{5.2}$$

where $\sigma_{process}{}^{max}$ and $\sigma_{process}{}^{min}$ are the process standard deviation values associated with the maximum and minimum doses to product respectively. These $\sigma_{process}$ values are multiplied by a coverage factor k depending on the level of confidence required. Different values of k can be selected for UF_{upper} and UF_{lower} depending on the requirements of the process. Using the values of UF obtained above, two statistically based values for the highest and lowest dose values at the maximum and minimum dose positions can be defined for use in the process. These are designated $D_{max}{}^{limit}$ and $D_{min}{}^{limit}$ respectively:

$$D_{max}{}^{limit} = D_{max,acc} * UF_{upper} \tag{5.3}$$

$$D_{min}{}^{limit} = D_{ster} * UF_{lower} \tag{5.4}$$

The routine monitoring location(s) can be at the locations of maximum and minimum dose or at a separate monitoring location. For processes with routine dose measured at a separate monitoring location, the range of target monitoring doses can be calculated from Formulae (5.3) and (5.4) as follows:

$$D_{target}{}^{upper} = D_{max}{}^{limit} / R_{max/mon} \tag{5.5}$$

$$D_{target}{}^{lower} = D_{min}{}^{limit} / R_{min/mon} \tag{5.6}$$

5.4.3 Choice of target processing parameters

The target processing parameters can be any combination within the operational specification of the irradiator that maintains the required dose distribution and $\sigma_{process}$ and that targets a minimum dose to product at or above $D_{min}{}^{limit}$ and a maximum dose to product at or below $D_{max}{}^{limit}$. Whatever target dose (D_{target}) is chosen, a distribution of results above and below this value will be obtained during routine monitoring of the irradiation process.

The choice of $D_{target} = D_{target}{}^{lower}$ can be made in the case where the facility is aiming for operational efficiency. Operation at the lowest dose possible will increase the amount of product that can be irradiated in a given time period.

D_{target} can be chosen based on historic knowledge. In an established facility, and where dose specifications are easily met within the process, a choice can be made to use a targeting buffer to determine $D_{target}{}^{upper}$ and $D_{target}{}^{lower}$. The calculation of UF_{upper} and UF_{lower} should still be performed in order to verify that the variability associated with the process fits within the targeting buffers. An example of a process using a targeting buffer can be found in Annex A, Example 2.

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Another strategy is to choose a target dose that is near the middle of the range of target doses between D_{target}^{upper} and D_{target}^{lower}. This strategy would put the process at a lower risk for an out of specification measurement.

Special causes can be taken into consideration when setting up processing parameters. Examples of special causes include anticipated changes to dose delivery as a result of density or processing category transitions in gamma or X-ray, or effects due to process interruptions. These effects are characterized as part of OQ or through a combination of OQ and PQ studies.

In gamma irradiators transitions between processing categories might be accomplished by scheduling product that fits into both processing categories when parameters are changed, as applicable (see 5.2.3). Similarly, transitioning between products with different densities might be performed by processing products in a sequence where a change in parameters from one density to the next would result in doses within specification for all product in the irradiator. For examples of the calculation of transition effects in gamma, see Annex A, Examples 1 and 2.

Process interruptions can affect maximum and minimum doses differently. The effect of process interruptions can be included when setting up processing parameters if the magnitude of the effect still allows the process to meet dose specifications. See 6.3.5 for more information on process interruptions, and Annex A, Examples 2-4 for their application in setting processing parameters.

The established process target dose ensures, through process monitoring, that D_{ster} and $D_{max,acc}$ for the product are met on a routine basis, within the defined level of confidence.

5.4.4 Assessing process capability

Process capability is a measure of the ability of a process to produce an output within specification.

The range of process target doses provides a first indication of whether or not a process will be capable. For example, if D_{target}^{lower} is higher than D_{target}^{upper}, this means that specifications cannot be met for a given process without changing either the dose specifications, the product loading configuration, the level of confidence, or working to reduce components of $\sigma_{process}$. Annex A, Example 3 provides an example of a process with tight dose specifications.

It is possible to operate when D_{target}^{lower} is equal to D_{target}^{upper}, but an irradiator operator can choose to specify a minimum difference between the two based on the ability to reliably target the process. This amount will depend on both irradiator capabilities and facility policies.

NOTE In process establishment, all relevant sources of measurement uncertainty and variability were considered. During routine processing where there are no special cause events, only a subset of variability will be apparent, thus when measuring the capability of a process, only observed variability is considered.

More information on process capability assessments can be found at ASTM E2281[9].

6 Routine monitoring and control

6.1 General

Routine monitoring and control represent the specific activities to ensure process specifications are achieved.

Routine process controls should be administered to ensure that products are processed to the requirements specified in ISO 11137-1. Process controls during routine processing include proper receipt of product at the irradiator, scheduling, product loading, storage, handling, irradiation, dose monitoring, unloading, product release, and shipment of product. For some of these items, the elements that need to be considered are common to gamma, electron beam, and X-ray, while other items possess elements that are unique to either gamma, electron beam, or X-ray.

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6.2 Product handling

6.2.1 Receipt of product

Upon receipt of product at the irradiation facility or department, the product or shipment should be verified for the correct lot or batch, storage specifications if applicable, processing specifications, and product count, including a count of products designated for testing purposes, and products which are damaged upon receipt, in accordance with written procedures.

Storage of product prior to irradiation should be in an area designated for products which are non-irradiated and should provide necessary facilities for those products which require storage under specified environmental conditions.

NOTE It is common industry practice to have non-sterile products labelled sterile which are sent to a contract irradiator to receive a dose to render the product sterile. Regulatory agencies typically have specific requirements that need to be met when non-sterile product that is labelled sterile is shipped to a contract irradiator/sterilizer.

6.2.2 Loading

The following items should be considered when loading product into the irradiation container:

a) product should be loaded into the irradiation containers in accordance with the designated product-loading configuration;

NOTE Each loading configuration to be used during routine processing, including partially filled irradiation containers, is based on a dose mapping study. A specified loading configuration, as an output of a dose mapping study, is a requirement of ISO 11137-1:2006 9.4.3.

b) dosimeters should be placed at designated locations and frequency per established procedures (see 6.3.3);

c) product count should be documented for each run. Products designated for testing purposes should be included in the counts; however, this should be noted in the processing records;

d) any partially filled irradiation containers should be noted in the processing records for the product run;

e) any discrepancies identified during loading should be addressed per established procedures.

6.2.3 Unloading

As product is unloaded from the irradiator, the following should occur in accordance with documented procedures:

a) count verification;

b) palletization per established specifications, if required;

c) retrieval of samples designated for testing purposes;

d) retrieval of dosimeters, verification of correct placement, time/date of retrieval, and storage of dosimeters until measured;

e) identification of damaged product;

f) identification of product status and storage in an appropriate designated area, taking into account the need for segregation between irradiated and non-irradiated product.

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6.2.4 Storage

Post irradiation, products should be stored in the designated area. If necessary, store under specified environmental conditions.

6.2.5 Shipment

Prior to shipment of product, the following should occur:

a) product counts at receipt, load, unload, and prior to final shipment should be compared and discrepancies documented and resolved;

b) product should be inspected for damage and identified where needed;

c) verify that process specifications have been met;

d) product should be released for shipment (see Clause 7).

6.3 Processing of product

6.3.1 General

Products should only be processed using an irradiator that has been validated in accordance with requirements in ISO 11137-1 and in accordance with documented procedures that ensure that established process specifications are met. Doses should be monitored using a calibrated dosimetry system. The dosimetry system should be calibrated using established procedures and be traceable to national or international standards. The uncertainty in the measurement of dose should be determined and documented.

6.3.2 Processing parameters

The following should be monitored and documented during the irradiation process:

a) position of the gamma source rack(s) for gamma;

NOTE Some facilities have multiple rack positions.

b) critical beam parameters (e.g. beam current, scan current and cycle if applicable, etc.) for electron beam and X-ray;

c) cycle timer settings or conveyor speed(s) in the irradiation zone (see 4.3);

d) changes in the cycle timer setting or conveyor speed part way through the irradiation process;

e) process interruptions (if any);

f) location of irradiation containers throughout the irradiation process, including process interruptions;

g) identification of irradiation containers with monitoring dosimeters and information on the time/date that they are in the irradiator.

In meeting the requirement of ISO 11137-1 for control and monitoring of the electron beam or X-ray process, it is important to differentiate critical beam parameters from secondary parameters. Critical beam parameters can be defined as those that, if they deviate from the specifications, would result in a loss of control over the validated state of operation. Critical parameters are those which affect the energy level of the electron beam, average beam current, scan width and scan uniformity as applicable. Secondary parameters can reasonably change without affecting the characteristics of the electron beam, including parameters relating to, for example, the cooling or vacuum systems.

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The ability to monitor, control, and document the state of control of critical beam parameters is an important factor in defining routine processing requirements.

6.3.3 Location of dosimeters

It is a requirement of ISO 11137-1:2006, 9.4.3 and 9.4.4 that a process specification be generated as an outcome of performance qualification dose mapping. The process specification includes the location of the routine monitoring position(s). For processes where the dose to the process load is not influenced by surrounding product (i.e. electron beam), the location can be either within the irradiation container or at an outside location adjacent to and/or travelling with the irradiation container.

6.3.4 Partially filled containers

Partially filled containers should be irradiated in accordance with documented procedures. The practice of monitoring partial loading configurations should be validated. The effect on dose (if any) due to partially filled containers should be taken into account in assessing acceptability for use in the process. More information on partially filled containers can be found in ISO 11137-3.

NOTE In practice, each type of partially filled container in electron beam requires a separate dose mapping exercise.

6.3.5 Process interruptions

If interruptions of the irradiation process occur, the effect of the interruption on the magnitude and distribution in dose should be quantified based on previous qualification studies (see ISO 11137-3).

