Guide on the establishment of the maximum acceptable dose ($D_{max,acc}$) for a product

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0. Introduction

EN ISO 11137-1:2015 clause 7.1 requires the primary manufacturer to specify the product to be sterilized, including the packaging materials.

It is also a requirement in EN ISO 11137-1:2015 – clause 8.1 - to establish the maximum acceptable dose ($D_{max,acc}$) for the specified product: "When treated with the maximum acceptable dose, product shall meet its specified functional requirements throughout its defined lifetime." In this context "product" should be interpreted as including its packaging system, where packaging system is as defined in 3.1.7 of ISO 11137-2:2013 a combination of the sterile barrier system and protective packaging. In the informative clause A.8.1.1 of EN ISO 11137-1:2015 Annex A it is recommended to include safety assessments, including biological safety (see ISO 10993-1), using appropriate tests with specific acceptance criteria.

"Establish" is defined in EN ISO 11137-1:2015– definition 3.13 – as "determine by theoretical evaluation and confirm by experimentation". Therefore, the requirement to establish a maximum acceptable dose for product implies that an experimental test programme involving product irradiation needs to be specified and carried out by the primary manufacturer.

Basic technical requirements in EN ISO 11137-1:2015 for establishing $D_{max,acc}$ include availability of product representative of that produced routinely, a facility capable of assessing product with regard to its intended functions, an irradiator capable of delivering accurately and precisely the doses and a dosimetry system capable of measuring accurately and precisely the delivered doses. Although not a requirement, it is recommended that product is sampled from different manufacturing batches in order to take variations in raw materials and the manufacturing process into account.

This document is intended to provide practical and generically applicable guidance for setting up an experimental programme to establish $D_{max,acc}$, with emphasis on dose delivery and measurement, and to interpret the results of the experimental programme. Sections 2 to 5 describe these aspects and should be read and used together. Section 6 presents ways of specifying $D_{max,acc}$ based on the dosimetric data from the irradiations in the study and the results of the product testing, and 2 examples are given.

Methods for product testing and evaluation of product properties are not discussed, because these are product specific. The primary manufacturer could apply risk assessment techniques, for example those described in ISO 31010, to evaluate whether certain test methods should be included in the experimental programme. An evaluation of the product's packaging system (combination of sterile barrier system and protective packaging) should be included in the test programme and should be performed in accordance with ISO 11607-1.

1. Definitions

Dose Uniformity Ratio (DUR) – ratio of the maximum to the minimum dose in an irradiation container.

Irradiation container - holder in which product is transported through the irradiator. The holder can be a carrier, cart, tray, product carton, pallet or other container.
[EN ISO 11137-1:2015]

Performance Qualification (PQ) - process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification.
[EN ISO 11137-1:2015]

Processing category – group of different products that can be irradiated together. Processing categories can be based on, for instance, composition, density or dose requirements.
[EN ISO 11137-1:2015]

2. Selection of doses, dose tolerances and quantity of product

EN ISO 11137-1:2015 does not contain requirements for selected doses, dose tolerances or sample quantities in establishing the maximum acceptable dose for product. Selection depends on the product and the properties to be tested, and guidance is given below.

2.1 Selected doses.

The selected dose level(s) should refer to the lowest dose delivered to (sets of) product samples in the test programme, and should take into account the (anticipated) sterilization dose D_{ster} for the product, the expected maximum dose received by the product during routine processing (or the Dose Uniformity Ratio, DUR), as well as the expected effects of ionizing radiation on the product.

The sterilization dose for the product might not be known when the doses for product irradiation in support of establishing $D_{max,acc}$ are selected. However, knowledge about product bioburden might allow estimation of a required sterilization dose, and if product is known or expected to have a low $D_{max,acc}$ one might, concurrent with establishing $D_{max,acc}$, consider

- reducing the sterilization dose (for instance by reducing product bioburden or by choosing a different method for establishing the sterilization dose),
- reducing the DUR or
- reducing the routine irradiation process' variability in order to obtain a process that is capable of not impairing the product properties.

Knowledge about expected effects of ionizing radiation on the product can be based on prior experience of the primary manufacturer and / or of the irradiation service provider; or can be based on the available literature. AAMI TIR 17:2008 provides a summarizing overview of material compatibility to different kinds of sterilization processes, including exposure to ionizing radiation, and can together with the documents it references be consulted to provide a rationale for the selected dose(s).

