BBF Sterilisationsservice GmbH
Dosimetry
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Explanations on how to perform dose distribution measurements

The performance of dose distribution mapping serves (in addition to the microbiological establishing of the sterilization dose) the development and validation of radiation sterilization. The aim here is to demonstrate that the required sterilization dose is achieved and that the maximum acceptable (without compromising safety, quality or performance) dose is not exceeded.
Before performing a dose distribution measurement, both the required sterilization dose and the maximum acceptable dose must be determined and specified. Furthermore, the packing configuration of the products within the product carton and irradiation container must be determined.
Note: The specifications and the packing arrangement are QM documents that are subject to document and change management as part of the customer's QWM system.
The requirements and procedures are described in various ISO/ASTM/and AAMI standards. In our opinion, the three most important are ISO 11137-1, ISO 11137-3 and AAMI TIR29.
Before going on, a few definitions are given to make the following explanations a little easier to understand.

Product specification	Is given by the dose limits (sterilization dose and maximum acceptable dose). Dose mapping verifies that all readings at all locations of the irradiation container meet the product specification.
DUR Dose uniformity ratio	The relative dose window is the quotient of the maximum and minimum dose occurring within an irradiation unit (=D_{max}/D_{min}). In contrast to the absolute dose window, this quotient is characteristic for a defined packing arrangement and independent of the absorbed dose level (or the irradiation time).
Dose window	The absolute dose window specifies the range from minimum to maximum dose that can occur in an irradiation unit at different locations within the irradiation unit for a given irradiation time.
Sterilization dose D_{ster}	Minimum dose that must be achieved at all locations of an irradiation unit to ensure the achievement of sterility
Maximum acceptable dose $D_{max,acc}$	The highest dose at which a product can be irradiated without suffering loss of integrity or function over its intended lifetime.
D_{min}	**Minimum dose** or absorbed minimum dose means the lowest radiation dose occurring at a defined irradiation container. The minimum dose must not be lower than the sterilization dose.
D_{max}	Maximum dose or absorbed maximum dose means the highest radiation dose occurring at a defined irradiation container. The maximum dose must not be higher than the maximum acceptable dose.
Reference dose D_{mon}	The dose measured during routine irradiation at a defined location of the irradiation container, which is proportionally related to the sterilization dose and the maximum acceptable dose.
AF_{min} AF_{max}	**Adjustment factors / dose quotients**: The dose measured at the routine monitoring point is proportionally related to both the minimum dose determined for the specific packing arrangement and the corresponding maximum dose. $AF_{min}=D_{min}/D_{mon}$ $AF_{max}=D_{max}/D_{mon}$
$(AF_{min})_{corr}$ $(AF_{max})_{corr}$	**Corrected adjustment factors / corrected dose quotients:** To account for measurement uncertainty, the determined dose quotients must be corrected by the amount of two times the standard deviation (k=2) from at least three measurements. $(AF_{min})_{corr}$= Mean(AF_{min})-2*sd(AF_{min}); $(AF_{max})_{corr}$= Mean(AF_{max})+2*sd(AF_{max})

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Process specification D_{target}^{lower} D_{target}^{upper}	**Target dose range** for the routine monitoring point at which it can be assumed that the irradiation process is under statistical control and provides reliable results. Taking into account the measurement uncertainty, the corrected dose ratios and the product specification are used to determine the process specification that defines the target dose range at the routine monitoring point. $D_{target}^{lower} = D_{ster}/(AF_{min})_{corr}$ $\quad$ $D_{target}^{upper} = D_{max,acc}/(AF_{max})_{corr}$
Release specification D_{mon}^{ster} $D_{mon}^{max,acc}$	**Acceptance dose range** for the routine monitoring point where it is ensured that the individual result is within the product specification. This range does not allow any statement on the reliability of the irradiation process. For this purpose, the sterilization dose and the maximum permissible dose are converted to the routine measuring point without taking into account the measurement uncertainty using the mean values of the dose quotients. $D_{mon}^{ster} = D_{ster}/AF_{min}$; $\quad$ $D_{mon}^{max,acc} = D_{max,acc}/AF_{max}$
Routine Monitoring Point (RMP)	Designates the location within the irradiation container where the reference dose is measured.
Coverage Factor k	It is a multiplier of the standard deviation that determines the confidence level of a measurement. The following relationships apply:

Coverage factor	One-sided confidence level	Two-sided confidence level
k=1	approx. 84%	approx. 68%
k=2	approx. 98%	approx. 95%
k=3	approx. 99,5%	approx. 99%

According to ISO 11137-3 (D.3), the calculation of the process limits is based on a one-sided confidence level, since the requirement is to comply with the limits and not to exceed them.