For gamma, the effect of a process interruption on the dose is normally a small increase in dose delivered due to the additional time the product is exposed to the source rack as it travels to and from the irradiation position.

For electron beam or X-ray, the effect of a process interruption on the magnitude and distribution of dose can depend on the cause of the interruption and of the design of the irradiation facility. For example, an interruption caused by a fault in the conveying system where there is a delay in turning off the beam can cause an overdose, whereas a fault in the beam where the conveying system is not able to stop instantly can cause an underdose. See also Table 2.

This effect on dose (if any) should be taken into account in assessing the conformance of the process.

6.3.5.1 Interpreting dosimeters following a process interruption

For process interruptions where there is a dosimeter in the irradiation zone, the dosimeter will measure two or more fractions of dose. The effect of fractionation on dosimeter response, as well as the effect of any extra time while the cause of the interruption is resolved on dosimeter response should be characterized as part of the dosimetry system calibration. The effect of the process interruption on dose might or might not be measured depending on dosimeter location relative to the source of radiation when the interruption occurred.

6.3.5.2 Process interruptions which require the movement of irradiation containers

If it is necessary to move irradiation containers as the result of an interruption, it is essential to place product into the validated loading configuration, with all individual packages in the same positions and orientations within the irradiation container at the same position where it was previous to interruption. The verification that product has been returned to the same positions and orientation as prior to the interruption should be documented.

6.3.5.3 Process interruptions for products capable of supporting microbial growth

For product capable of supporting microbial growth, the process specification should include the maximum interval of time that can elapse between the completion of manufacture and the completion

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of sterilization, and the conditions of storage and transportation to be applied during the time interval, including irradiation (see 4.3 if applicable). The interval of time during the process interruption, therefore, will affect whether or not the specification is met.

For product not capable of supporting microbial growth, the effect of dose on microorganisms is cumulative; thus, the interruption of the process in the irradiator does not necessitate action to prevent growth of microorganisms.

The determination of whether a product will support microbial growth is made by the product manufacturer.

6.3.6 Transitions between densities

In gamma and X-ray irradiators, products of different density can be run sequentially provided that the effect of doing so has been quantified. The results of transition validation studies can be used to demonstrate that, for a selected cycle time or conveyor speed, all products will meet their required dose specifications (see ISO 11137-3).

6.4 Special processing conditions

6.4.1 Off-carrier processing

Off-carrier processing in gamma or X-ray is a term used to describe the irradiation of products that does not use a conventional irradiator pathway, for example, a product that is placed in a static position behind the path of irradiation containers and where the product is rotated manually part way through irradiation. It is also common to use fixtures at a position outside the path of irradiation containers, on which product is placed that rotate automatically at a fixed speed (for example, on a motorized turntable) to uniformly irradiate product. Off-carrier processes can be used, for example, for process definition (see ISO 11137-1:2006, Clause 8) or for augmenting dose to products outside of normal processing conditions.

Irradiation containers in off-carrier processing should be dose mapped. Alternatively, dose should be measured in each container using a sufficient number of dosimeters to identify the minimum and maximum doses. The dosimeter locations should be documented and could be selected based on previous dose mapping studies including OQ.

In the absence of precise knowledge of the expected dose delivery characteristics for an off-carrier process for a given product, it can be necessary to interrupt the irradiation at certain intervals throughout the irradiation to measure doses. The effect of these interruptions to irradiation of product in the main irradiator pathway(s) should be known and the number of irradiation intervals to the off-carrier process designed accordingly.

Off-carrier processing in electron beam is generally not applicable.

The calibration of the dosimetry system needs to be valid for its conditions of use, which can be different between a conventional irradiator pathway and an off-carrier process.

NOTE See ISO 11137-3 and ISO/ASTM 51261[3] for further guidance.

6.4.2 Irradiation of product under modified environmental conditions

6.4.2.1 General

Irradiation of product at temperatures below ambient and/or in a modified atmosphere environment can be used for products that support microbial growth or that are sensitive to ionizing radiation.

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6.4.2.2 Dosimetric considerations for validating and processing in a modified environment

Product irradiated under modified environmental conditions presents a challenge to dosimetry. Dosimetry systems used under these conditions can require a specific calibration because of the effect of the modified environment on dosimeter response (see ISO/ASTM 51261[3]). If the routine monitoring dose location, selected for PQ tests, is outside of the insulated container in order to provide an ambient measurement, it is still possible that the refrigerant internal to the container can affect the temperature at the routine monitoring position. This temperature should be confirmed to ensure the validity of the dosimetry system calibration.

In order to dose map product processed at low temperatures, for example products that are packaged inside an insulated container with refrigerant materials, it is often possible to perform PQ dose mapping under ambient conditions using an appropriate surrogate material to mimic the radiation shielding effects of the refrigerants. The bulk density of the simulated material should approximate the density of the refrigerant and have similar radiation absorption characteristics. In addition, the location of the simulated refrigerant within the insulated container should be the same as the actual refrigerant. If the refrigerant consists of sealed packets of wet ice, the simulated refrigerant will have a bulk density of approximately 1 g/cm^3. In this case, sheets of plastic might provide and appropriate simulation of the refrigerant. When the refrigerant has a bulk density less than 1 g/cm^3, such as pellets of dry ice, a laminate of plastic sheet and corrugate might suffice as the simulated refrigerant. Other materials such as plastic pellets, salt pellets, or rice might also provide an appropriate simulation of the refrigerant.

6.4.2.3 Process considerations when using refrigerants

The use of refrigerant provides other unique challenges in processing product. The high-density nature of the refrigerant can affect locations of maximum and minimum doses and can cause significant shielding of the product from the radiation source depending on the orientation of the refrigerant, product and radiation source. It is important, therefore, that the refrigerant is confined to a specified location or locations within the irradiation container. Also, the volume or density of the refrigerant can change between when the product is shipped, when it is loaded into the irradiator, and over the course of the irradiation, as dry ice evaporates or wet ice melts. Dose mapping exercises should be designed to measure any shadowing effect of the refrigerant on the product and to take into account anticipated changes in refrigerant during irradiation. Procedures can be put in place to verify the amount of refrigerant or add refrigerant to an insulated irradiation container before (and if required during) irradiation.

Irradiation of product at low temperatures can require specific monitoring and control to ensure the product remains within a temperature range specified for irradiation. This could be done by controlling the quantity and condition of refrigerant that is added for irradiation, if applicable, and the period of time that the product resides outside of controlled storage conditions. Many products, and commonly biologics/tissues[7], that remain in a refrigerated state for irradiation are shipped and irradiated in the same insulated shipping container. The cooling and product box packing requirements for transportation could be different from those required for irradiation, therefore separately validated containers or cooling systems might be used for irradiation. For example, the amount and orientation of the refrigerant required to maintain temperature during transportation could be different from that required to maintain temperature during irradiation. Repacking the product boxes at the irradiator site into a separately validated insulated irradiation container could allow for a loading configuration with less refrigerant to improve dose uniformity.

6.4.2.4 Process interruptions when using modified environmental conditions

In the event of interruption of the irradiation process being carried out under modified environmental conditions it can be necessary to move product to controlled storage conditions until the process can be resumed, thereby ensuring that product remains within the specified temperature and/or atmosphere.

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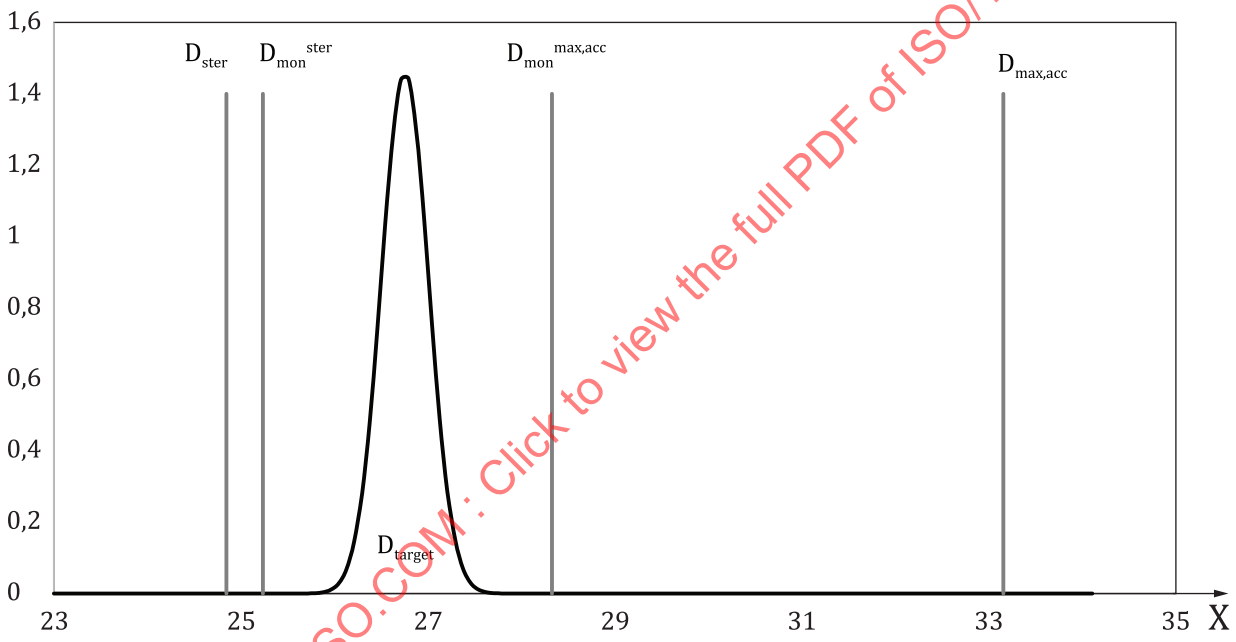
6.5 Process output interpretation

6.5.1 General

Measurement of dose at the routine monitoring position(s) is carried out in order to show that the process is under a state of control and the product is irradiated within its required specifications, i.e. that dose to product is greater than or equal to D_{ster} and does not exceed $D_{max,acc}$. The interpretation of the dose will depend on how the process was established and rules and actions defined by established procedures.