It is beneficial to select multiple doses in the experimental programme. It allows trending of the product's properties as a function of dose, potentially up to the point where an unacceptable change in one or more properties is found. If this approach is taken, then it might make it possible to determine a greater value for $D_{max,acc}$ than when only a single dose level is chosen in the programme, since the single dose level might be chosen low in order to maximize the probability of rendering acceptable outcome of product performance tests at this dose.

A greater value for $D_{max,acc}$ and thereby a greater dose span between $D_{max,acc}$ and D_{ster} might allow

- more efficient processing (more product per irradiation container) as well as operational flexibility (integration into processing categories) at the irradiator to be used for routine processing. Consultation with the irradiator operator is recommended regarding the capabilities of the irradiator to deliver a dose within specified tolerances to the product during routine processing.
- easier transfer to another irradiator,
- re-processing in case of a non-conforming irradiation process, and
- processing at an augmented sterilization dose.

Un-irradiated product samples should be included as controls in the test programme.

2.2 Quantity of product samples per selected dose.

The necessary quantity of representative product samples per selected dose depends on the test programme for the product and whether samples can be re-used for testing or not. The quantity might also depend on the statistical confidence level of each test, and on accelerated as well as real time ageing studies [1]. Guidance on calculating the sample quantity to estimate, with specified precision, the average for a characteristic of a process is given in ASTM E122.

When more than a single dose level is chosen in the experimental study to establish $D_{max,acc}$, the quantity of product irradiated at all dose levels might not need to be the same. One could for instance consider trending of the product's properties as a function of dose with a few products per dose up to the point where an unacceptable change in one or more properties is found, and to perform a closer examination with more products around this dose level.

[1] EN ISO 11137-1:2015– clause A.8.1.1 – states that "Accelerated ageing, however, is not a substitute for real time ageing."

2.3 Dose tolerances.

During establishment of the sterilization dose in accordance with ISO 11137-2, product samples are irradiated at a verification dose or incremental doses. The typical requirement is that these doses are delivered within +/-10% around the verification or incremental dose (+10% on the maximum dose to any part of any of the product items, -10% on the mean dose delivered to the product items).
Operators of irradiation facilities and medical device manufacturers might be familiar with these requirements, and a similar tolerance is often taken for sample irradiations in establishing a maximum acceptable dose, so that the aim of irradiation is that product items at a selected dose level are irradiated with a total dose distribution of +/- 10%, or a DUR less than 1.2.

Such a tolerance is often a good choice, but greater DUR might be acceptable, for example when product properties are based on literature or prior experience anticipated not to change significantly over a wider dose range.

For some very radiation-sensitive products, on the other hand, the DUR might need to be smaller than 1.2.

Analysis of the results might be more straightforward if the DUR is small.

The irradiator operator should be consulted regarding his capability to irradiate the product samples at the doses within the requested tolerances. It is generally not needed to irradiate at a specific dose, but the dose and dose distribution to the product must be known. For instance with a requested dose of 40 kGy, measured product doses between 40.5 kGy and 48.1 kGy or between 42.5 kGy and 50.0 kGy might both be acceptable for establishing $D_{max,acc}$. However, assuming that under both scenarios the testing of irradiated product rendered acceptable results, the actual value derived for $D_{max,acc}$ will be different for the two cases. If the approach is taken to specify $D_{max,acc}$ as the lowest dose measured on samples for which acceptable performance is found, in the first case $D_{max,acc}$ will be 40.5 kGy, while in the second it will be 42.5 kGy (Annex 1).

In exceptional cases it might be beneficial to irradiate different components of a product each to a specific set of doses. Reasons could be a largely different $D_{max,acc}$ for the individual components or reducing the dose uniformity ratio in the irradiations to establish $D_{max,acc}$. When product components rather than products are irradiated, care should be taken that the functionality and safety of the entire product is assessed.

3. Definition of the irradiation process for the product samples

(Irradiator / load configuration in irradiation container / process parameters)

EN ISO 11137-1:2015– clause 8.4.1 – requires a documented assessment when transferring a maximum acceptable dose to a radiation source different from that on which the dose is established. The assessment needs to demonstrate that the differences in irradiation conditions (in particular dose rate and temperature of product) do not affect the validity of the maximum acceptable dose under the actual conditions of routine product irradiation.