Packaging configuration

The success of radiation sterilization depends on the rays actually reaching the products to be sterilized. In fact, gamma radiation is attenuated when it passes through matter. This attenuation is all the more pronounced the denser the matter to be irradiated, i.e., the higher its specific gravity. An irradiation carton (partially) filled with air thus exhibits only a slight attenuation of the radiation, while a carton densely filled with metal parts, for example, absorbs a large part of the incident radiation.

This results in low packing density irradiation units generally receiving higher irradiation doses than high packing density units. In addition, high packing density products show a larger dose window than low packing density products.

In our continuously operating irradiation facility, in which 2 irradiation units are always positioned one behind the other in the beam path in alternating configurations, this also has further effects. Products with a low packing density allow a comparatively high proportion of radiation to pass through to the units behind them, while units with a high packing density allow only small amounts of radiation to pass through to the units behind them. At first glance, this may seem to be of minor importance for your own products, but overall, the process capability of the method suffers because the scattering range of the measurement results increases.

Having said this, we would like to give you the following hints for the creation of the packing arrangement:

As explained above, a high packing density results in lower irradiation doses. As a rule, the packing density of the cartons should therefore be limited to a value of about 0.20 g/cm³ as a maximum[1].

[1] *For orientation: the density of 0.2 g/cm³ corresponds to a maximum carton weight of 22 kg. Whether the required minimum dose (=sterilization dose) can then actually be achieved with this density must be shown by the can mapping. In case of doubt, we recommend keeping to a lower density.*

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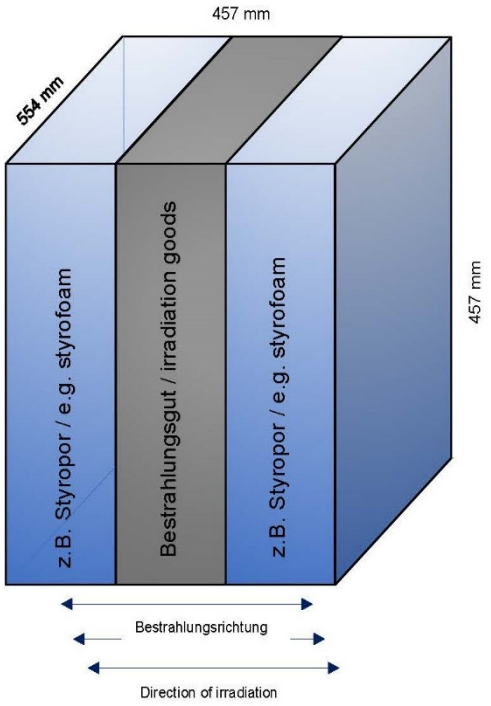
It should also be pointed out at this point that the packing density does not simply correlate with the carton weight. Rather, the decisive factor is that the weight is distributed uniformly over the volume of the carton. Empty areas within the carton should be avoided. If empty areas cannot be avoided (e.g. because the mass of the product packaging does not permit uniform filling or because there are not enough products available), these should be filled with dummy material of the same or at least similar density.

In the case of high-density products, Styropor or Styrodur (instead of material with the same density) can preferably be used as filling material. A vertical arrangement of the filling material along both long sides of the irradiation cartons (and thus perpendicular to the direction of irradiation) is strongly preferable because this arrangement usually results in smaller dose windows (see adjacent figure of a standard carton).



Basically, unsuitable for dose mapping or for the determination of the irradiation limits are single or incompletely filled irradiation cartons, although the standard requires that also such situations are to be matched with the determined limits.

Against this background, we would like to point out that in the future we will no longer perform dose distribution studies if we do not have the underlying packing configuration (together with its gross weight). This is due to the standard requirements on the one hand, but also to the fact that missing packing instructions often lead to failures in dose mapping and to unnecessary queries.