6.5.2 Using an acceptance range based on D_{mon}^{ster} and $D_{mon}^{max,acc}$

The simplest form of process acceptance involves decisions made on the basis of individual routine monitoring dosimeter results. For example, for a process with a D_{target} calculated in accordance with guidance provided in 5.4, any routine dosimeter result between D_{mon}^{ster} and $D_{mon}^{max,acc}$ might be taken as indicating a conforming irradiation process. This individual dose measurement provides no information about the state of control of the process, only the fact that dose specifications are being met. See Figure 3 for a graphical representation of an acceptance range based on D_{mon}^{ster} and $D_{mon}^{max,acc}$.



Key

X dose (kGy)

Figure 3 — Acceptance range based on D_{mon}^{ster} and $D_{mon}^{max,acc}$

This type of acceptance can be used, for example, in a gamma process with multiple products in the irradiator, where special cause effects due to transitions have been accounted for in setting up processing parameters, but there might not be a specific D_{target} for each individual product to compare with a measured monitoring dose.

Examples of using an acceptance range based on D_{mon}^{ster} and $D_{mon}^{max,acc}$ can be found in Annex A, Examples 1 and 2.

6.5.3 Using an acceptance range with alert and action levels

This approach places boundaries on the acceptance of doses outside of defined ranges around a chosen process target dose. Doses outside of these ranges can lead to further evaluation.

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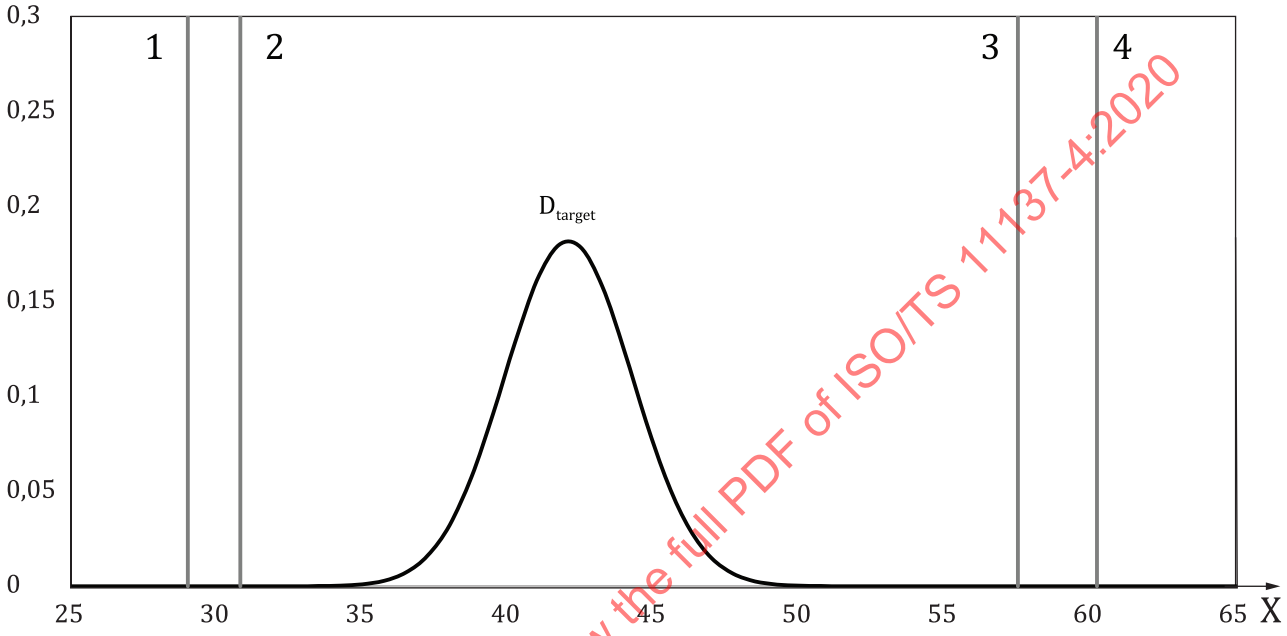
A set of rules is established which define alert and action levels for doses outside of a predicted range of monitoring values. Rules can follow known examples, such as Western Electric[14], or Nelson Rules[15], or can be defined by the user. The alert level can be based on the anticipated variation of the dose measurement due to observable events, e.g., observed variability from PQ mapping studies or historic data, or they can be based on the overall $\sigma_{process}$. Action levels are defined at intervals which are either outside the expectation of the process or which indicate that dose specifications are not being met. See Figure 4 for an example of action and alert levels which are well outside the expected variation of the process.



Key

X dose (kGy)
1 lower action
2 lower alert
3 upper alert
4 upper action

Figure 4 — Process acceptance ranges with action and alert levels

Examples of the use of an acceptance range with alert and action levels are given in Annex A, Examples 4 and 5.

6.5.4 Using an acceptance range based on process monitoring

For a process where the monitor dosimeter is used as a measure of process conformance, and not for an indirect measurement of maximum or minimum product dose, the process target doses are set using the guidance found in 5.4.2, but the components of $\sigma_{process}^{max}$ and $\sigma_{process}^{min}$ are derived from the measurement uncertainty and variability of the maximum and minimum doses only. The acceptable range of doses around D_{target} for this method are then based on the variability observed in the monitoring dosimeter location only. The method supposes that the relative shapes of the probability distribution functions around each of the maximum, minimum and monitoring dosimeter remain consistent and that the intrinsic variability of the monitoring dosimeter is sufficiently small to enable significant changes in the maximum and minimum probability distribution to be detected (see 4.2.1). For example, the relative shapes of the probability distribution functions do not change as dose is increased or decreased for a dose mapping exercise.

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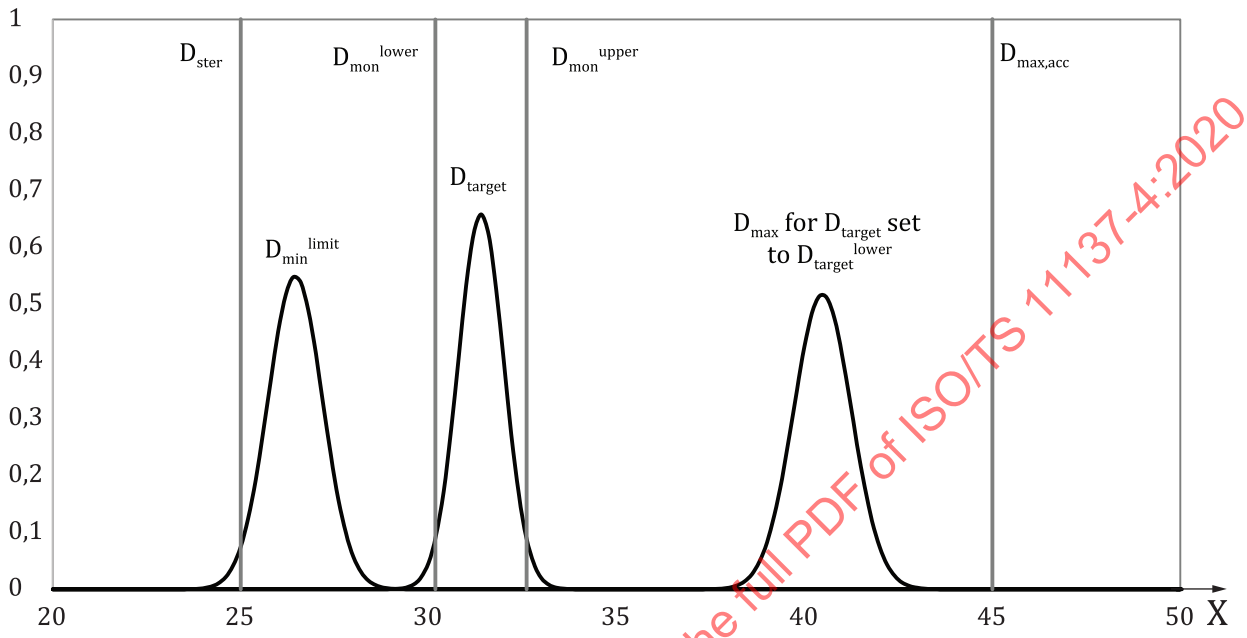
As a result, the acceptance range is based on the expected variation of the dose at the monitoring location which indicates minimum and maximum product doses are within the established specifications. The concept of D_{mon}^{ster} and $D_{mon}^{max,acc}$ are not meaningful for this method.

Figure 5 provides a pictorial representation of a monitoring dose, maximum and minimum doses and their associated probability distribution functions, as measured during PQ dose mapping for an example process.



Key

X dose (kGy)

Figure 5 — Expected probability distribution functions for an example process where D_{target} is set to D_{target}^{lower}

In this case processing parameters have been set for a D_{target} equal to D_{target}^{lower} at a confidence level of k = 2. For this process there is an expected distribution of measured D_{mon} above and below the target dose, as represented by the D_{target} probability distribution function shown in Figure 5, and an associated range of anticipated doses for each of D_{max} and D_{min}. As long as D_{mon} stays within the predicted probability distribution function, the values of D_{min} and D_{max} will stay within their predicted probability functions, also shown in Figure 5. Values of D_{mon} that are outside the anticipated range of measurements indicate that the process might not be in a state of control. For more information see Annex A, Example 3.

6.5.5 Investigation of a dose measurement outside of expectation

There will be cases when an out of specification dose is measured. There are several reasons that a dose reading could be out of specification, including, but not limited to the following:

a) the process delivered an unexpected outcome;

b) there were influence quantities that affected the dosimeter result that were not accounted for in determining the target dose ranges, therefore, it is possible that the established target dose range is not suitable for the process;

c) the monitoring dosimeter was not correctly positioned during the process;

d) improper product loading that affected pre-established dose ratios, which were obligatorily based on properly loaded product;

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e) the dosimeter reading is faulty;

f) product packaging is not consistent with when PQ was performed.