In many cases, the higher the dose rate, the lower the unwanted effects upon product. A product qualified by irradiation at a low dose rate will typically require minimal qualification to demonstrate compatibility for irradiation at a higher dose rate. Conversely, a product qualified at a high dose rate may require more substantial qualification for a low dose rate application. However, the user should be aware that there are cases where this simplification might not apply, for instance, for product that is temperature sensitive or that has a strong tendency to crosslink.

Whereas clause 8.4.1 in EN ISO 11137-1:2015 is written specifically considering transfer of $D_{max,acc}$ for product irradiation at different irradiation sources, it should also be considered when there is no such transfer, but if irradiation conditions (dose rate or product temperature, for example) in the same irradiator are significantly different between irradiations to establish $D_{max,acc}$ and those for routine product irradiation.

A common example where such an assessment is needed, is irradiation at dose levels greater than the calibrated range of the dosimetry system used to measure the dose during the test programme. Effects of ionizing radiation on polymers are generally cumulative, so fractionated irradiation might be used for establishing $D_{max,acc}$ in this case. The total dose can be taken as the sum of the doses in each irradiation, but product temperature under this incremental irradiation might be significantly different from (lower than) that when the dose had not been delivered in fractions such as it might be done during routine product irradiation. This could affect the validity of the established maximum acceptable dose.

3.1 Gamma irradiation

Irradiations for establishing $D_{max,acc}$ using gamma irradiation are commonly performed in a dedicated test irradiator (or using a dedicated conveyor pathway or off-carrier location in an existing irradiator used for routine processing). Under these conditions irradiation might be carried out with different dose rate and different irradiation temperature than used during routine processing. Using the same irradiation containers for establishing $D_{max,acc}$ and for routine processing has the possible benefit of minimizing differences in irradiation conditions (dose rate and temperature). In such irradiation containers the product for testing should be placed in a volume with minimal dose gradients, which typically is at the center of the irradiation container. This allows irradiation of the product items with almost homogeneous dose distribution in order to reach the required dose tolerances.

The quantity of product (or product components) for $D_{max,acc}$ testing presented together for irradiation depends on the DUR that is deemed necessary, reference section 2. For a larger acceptable DUR, typically a larger quantity of product can be irradiated together in an irradiation container.

3.2 Electron beam irradiation

Irradiations for establishing $D_{max,acc}$ for electron beam irradiation should preferably be performed in the same irradiator as that used for routine processing in order to minimize possible differences of irradiation conditions between irradiation for testing and for processing. If different irradiators are used for establishing $D_{max,acc}$ and for routine processing, the dose rate of the irradiators should be similar or an assessment of the effect of differences in irradiation conditions on product performance should be made.

In electron beam irradiation for $D_{max,acc}$ testing typically only a single layer of product is irradiated in order to minimize DUR. Product might be placed in-between thin layers of a radiation resistant material (for instance a few mm of polystyrene). The plates serve to scatter the electron beam leading to a more uniform dose distribution and also to limit the degree of backscatter from metal components of conveyor or irradiation container. Irradiation occurs normally from 2 opposite sides.

Product temperature during e-beam irradiation can be significantly different between a single layer of product and product presented together in a carton due to, for example, differences in cooling between a single layer of product and product within a carton. Such differences between the irradiation conditions during routine processing and those during irradiations to establish $D_{max,acc}$ should be minimized, or their affects evaluated.

3.3 X-ray irradiation

Irradiations for establishing $D_{max,acc}$ for X-ray irradiation should preferably be performed in the same irradiator as that used for routine processing in order to minimize possible differences between irradiation for testing and for processing. If different irradiators are used for establishing $D_{max,acc}$ and for routine processing, the dose rate of the irradiators should be similar or an assessment of the effect of differences in irradiation conditions on product performance should be made.

The quantity of product (or product components) for $D_{max,acc}$ testing presented together for irradiation depends on the DUR that is deemed necessary, reference section 2. For larger DUR, typically a larger quantity of product can be irradiated together in an irradiation container.

4. Selection and calibration of dosimetry system

In general, the dosimetry systems used for PQ dose mapping or routine dose monitoring in radiation processing will be suitable for measurement of the greater doses used to establish $D_{max,acc}$, provided they have been calibrated at these greater doses. To be able to measure the doses in the experimental programme fractionated irradiation might be needed (reference section 3).

Calibration of the dosimetry systems should be carried out in accordance with documented procedures, such as those described in ISO/ASTM 51261. The uncertainty of the dosimetry systems should be determined and assessed against the requirements for dose tolerances in the experimental programme (see 2.3). If the calibration procedures in ISO/ASTM 51261 are followed, resulting uncertainties should be in the region of 3% to 6% ($k=2$).

When using gamma irradiation in a dedicated test irradiator (or using a dedicated conveyor pathway or off-carrier locations in existing irradiators for routine processing), consideration should be given to the effect on dosimeter response of the conditions associated with such use. If irradiation calibration conditions for the dosimetry systems used for PQ dose mapping or routine dose monitoring in radiation processing are significantly different from the irradiation conditions for $D_{max,acc}$ testing, e.g. with respect to dose rate and temperature, then separate calibration of the dosimetry systems might be needed for the test programme to establish $D_{max,acc}$.

5. Specifying dose monitoring practice

Where practicable, replicate dose mapping exercises should be performed on product in the load configuration defined for $D_{max,acc}$ testing in order to quantify and potentially reduce measurement uncertainties of dose to product. Without data from a replicate dose mapping exercise for a product in the load configuration defined for $D_{max,acc}$ testing, sufficient dosimeters should be placed in each irradiation container to identify the locations of and measure the minimum and maximum doses.

The uncertainty associated with the dose measurements should be quantified and minimized as it will feed through directly into uncertainty in the determined $D_{max,acc}$. An uncertainty budget should be established to determine if uncertainty associated with dose measurements contributes significant uncertainty to the determined $D_{max,acc}$. If the contribution is significant, the test programme should be reviewed and, if possible, changes made to reduce uncertainties.

When fractionated irradiation is used, the same dosimeters can be used to monitor the total dose if the dosimetry system is calibrated for such conditions of use. Alternatively, each irradiation can be monitored separately by dosimeters. This approach provides information on each of the fractionated irradiations.

6. Interpretation of dosimeter measurements

Selection of the basis for determination of $D_{max,acc}$ from the dosimetry data and product performance tests is the responsibility of the primary manufacturer and different approaches for using the dosimetric data from the test irradiations can be taken. It is important to be conservative when estimating $D_{max,acc}$. The risk of having estimated a too small value for $D_{max,acc}$ is that product might not meet all of its specifications after routine irradiation.

A conservative estimate of $D_{max,acc}$ could be the lowest measured dose for a group of product irradiated at a selected dose level and rendering acceptable test results. For small DURs and in cases where the governing functional specifications are driven by average values for a product (e.g. color change) using the average dose measured for samples rendering acceptable test results might be acceptable.

When more than a single dose measurement is available for the minimum dose to a group of samples rendering acceptable test results, for instance when product is irradiated in different irradiation containers and each of these is monitored at positions of minimum and maximum dose or when dosimeters are placed at the minimum dose position for more than one replicate sample that is irradiated at the same dose, a statistical approach could be taken to specify $D_{max,acc.}$ The minimum dose measurements are for both described scenarios sampled from a probability distribution characteristic for the irradiation and monitoring process, and can be used to calculate

- the average measured minimum dose (Avg. D_{min}) for samples rendering acceptable test results, which can then be used as an estimator for the mean of the entire population.

- the dose value, D_{crit},

  $D_{crit} = (\text{Avg. } D_{min}) - k \times \sigma_{Dmin}$

  Where σ_{Dmin} is the standard deviation of the minimum dose measurements.

  For normal (Gaussian) distributions the approximate single-sided confidence levels obtained by different selections of k are:

  $k = 1$ 84 % confidence level,
  $k = 2$ 98 % confidence level,
  $k = 3$ 99.5 % confidence level.

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

References

EN ISO 11137-1:2015; Sterilization of healthcare products – radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices.

ISO 31010; Risk management – risk assessment techniques.

ISO 11607-1; Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems.

ISO 11137-2:2013; Sterilization of healthcare products – radiation – Part 2: Establishing the sterilization dose.

ISO 11137-3:2006; Sterilization of healthcare products – radiation – Part 3: Guidance on dosimetric aspects.

AAMI TIR 17:2008; Compatibility of materials subject to sterilization.

ASTM E122 - 09e1; Standard Practice for Calculating Sample Size to Estimate, With Specified Precision, the Average for a Characteristic of a Lot or Process.