A review of processing parameters can provide information that can aid in an investigation. This can involve a review of parameters critical to dose delivery as outlined in 4.3. For electron beam, a review of monitored machine parameters will provide information as to whether or not the process deviated from set parameters. For gamma, a review of product in the irradiator, and verification that loading configurations were followed, and that product placed in irradiation containers was the correct weight can provide information about whether or not the process followed set parameters. In all cases, actions should be reviewed against set operating procedures.

The ability to collect and analyse data over time can be useful in the investigation of an out of specification dose. More information on the collection and analysis of data can be found in 6.6. An example of the use of processing parameter data in investigation of a dose measurement outside of expectation can be found in Annex A, Example 5.

If a cause of an out of specification monitoring value cannot be determined, procedures should be in place for how to evaluate a dosimetric outlier, how to deal with the potential for a non-conforming process and actions to be taken.

6.6 Collection and analysis of data

6.6.1 General

Processing data can be accumulated, organized, and reviewed to evaluate process stability. These data can include, for example, results of dose measurements, processing parameters, identification of equipment used in processing or monitoring activities and non-conformances. The method of analysis depends on the data type, the irradiator design, and application.

The results of this analysis can be used to identify processing runs that have approached the processing specification limit and possible process trends, allowing for corrective actions to be taken.

NOTE For irradiation facilities that process a large number of products, an analysis of a representative subset of product can be acceptable.

There are multiple methods available to collect and analyse data to demonstrate that a process is in a state of control and to define evaluation criteria about whether or not product consistently meets processing specifications based on the outcome of dose measurements.

6.6.2 Dosimeter data trending

A useful tool in monitoring process performance is trending dosimeter data over time. Figure 6 shows a histogram of monitored dosimeter values over time for a specific process.

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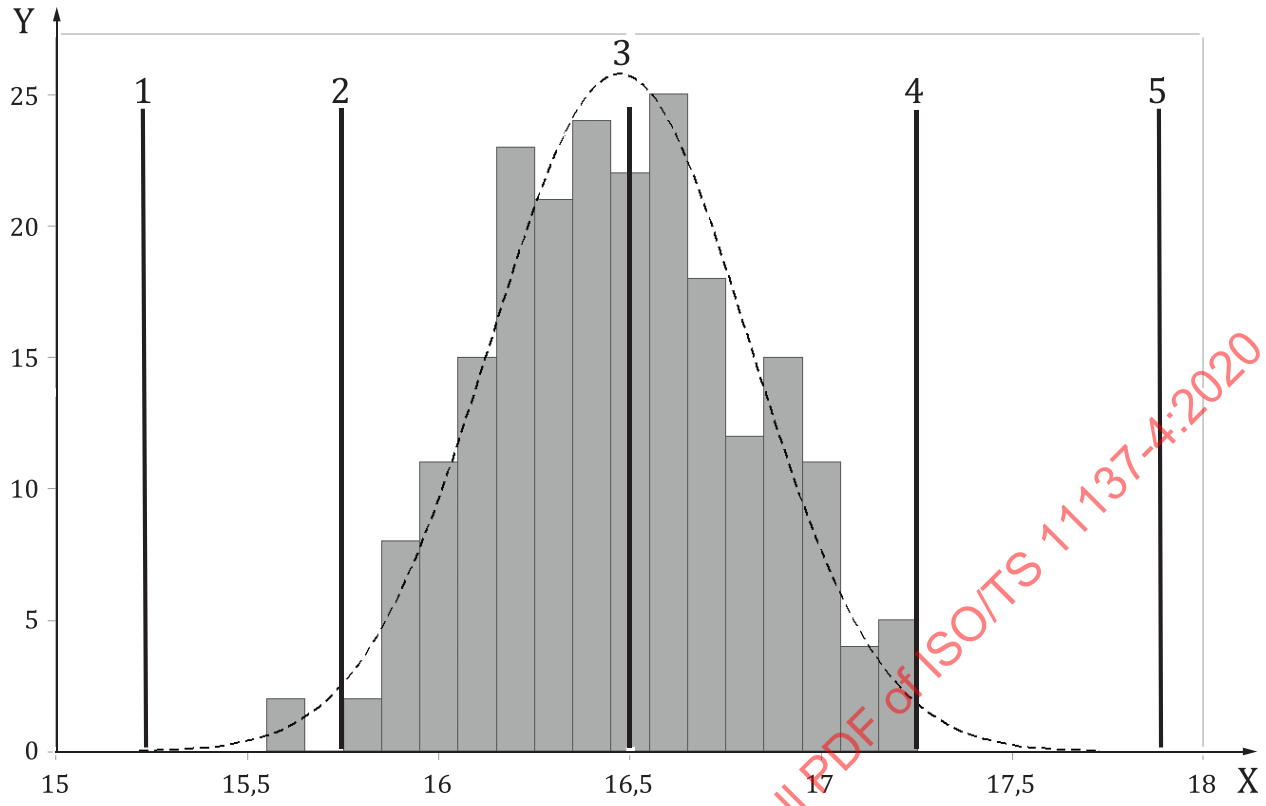

Key

X dose (kGy)
Y frequency
1 lower action level
2 lower alert level
3 chosen target
4 upper alert level
5 upper action level

Figure 6 — Monitoring dosimeter value histogram for an example process

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The data are expected to fall within a certain window of normal process variation, and in this example, alert levels determined based on the expected variation of results around the chosen process target dose. Action levels here have been set based on the minimum and maximum possible target doses for the process. Plotting the data provides a visual confirmation that the process is behaving as expected. A histogram that is not symmetric, i.e. with more dose values trending towards either the lower or higher alert levels, can indicate that something in the process is not as expected and allow the operator to investigate before an out of specification result is measured.

6.6.3 Parametric data trending

Another useful tool in data trending is the ability of irradiators to store and display monitored processing parameters as a function of time. Individual machine parameters can be monitored and controlled through software that will interrupt a process if an out of tolerance condition is detected. For electron beam and X-ray it can be possible to also track combined dose critical parameters (beam current, beam width and process speed) to calculate a parametric process variation which is monitored to ensure the process is in control within a specified tolerance.

Using automatic control of machine parameters, the risk of an undetected nonconformance between routine dose measurements is mitigated. Similarly, if a dosimeter reading is out of specification, it

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is easy to look at trend data to investigate if there is an obvious cause. See Annex A, Example 5 for an example of the application of parametric trending in decision rules around an out of specification dosimeter reading.

Another example of where these data can be particularly useful is if there is an out of specification measurement with a low frequency of monitoring dosimeters. If the out of specification measurement can be attributable to machine performance isolated over a specific period of time, this could allow a determination of which products were affected rather than including every product since the previous monitoring dosimeter that was within specification.

6.6.4 Statistical process control

Statistical process control (SPC) is a specific form of data trending which relies on the collection and analysis of multiple dose points over a series of similar measurements in order to demonstrate the performance of a process over time.

The monitoring dose specification for routine irradiation should be based on D_{target} and the expected range of dose measurements above and below D_{target}. Measurement results for a given irradiation run that fall within the range of expected results for the monitored location(s) verifies the process was in a state of control and, therefore, verifies that product received doses within its required specifications.

Monitoring doses that fall outside of the range of expected doses can still indicate that dose specifications have been met but can indicate that the process is no longer in a state of control and can, therefore, be used to trigger an alert or action (see 6.5.3). In SPC, part of the justification for accepting a dose point that falls outside of expectation is a comparison of this dose measurement with previous measurements. For example, if measurements made over time display a scatter of values around a mean which is consistent with a gaussian distribution, and a single dose value goes out of specification where limits have been set at k = 2, then this can be attributable to the expected 5 % of values that will fall outside the limits. Guidance on interpretation of successive values of a process characteristic can be found in ASTM E2587-16[10].

SPC also allows for ongoing monitoring of process doses in order to identify patterns of response and potentially predict failures before they occur. For example, doses can remain within prescribed limits, but if the doses are consistently trending in one direction, this can trigger an investigation before an out of specification dose is measured.

One useful analysis technique of SPC is a control chart. Control charts are graphical representations of the output of a process, such as plots of routine monitoring doses. The plots are often made as ratios of measured doses divided by selected target doses. The comparison of actual results versus expected results provides an objective evaluation of control of the process.

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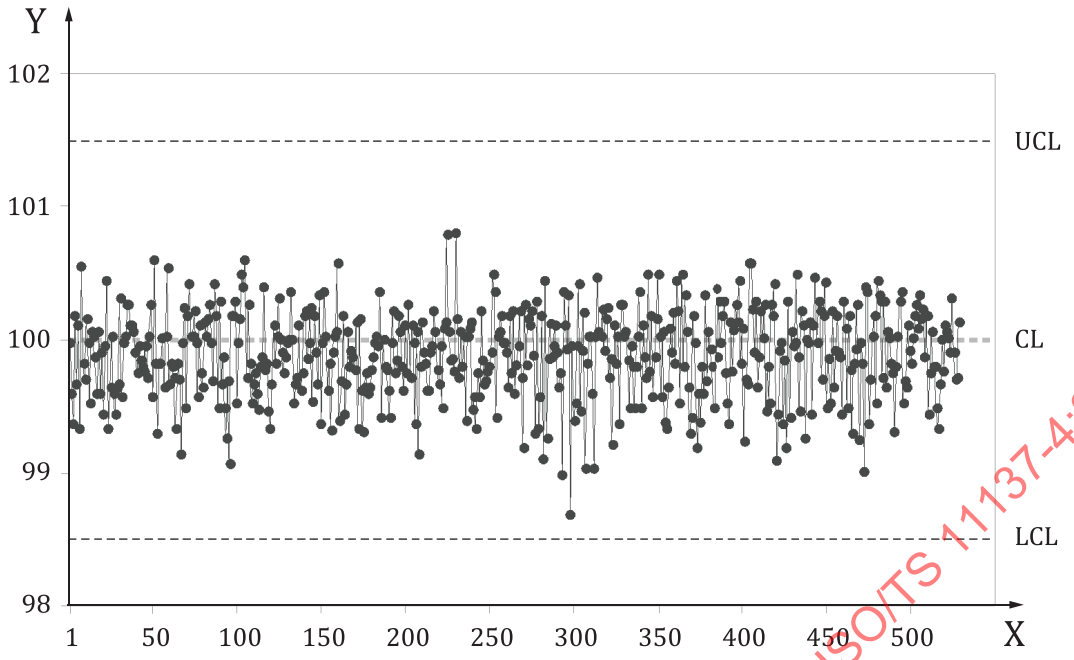

Key

X	number of measurements
Y	calculated dose/target dose (%)
UCL	upper control limit
CL	centre line
LCL	lower control limit

Figure 7 — Process control chart for an example irradiator, trended over time

Figure 7 is an example of a control chart which represents the parametric process variation (6.6.3) for a given irradiator over more than 500 measurements.