ISO/ASTM 51261:2013; Standard Practice for Calibration of Routine Dosimetry Systems for Radiation Processing

Annex 1: examples

EXAMPLE 1

Experimental Protocol:

Irradiate 3 discrete batches of product samples at a minimum dose of 40.0 kGy, with a DUR below 1.20
All samples from the 3 batches of product are loaded in a single irradiation container
The dose to the products is measured by calibrated dosimeters at positions of minimum (Dmin) and maximum (Dmax) dose.
Test 3 samples from each batch for functionality/safety requirements, at time intervals up to the defined shelf-life.

Scenario 1:

Selected dose (kGy)	40.0 kGy
Dmin (kGy)	40.5
Dmax (kGy)	48.1
DUR	1.19
Functionality/Stability test results	PASS

Scenario 2:

Selected dose (kGy)	40.0 kGy
Dmin (kGy)	42.5
Dmax (kGy)	50.0
DUR	1.18
Functionality/Stability test results	PASS

[1] Acceptance criteria: All replicate samples from 3 batches PASS functionality and safety requirements.

Possible values of $D_{max,acc}$

[2] $D_{max,acc}$ = The lowest dose to replicate samples that meet [1]

$D_{max,acc}$ (kGy)	40.5

$D_{max,acc}$ (kGy)	42.5

[3] $D_{max,acc}$ = The average minimum dose (Avg. D_{min}) to replicate samples that meet [1]

$D_{max,acc}$ (kGy)	NA

$D_{max,acc}$ (kGy)	NA

[4] $D_{max,acc}$ = (Avg. D_{min}) - k $\times \sigma_{Dmin}$
Assume Gaussian distribution of minimum doses to replicate samples that meet [1] and use approximate confidence levels

$D_{max,acc}$ (kGy)	NA	$k = 1$
	NA	$k = 2$
	NA	$k = 3$

$D_{max,acc}$ (kGy)	NA	$k = 1$
	NA	$k = 2$
	NA	$k = 3$

[5] $D_{max,acc}$ = The average dose to replicate samples that meet [1]

$D_{max,acc}$ (kGy)	44.3

$D_{max,acc}$ (kGy)	46.3

EXAMPLE 2

Experimental Protocol:

Irradiate 3 discrete batches of product samples at the selected dose +/-10%. 2 dose values are selected.
The dose to the samples from each batch of product shall be measured by calibrated dosimeters at positions of minimum (Dmin) and maximum (Dmax) dose.
Test 3 samples from each batch for functionality/safety requirements, at time intervals up to the defined shelf-life.

Selected dose	45.0 kGy					
Batch Number	1	2	3	Avg.	Stdev.	CV
Dmin (kGy)	43.5	44.6	44.0	44.0	0.551	1.3%
Dmax (kGy)	48.0	49.4	48.6	48.7	0.702	1.4%
DUR	1.10	1.11	1.10	1.10	0.006	0.5%
Functionality/Stability test results	PASS	PASS	PASS			

Selected dose	55.0 kGy					
BatchNumber	1	2	3	Avg.	Stdev.	CV
Dmin (kGy)	50.0	51.5	50.8	50.8	0.751	1.5%
Dmax (kGy)	55.1	57.0	56.5	56.2	0.985	1.8%
DUR	1.10	1.11	1.11	1.10	0.006	0.5%
Functionality/Stability test results	PASS	FAIL	PASS			

[1] Acceptance criteria: All replicate samples from 3 batches PASS functionality and safety requirements.

Possible values of $D_{max,acc}$

[2] $D_{max,acc}$ = The lowest dose to replicate samples that meet [1]

$D_{max,acc}$ (kGy)	43.5

[3] $D_{max,acc}$ = The average minimum dose (Avg. D_{min}) to replicate samples that meet [1]

$D_{max,acc}$ (kGy)	44.0

[4] $D_{max,acc}$ = (Avg. D_{min}) - k $\times\sigma_{Dmin}$
Assume Gaussian distribution of minimum doses to replicate samples that meet [1] and use approximate confidence levels

$D_{max,acc}$ (kGy)	43.4	$k = 1$
	42.9	$k = 2$
	42.3	$k = 3$

[5] $D_{max,acc}$ = The average dose to replicate samples that meet [1]

$D_{max,acc}$ (kGy)	46.4

Contributors

This document has been prepared by the Dosimetry Group of the Panel on Gamma and Electron Irradiation. It has been reviewed and approved by Panel members.

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