SPC is commonly used in processes other than radiation processing, and guidance on the application of SPC can be found in ISO 11462-2[1] and in References [10], [13], [14] and [15].

NOTE The control systems of some irradiator designs have the ability to capture and trend irradiator parameters over time. This information can be used in conjunction with and/or as an aid to SPC of measured doses.

7 Release of product from the irradiation process

Upon completion of the irradiation process, the processing history records should be reviewed and approved.

Processing history records typically include the following:

a) receiving records;

b) product count verification and records of discrepancies and actions taken (if applicable);

c) loading and unloading records;

d) processing records;

e) conveyor operation and/or pathways;

f) for electron beam and X-ray facilities, beam characteristics and conveyor speed;

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g) for gamma facilities, cycle time;

h) processing deviations and associated investigations and corrective action;

i) dosimetry data records;

j) certification of process conformance.

At a minimum, the processing history records should consist of those identified in ISO 11137-1 and the quality management system of the facility.

8 Maintaining process effectiveness

8.1 General

Maintaining process effectiveness provides input to the "review" step in establishing process target doses as illustrated in Figure 1.

8.2 Assessment of changes made to the product

Any changes to the product, the product packaging or the manner in which the product is presented to the source of radiation should be assessed, regardless of the radiation modality. A change to the primary packaging can have negligible impact in a gamma or X-ray facility, but can affect dose distribution in an electron beam facility. A change in product orientation within the box can have an impact in gamma, electron beam and X-ray facilities and needs to be assessed.

Changes to the product are often made with the intention of not changing the conclusions of PQ. Evaluation criteria are usually based on the effect the change has on dose magnitude and distribution, and this evaluation might or might not need specific experiments. Depending on the assessment, a repeat of PQ dose mapping might be needed.

NOTE Mathematical models can be used to assess the potential effect of changes to process or product on dose distribution.

8.3 Assessment of changes made to the equipment

As part of the change control process, the established process control inputs and targets should be evaluated and any adjustments to the process targets or monitoring values documented. Changes to individual components of the irradiator or calibrated dosimetry system should also be assessed for the effect on the qualified state of the sterilization process.

Changes to the irradiator are often made with the intention of not changing the OQ status of the irradiator. The evaluation criteria are the same, regardless of the intent of the change to the irradiator.

Evaluation and acceptance criteria need to be developed and applied to the comparison of OQ data before and after a change is made in order to determine whether or not the OQ status of the irradiator has changed, i.e. the dose distribution after the change can be classified as being "equivalent" or has not significantly changed relative to the dose distribution before the change. To avoid small changes accumulating and not being detected, the comparison of dose mapping data after a change should be made against data obtained when the process was established.

NOTE ISO 11137-1:2006, Tables A.1, A.2 and A.3 provide guidance on requalification activities associated with changes to gamma, electron beam and X-ray irradiators.

Further, ISO 11137-1:2006, A.12.4 states that if requalification measurements show that the IQ and/or OQ status of the irradiator has changed, then PQ might have to be repeated.

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Annex A
(informative)

Examples of setting process target dose ranges and interpretation of process output

A.1 General

The examples for this Annex have been selected to illustrate the different methodologies presented in this document. The calculation template is consistent throughout the Annex, but different components of uncertainty and variability are included or excluded depending on the specifics of each example. Table A.1 provides a reference to what methods and considerations are included in each example.

Table A.1 — Example matrix

Example	Modality	Use of D_{mon}	Additional inputs	Acceptance and analysis	Other considerations
#1	Gamma	Measure (4.2.2)	Transitions (6.3.6)	Simple D_{mon}^{ster} and $D_{mon}^{max,acc}$ (6.5.2)	Looks at process setting for two conditions: quiet and transition.
#2	Gamma	Monitor/ measure (4.2.4)	Transitions (6.3.6) and Process interruptions (6.3.5)	Simple D_{mon}^{ster} and $D_{mon}^{max,acc}$ (6.5.2)	Inclusion in a processing category, use of a targeting buffer in process factor calculations.
#3	Electron beam	Monitor (4.2.3)	Process interruptions (6.3.5)	Process monitoring (6.5.4)	Process has challenging dose specifications
#4	Electron beam	Monitor (4.2.3)	Process interruptions (6.3.5) Machine variability using limits of critical process parameters (5.3.3)	Process monitoring (6.5.4) and Alert and action (6.5.3) SPC (6.6.4) Western Electric Rules[14]	Different dosimetry system is used for dose mapping and monitoring
#5	Electron Beam	Measure (4.2.2)	Machine variability using historic measurements (5.4.3)	Alert and action (6.5.3) Parametric (6.6.3)	Decision rules based also on parametric data trending

The examples in this Annex have been provided by several irradiator operators using actual data sets. The level of uncertainty generated by the different methods should not be used as an indication of the quality or the limitation of the method, nor should it be inferred that one method is superior to another. The application of different approaches will depend on the unique circumstances around each product and/or facility and the assumed risks associated with running a particular process.

All examples include graphical representations of minimum, maximum and/or monitoring doses in order to illustrate the anticipated range of values that may be expected for a given process.

The examples provide calculations of multiple factors used in setting up a process. In all cases numbers are shown as rounded, but non-rounded numbers are used up to the final calculation.

The examples include components of uncertainty derived from replicate information, but the calculations for how this is done are not explicitly shown. The spread of dose ratios around a sample mean can be assessed two different ways: by the standard deviation of the values in the sample or the standard deviation of the mean, which takes into account the number of values in the sample. As the

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mean of measured dose ratios is used in subsequent calculations, the standard deviation of the mean is applied when assessing σ_{ratio} in the examples in the Annex.

Standard Deviation of the mean = $\sigma/\sqrt{n}$, with n the number of values in the sample and σ the standard deviation of the values in the sample

The estimate of the standard deviation of the mean might be improved by pooling data from several dose mapping runs.

A.2 Example 1

A.2.1 Example description

This example represents products sterilized in a gamma irradiator located at a medical device manufacturer. In this example, there are a limited number of products so the ability to schedule the irradiator can be straightforward.

In this example, we look at two cases that could be encountered: 1) transitioning product into an irradiator with lower density product present, and 2) setting up the process to efficiently process when there is only one product present after the transition is complete.

In a gamma irradiator where there are transitions between products, it might not be practicable to calculate an expected process target dose for each irradiation container within the irradiator, apart from the knowledge that it will be within a calculated range. In this case, the monitoring dosimeter is used to make an indirect measurement of maximum and minimum dose to the product, rather than as a process monitoring tool. Similarly, the acceptance range is based on D_{mon}^{ster} and $D_{mon}^{max,acc}$.

A.2.2 Process specification

Sterilization dose, D_{ster}	25	kGy
Maximum acceptable dose, $D_{max,acc}$	34	kGy

A.2.3 PQ dose measurements

Mapping dosimetry system Alanine

Routine dosimetry system Same as mapping, D_{mon} location on outside of container

Cycle time for dose map, $CT_{DoseMap}$ 133 s

Table A.2 — Example 1 dose mapping data

	Container 1	Container 2	Container 3	Container 4	Container 5	Container 6
D_{min} kGy	26,7	26,7	26,4	26,8	26,9	26,2
D_{max} kGy	31,0	32,1	32,2	32,1	32,3	32,2
D_{mon} kGy	26,9	27,2	26,7	27,0	27,5	27,1

Table A.3 — Example 1 dose mapping ratios

Ratios	Container 1	Container 2	Container 3	Container 4	Container 5	Container 6
$R_{max/min} = D_{max}/D_{min}$	1,16	1,20	1,22	1,20	1,20	1,23
$R_{max/mon} = D_{max}/D_{mon}$	1,15	1,18	1,21	1,19	1,17	1,19
$R_{min/mon} = D_{min}/D_{mon}$	0,99	0,98	0,99	0,99	0,98	0,97

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Table A.4 — Example 1 dose and ratio averages

PQ doses	Average	σ_{map} (%)
D_{min} kGy	26,6	0,99 (σ_{min})
D_{max} kGy	32,0	1,52 (σ_{max})
D_{mon} kGy	27,1	1,01 (σ_{mon})

Ratios	Average	σ_{ratio} (%)
$R_{max/min} = D_{max}/D_{min}$	1,20	0,80 ($\sigma_{max/min}$)
$R_{max/mon} = D_{max}/D_{mon}$	1,18	0,62 ($\sigma_{max/mon}$)
$R_{min/mon} = D_{min}/D_{mon}$	0,98	0,42 ($\sigma_{min/mon}$)

A.2.4 Components of $\sigma_{process}$

Components related to dosimetry system calibration and reproducibility

Calibration uncertainty, σ_{cal}	1,2	%	includes laboratory, curve fit and influence quantities
$\sigma_{rep} = \sigma_{mon}$ = **standard deviation of** D_{mon}	1,01	%	measured variability of monitoring dosimeter

Components related to process variability not measured in PQ

Process interruption, $\sigma_{interruption}$	0,0	%	Measurements in OQ demonstrate single process interruptions are too small to measure, facility rules determine number of interruptions allowed
Transitions, $\sigma_{transition}^{max}$	2,5	%	For planned transitions from lower densities, studies demonstrate overall maximum dose within an irradiation container increases while other doses remain in specification
Machine variability, σ_{mach}	0,0	%	σ_{mach} is captured in PQ study as determined by a comparison with data from OQ. Regular corrections to cycle time are made to compensate for change in source activity.

Components related to the indirect measurement of the minimum and maximum dose in routine operation

$\sigma_{min/mon}$ = **standard deviation of the mean of** $R_{min/mon}$	0,42	%
$\sigma_{max/mon}$ = **standard deviation of the mean of** $R_{max/mon}$	0,62	%
$\sigma_{mach,comb} = \sqrt{(\sigma_{rep}^2 + \sigma_{mach}^2)}$	1,01	%

Because the transition is from a lower density product, D_{target}^{lower} and the associated cycle time only has to be calculated for the steady state. D_{min} is increased during transition as compared to the steady state and the aim of the process qualification is to obtain a minimum cycle time which allows to meet the minimum dose specification during both stages of the irradiation process i.e. transition and steady state.

Calculation of $\sigma_{process}^{max}$ when considering a *transition* from a lower density

$\sigma_{process}^{max} = \sqrt{[\sigma_{cal}^2 + (\sigma_{max/mon})^2 + (\sigma_{mach,comb})^2 + (\sigma_{transition}^{max})^2]}$ 3,01 %

After transitioning in, for *steady state*, $\sigma_{process}^{max}$ is recalculated as follows:

$\sigma_{process}^{min} = \sqrt{[\sigma_{cal}^2 + (\sigma_{min/mon})^2 + (\sigma_{mach,comb})^2]}$	1,62	%
$\sigma_{process}^{max} = \sqrt{[\sigma_{cal}^2 + (\sigma_{max/mon})^2 + (\sigma_{mach,comb})^2]}$	1,69	%

A.2.5 Process factors

Selected k **(max)**	2
Selected k **(min)**	2

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Process factor calculations

Transitioning from lower density		*Steady state*	
		$UF_{lower} = 1/(1 - k * \sigma_{process}^{min}/100)$	1,03
$UF_{upper} = 1/(1 + k * \sigma_{process}^{max}/100)$	0,94	$UF_{upper} = 1/(1 + k * \sigma_{process}^{max}/100)$	0,97

A.2.6 Process target dose range calculation

Transitioning from lower density			*Steady State*		
			$D_{min}^{limit} = D_{ster} * UF_{lower}$	25,8	kGy
$D_{max}^{limit} = D_{max,acc} * UF_{upper}$	32,1	kGy	$D_{max}^{limit} = D_{max,acc} * UF_{upper}$	32,9	kGy
			$D_{target}^{lower} = D_{min}^{limit} / R_{min/mon}$	26,3	kGy
$D_{target}^{upper} = D_{max}^{limit} / R_{max/mon}$	27,1	kGy	$D_{target}^{upper} = D_{max}^{limit} / R_{max/mon}$	27,8	kGy

Figure A.1 is a graphical representation of the probability distribution functions associated with the following parameters when transitions are taken into account:

a) D_{min}^{limit} associated with D_{target}^{lower}

b) D_{max}^{limit} associated with D_{target}^{upper}, including transitions

c) D_{max}^{limit} associated with D_{target}^{upper}, steady state

Cycle time calculation (adjustment will be required to account for Cobalt-60 decay in future calculations)

Transitioning from lower density			*Steady State*		
			$CT_{minimum} = (CT/D_{mon})_{DoseMap} * D_{target}^{lower}$	129	s
$CT_{maximum} = (CT/D_{mon})_{DoseMap} * D_{target}^{upper}$	133	s	$CT_{maximum} = (CT/D_{mon})_{DoseMap} * D_{target}^{upper}$	137	s

For transitioning product into the irradiator from lower density product, any cycle time within the calculated range of 129 s to 133 s can be chosen, provided it is also appropriate for the product already in the irradiator. The allowable maximum cycle time is less when transitioning from a lower density than it is during steady state operation. Once the transition is complete, the cycle time can be adjusted to any value within the calculated range of steady state cycle times.

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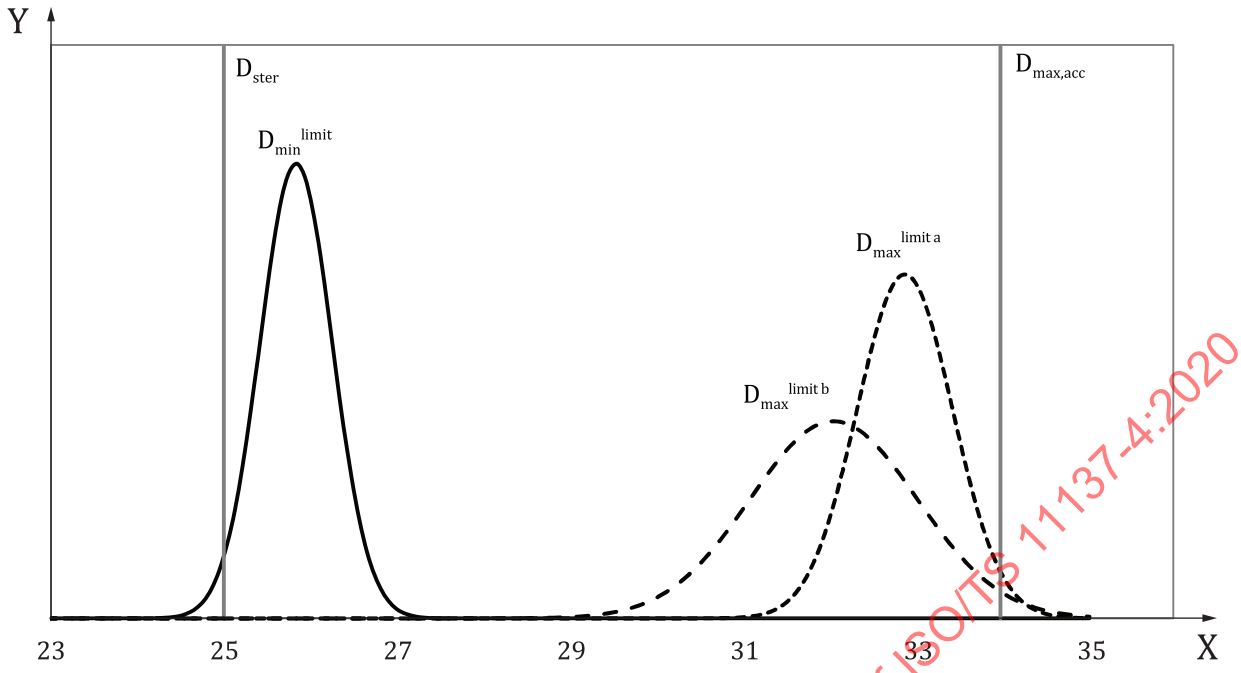

Key

X dose (kGy)

Y relative distribution

a Steady state.

b Transition.

Figure A.1 — Variation of minimum and maximum dose to product during operation at $D_{target} = D_{target}^{lower}$ (solid line) and $D_{target} = D_{target}^{upper}$ (dashed line) for both steady state and with transitions taken into consideration

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A.2.7 Example of application of an acceptance range

The doses at the monitoring location which correspond to the sterilization and maximum acceptable doses are calculated as follows:

$D_{mon}^{ster} = D_{ster}/R_{min/mon}$	25,4	kGy
$D_{mon}^{max,acc} = D_{max,acc}/R_{max/mon}$	28,8	kGy

Product is conforming as long as D_{mon} measured in routine operation is between D_{mon}^{ster} and $D_{mon}^{max,acc}$.

Cycle time chosen, CT_{Chosen}	133	s
$\sigma_{process}^{mon} = (\sigma_{mach,comb})$	1,01	**%**

Figure A.2 shows the probability distribution function during the steady state, based on $\sigma_{process}^{mon}$ for the monitoring dose for the cycle time chosen and the associated limits associated with D_{mon}^{ster} and $D_{mon}^{max,acc}$.

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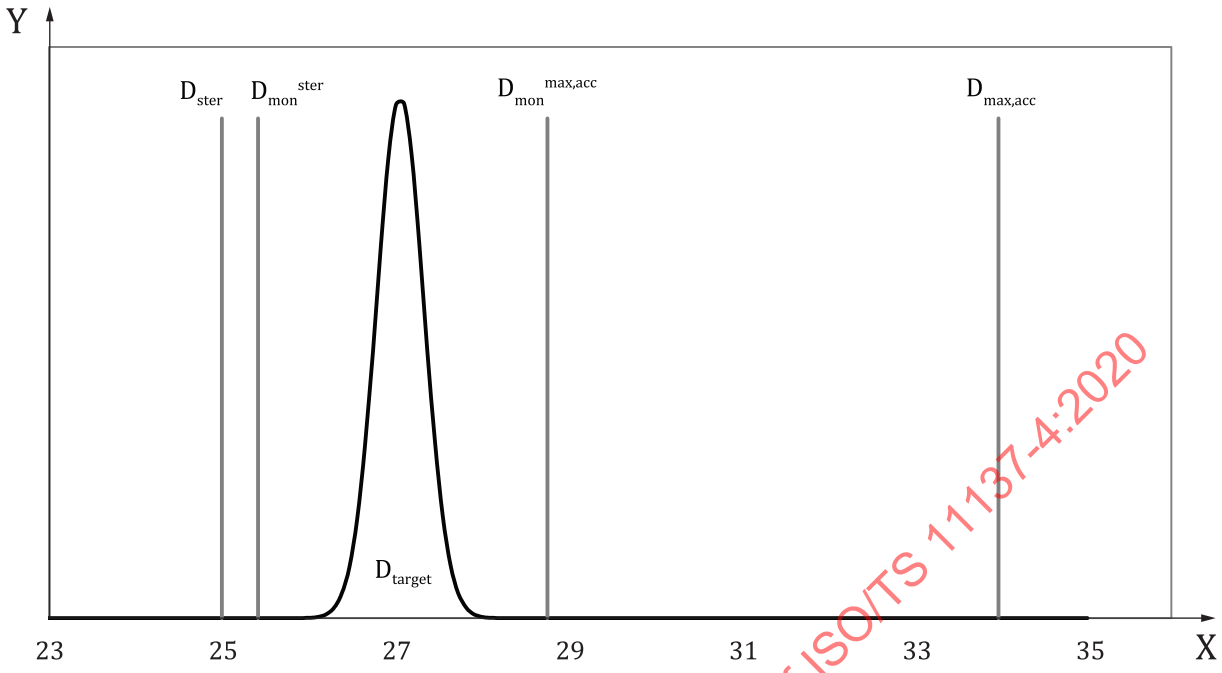

Key

X dose (kGy)

Y relative distribution

Figure A.2 — Variation of dose to the monitoring position during steady state operation at the chosen process target dose for an acceptance range between D_{mon}^{ster} and $D_{mon}^{max,acc}$

A.2.8 Additional considerations

The calculations pertain to two scenarios: product transitioning into an irradiator with other product at a lower density; and quiet system conditions for that product. The same calculation should be performed for the product when it transitions out, followed by another product whose density has not yet been defined. These types of calculations are possible when there is a limited number of products qualified in an irradiator, but a more practical solution could be the use of processing categories as specified in 5.2.3 and illustrated in A.2 Example 2.

A.3 Example 2

A.3.1 Example description

This example represents products sterilized in a gamma irradiator located at a contract facility that irradiates many different products, which can be mixed in the irradiator at the same time.

In this example, the acceptable range of processing parameters for a given product is determined to see if it can be included in one or more existing processing categories. The calculation of Process Factors is done as a check against targeting buffers that are based on historical data.

In a gamma irradiator where there are transitions between products, it might not be practicable to calculate a process target dose for each irradiation container within the irradiator, apart from the knowledge that it will be within a calculated range. In this irradiator design, the D_{mon} position is at the minimum dose location. The operator is able to use the monitoring dosimeter to make a direct measurement of minimum dose and an indirect measurement of maximum dose to the product. Similarly, the acceptance range is based on D_{mon}^{ster} and $D_{mon}^{max,acc}$.

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A.3.2 Process specification

Sterilization dose, D_{ster}	13,1	kGy
Maximum acceptable dose, $D_{max,acc}$	30,0	kGy

A.3.3 PQ dose measurements

Mapping dosimetry system PMMA

Routine dosimetry system Same as mapping, D_{mon} location inside irradiation container

Cycle time for dose map, $CT_{DoseMap}$ 180 s

Table A.5 — Example 2 dose mapping data

	Container 1	Container 2	Container 3
D_{min} kGy	15,8	15,4	16,0
D_{max} kGy	18,4	17,9	18,3

Table A.6 — Example 2 dose mapping ratios

Ratios	Container 1	Container 2	Container 3
$R_{max/min} = D_{max}/D_{min}$	1,16	1,16	1,14

Table A.7 — Example 2 dose and ratio averages

PQ doses	Average	σ_{map} (%)
D_{min} kGy	15,7	1,94 (σ_{min})
D_{max} kGy	18,2	1,45 (σ_{max})

Ratios	Average	σ_{ratio} (%)
$R_{max/min} = D_{max}/D_{min}$	1,16	0,57 ($\sigma_{max/min}$)

A.3.4 Components of $\sigma_{process}$

Components related to dosimetry system calibration and reproducibility

Calibration uncertainty, σ_{cal}	2,1	%	includes laboratory, curve fit and influence quantities
$\sigma_{rep} = \sigma_{min}$ = **standard deviation of** D_{min}	1,94	%	measured variability of monitoring dosimeter

Components related to process variability not measured in PQ

Process interruption, $\sigma_{interruption}$	NA	%	Measurements in OQ demonstrate a measurable change in maximum dose to locations closest to the source rack during an interruption of a fixed magnitude of $D_{interrupt}$ = 1 kGy
Transitions, $\sigma_{transition}$	2,0	%	Historic information shows that for similar density products in surrounding containers, overall maximum and minimum doses can be affected differently by transitions
Machine variability, σ_{mach}	0,0	%	σ_{mach} is captured in PQ study as determined by a comparison with data from OQ. Regular corrections to cycle time are made to compensate for change in source activity.

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Components related to the measurement of the process in routine operation

$\sigma_{max/min}$ = standard deviation of the mean of $R_{max/min}$	0,57	%
$\sigma_{mach,comb} = \sqrt{(\sigma_{rep}^2 + \sigma_{mach}^2)}$	1,94	%

Calculation of $\sigma_{process}$

$\sigma_{process}^{min} = \sqrt{[\sigma_{cal}^2 + (\sigma_{mach,comb})^2 + (\sigma_{transition})^2]}$	3,49	%
$\sigma_{process}^{max} = \sqrt{[\sigma_{cal}^2 + (\sigma_{max/mon})^2 + (\sigma_{mach,comb})^2 + (\sigma_{transition})^2]}$	3,54	%

A.3.5 Process factors

Selected k (max)	2
Selected k (min)	2

Process factor calculations, comparison with standard buffers used at the facility

Calculation using $k * \sigma_{process}$		Calculation using 10 % upper and lower buffers	
$UF_{lower} = 1/(1 - k * \sigma_{process}^{min}/100)$	1,08	$UF_{lower} = 1 + (\text{lower buffer})$	1,10
$UF_{upper} = 1/(1 + k * \sigma_{process}^{max}/100)$	0,93	$UF_{upper} = 1 - (\text{upper buffer})$	0,90

The standard buffer provides a more conservative calculation of process factors, the buffers can thus be applied for subsequent calculations.

A.3.6 Process target dose range calculation

$D_{min}^{limit} = D_{ster} * UF_{lower}$	14,4	kGy
$D_{max}^{limit} = D_{max,acc} * UF_{upper} - D_{interrupt}$	26,0	kGy

$D_{target}^{lower} = D_{min}^{limit}$	14,4	kGy
$D_{target}^{upper} = D_{max}^{limit} / R_{max/min}$	22,5	kGy

Figure A.3 is a graphical representation of the probability distribution functions associated with the following parameters:

a) $D_{min}^{limit} = D_{target}^{lower}$

b) D_{max}^{limit} associated with D_{target}^{upper}

Cycle time calculation (adjustment will be required to account for Cobalt-60 decay in future calculations)

$CT_{minimum} = (CT/D_{mon})_{DoseMap} * D_{target}^{lower}$	165	s
$CT_{maximum} = (CT/D_{mon})_{DoseMap} * D_{target}^{upper}$	322	s

There are two existing processing categories with an acceptable density range which have chosen cycle times of 200 s and 250 s. This product can be part of either of these processing categories.

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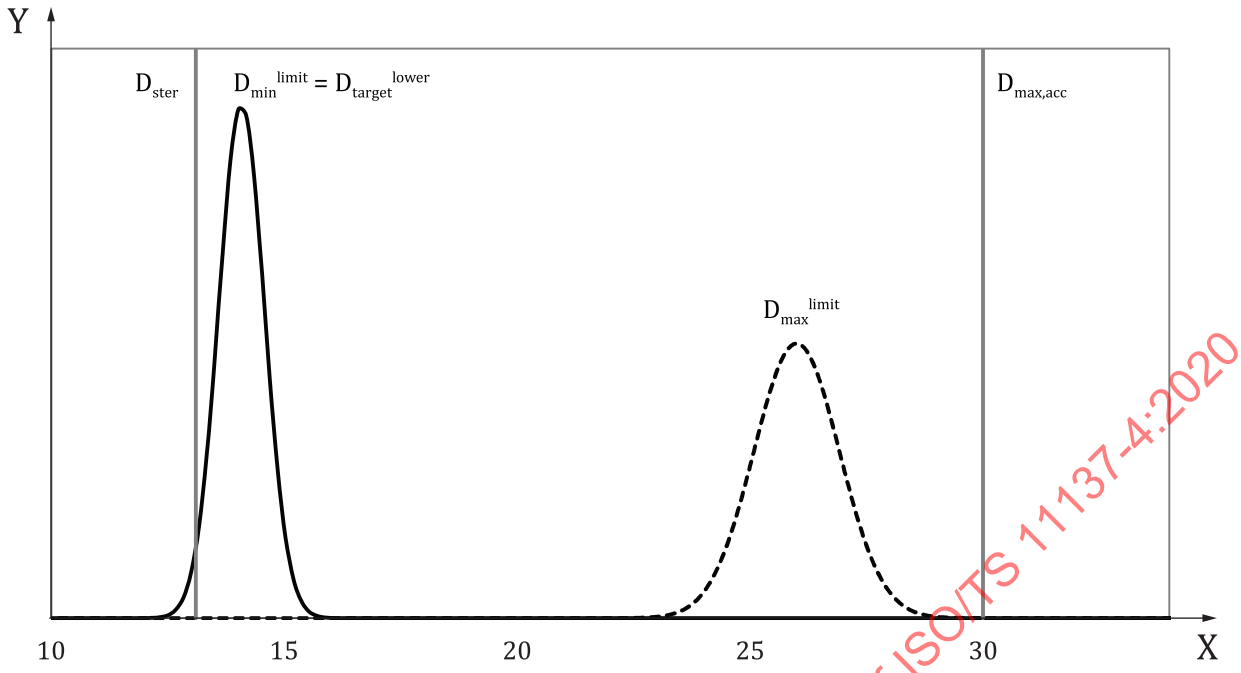

Key

X dose (kGy)

Y relative distribution

Figure A.3 — Variation of minimum and maximum dose to product during operation at $D_{target} = D_{target}^{lower}$ (solid line) and $D_{target} = D_{target}^{upper}$ (dashed line)

A.3.7 Example of application of an acceptance range

The doses at the monitoring (minimum dose) location which correspond to the sterilization and maximum acceptable doses are calculated as follows:

$D_{mon}^{ster} = D_{ster}$	13,1	kGy
$D_{mon}^{max,acc} = D_{max,acc}/R_{max/min}$	25,9	kGy

Product is conforming as long as D_{min} measured in routine operation is between D_{mon}^{ster} and $D_{mon}^{max,acc}$.

Cycle time chosen, CT_{Chosen}	200	s

$\sigma_{process}^{mon} = \sqrt{[(\sigma_{mach,comb})^2 + (\sigma_{transition})^2]}$ 2,79 **%**

Figure A.4 shows the probability distribution function when the product is included into the defined processing category that has a chosen cycle time of 200 s, based on $\sigma_{process}^{mon}$ for the monitoring dose for the cycle time chosen and the associated limits associated with D_{mon}^{ster} and $D_{mon}^{max,acc}$.

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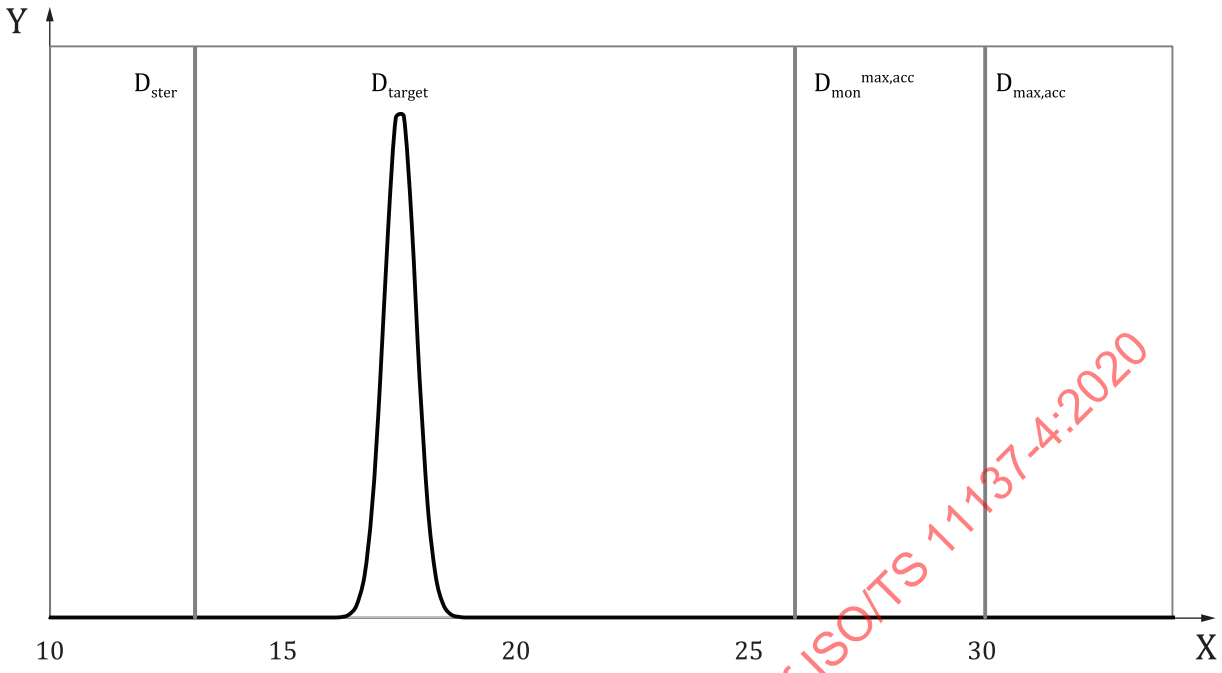

Key

X dose (kGy)

Y relative distribution

Figure A.4 — Variation of dose to the monitoring position during operation at the chosen parameters for an acceptance range between D_{mon}^{ster} and $D_{mon}^{max,acc}$

A.3.8 Additional considerations

This example used a targeting buffer as part of the calculation, but the validity of the buffer chosen was verified. In the case where the calculated process factors provide a more conservative value than the traditional targeting buffers, the calculated values should be used. If it is found that the process factors consistently calculate as more conservative than the buffers then these default values should be re-evaluated.

Conversely, if the conservative nature of the targeting buffers mean that a process might not meet specifications but the use of the calculated process factors provides an acceptable result, the targeting buffer need not be used. Also, if the effect of the transitions considered in the example mean that the process might not meet specification, the transitions can be reduced or eliminated by creating a new processing category for this product and specific products which have minimal transition effects.

A.4 Example 3

A.4.1 Example description

This example represents products sterilized in an electron beam irradiator for an in-house process. For an irradiator where there is only one product irradiated at a time under the same processing conditions, process monitoring can be appropriate to demonstrate that the process is in a state of control.

In this example, process interruptions have been characterized and demonstrated to have a different effect on maximum and minimum dose.

The acceptance is based on process monitoring in order to determine if the process is in a state of control.

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A.4.2 Process specification

Sterilization dose, D_{ster}	25	kGy
Maximum acceptable dose, $D_{max,acc}$	45	kGy

A.4.3 PQ dose measurements

Mapping dosimetry system Alanine Film

Routine dosimetry system Same as mapping, routine dosimetry off-product

Conveyor speed for dose map, $CS_{DoseMap}$ 4,0 m/min

Table A.8 — Example 3 dose mapping data

	Container 1	Container 2	Container 3	Container 4	Container 5	Container 6
D_{min} kGy	20,1	21,1	20,9	21,0	20,6	20,3
D_{max} kGy	31,8	32,1	31,1	32,0	31,3	31,6
D_{mon} kGy	24,1	24,3	25,0	24,2	24,8	24,3

Table A.9 — Example 3 dose mapping ratios

PQ doses	Average	σ_{map} (%)
D_{min} kGy	20,7	1,95 (σ_{min})
D_{max} kGy	31,7	1,24 (σ_{max})
D_{mon} kGy	24,5	1,48 (σ_{mon})

Table A.10 — Example 3 dose and ratio averages

Ratios	Average
$R_{max/min} = D_{max}/D_{min}$	1,53
$R_{max/mon} = D_{max}/D_{mon}$	1,29
$R_{min/mon} = D_{min}/D_{mon}$	0,85

A.4.4 Components of $\sigma_{process}$

Components related to dosimetry system calibration and reproducibility

Calibration uncertainty, σ_{cal} 1,00 **%** includes laboratory, curve fit and influence quantities

σ_{cal} in this example is not included in the calculations of $\sigma_{process}$ as the user assumes the risk associated with a change in dosimetry system calibration, for example, that if there is a shift in dose measurements as a result of a new calibration, the process and/or target doses might need to be re-established.

$\sigma_{rep} = \sigma_{mon}$ = **standard deviation of** D_{mon} 1,48 **%** measured variability of monitoring dosimeter

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Components related to process variability not measured in PQ

Process interruption, $\sigma_{interruption}^{min}$	2,0	%	Min dose effect
Process interruption, $\sigma_{interruption}^{max}$	4,0	%	Max dose effect
Transitions, $\sigma_{transition}$	0,0	%	Transitions are mitigated with gaps between irradiation containers
Machine variability, σ_{mach}	0,0	%	σ_{mach} is fully captured in PQ study as verified by comparison with data from OQ

Components related to the measurement of the process in routine operation

$\sigma_{mach,comb} = \sqrt{(\sigma_{rep}^2 + \sigma_{mach}^2)}$ 1,48 %

Calculation of $\sigma_{process}$ when considering process interruptions

$\sigma_{process}^{min} = \sqrt{[\sigma_{min}^2 + \sigma_{mach}^2 + (\sigma_{interruption}^{min})^2]}$	2,79	%
$\sigma_{process}^{max} = \sqrt{[\sigma_{max}^2 + \sigma_{mach}^2 + (\sigma_{interruption}^{max})^2]}$	4,19	%
$\sigma_{process}^{mon} = (\sigma_{mach,comb})$	1,48	%

A.4.5 Process factors

Selected k **(max)**	2
Selected k **(min)**	2

Process factor calculations

$UF_{lower} = 1/(1 - k * \sigma_{process}^{min}/100)$	1,06
$UF_{upper} = 1/(1 + k * \sigma_{process}^{max}/100)$	0,92

A.4.6 Process target dose range calculation

$D_{min}^{limit} = D_{ster} * UF_{lower}$	26,5	kGy
$D_{max}^{limit} = D_{max,acc} * UF_{upper}$	41,5	kGy
$D_{target}^{lower} = D_{min}^{limit} / R_{min/mon}$	31,3	kGy
$D_{target}^{upper} = D_{max}^{limit} / R_{max/mon}$	32,1	kGy

Figure A.5 is a graphical representation of the probability distribution functions associated with the following parameters:

a) D_{target}^{lower}

b) D_{min}^{limit}

c) D_{max} associated with D_{target}^{lower}

Calculated range of processing parameters

$CS_{minimum} = (CS * D_{mon})_{DoseMap} / D_{target}^{upper}$	3,05	m/min
$CS_{maximum} = (CS * D_{mon})_{DoseMap} / D_{target}^{lower}$	3,12	m/min

The range of conveyor speeds is very narrow, but the process is deemed to be capable.

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