Processing categories

The relevant standards permit the formation of processing categories. These are groups of different products that can be sterilized together. The basis of such processing categories is usually a comparable (homogeneous) packing density of the irradiation cartons. Corresponding dose mapping studies must ensure that all products belonging to a processing category can be successfully sterilized with the same cycle time (=irradiation duration) and within a common target dose window for the routine monitoring point.

As a rule, the products with the lowest packing density and the products with the highest packing density in the dose mapping are each tested three times with completely and homogeneously filled irradiation units.

We strongly recommend not to set the packing density ranges too wide, as this usually leads to very narrow target dose limits for the RMP dose window, which then often cannot be met.

Basic Validation:

For successful validation of the packing configuration and reliable sterilization, two points are crucial in the context of dose distribution measurements (see also Figure 1):

A) The establishment of a target dose range for the routine monitoring point.

B) A statement on whether or with what reliability this dose window can be maintained in routine operation.

The establishment of a target dose window for the routine monitoring point

The evaluation of the dose distribution measurements is carried out according to the example in Annex A.4 of AAMI TIR29. However, the adjustment factors AF_{min} and AF_{max} defined there are calculated in the form of their reciprocal values and - taken into account accordingly[2] - in the subsequent calculations. According to this standard, it is mandatory to test 3 irradiation units, which are usually to be irradiated on different days. Taking into account the measurement uncertainty, the target dose values D_{target}^{lower} and D_{target}^{upper} are calculated from these 3 measurement series on the basis of k=2, which correspond to the respective sterilization dose or the maximum dose to be accepted (e.g. 25-50 kGy).

[2] *This procedure also essentially corresponds to the procedure according to ISO 11137-3.*

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If, during routine irradiation, the reference dose is within the target range determined in this way, it can be assumed with approximately 98% probability that the dose limits (e.g., 25-50 kGy) will be met.

Reliability of compliance with the determined dose window

The decisive factor for the reliability of the process is whether the reference dose, taking into account its measurement uncertainty, falls within the determined nominal range of the target dose range. To check this, the expanded measurement uncertainty of the routine or reference dose is determined.

Ideally, the scatter range (mean ± k*sd) of the reference dose without overlaps should lie within the target dose range defined by the RMP dose window. If this is not the case, a higher proportion of reference dose values that lie outside the RMP dose window must be expected during routine irradiations.

According to the relevant standards, the expanded measurement uncertainty should be considered on the basis of k=2, i.e., with twice the standard deviation, which corresponds to a probability of approx. 95%. If necessary, we also perform the evaluation on the basis of a coverage factor of k=3, which then corresponds to a probability of 99%.

Revalidation:

While the PQ is to be performed once with at least three irradiation units, it is recommended to repeat the dose distribution measurement at least annually on one irradiation unit to ensure that the product-specific irradiation process is still within the determined limits. Accordingly, the evaluation is performed against the RMP dose window determined in the baseline validation.

Furthermore, for the sake of clarity, we will show the validation history in the form of a reference to the base validation and the previous revalidation in the Dose Mapping reports in the future.

Single Batch Measurement

If no basic validation is available and less than three irradiation units are available for dose mapping, we will perform the evaluation as for revalidation, but the determined parameters cannot be transferred to further irradiation batches. In this case, a standard-compliant evaluation is not possible. Under certain circumstances, however, it is possible to subsequently combine three dose distribution measurements performed at different times (not too far in the past) into a basic validation.

In order to enable a smooth processing of dose distribution mappings, we ask for the following information with each corresponding order in the future:

1. The report number of the underlying base validation (this can be found in the upper right corner of each page of the Dose Mapping report);
   Alternatively, the indication that no base validation is available.
2. The process number from the released master batch record (if already available)
3. If you intend to combine several single batch measurements into one basic validation at a later point in time: the indication of the report numbers of all single batch validation reports that have already been created so far.
4. The reference to the tested packing configuration (including revision level);
5. For basic validations, the submission of the packing configuration (and its determined gross weight)

We hope to contribute to a better understanding of the Dose Mapping reports with these remarks.

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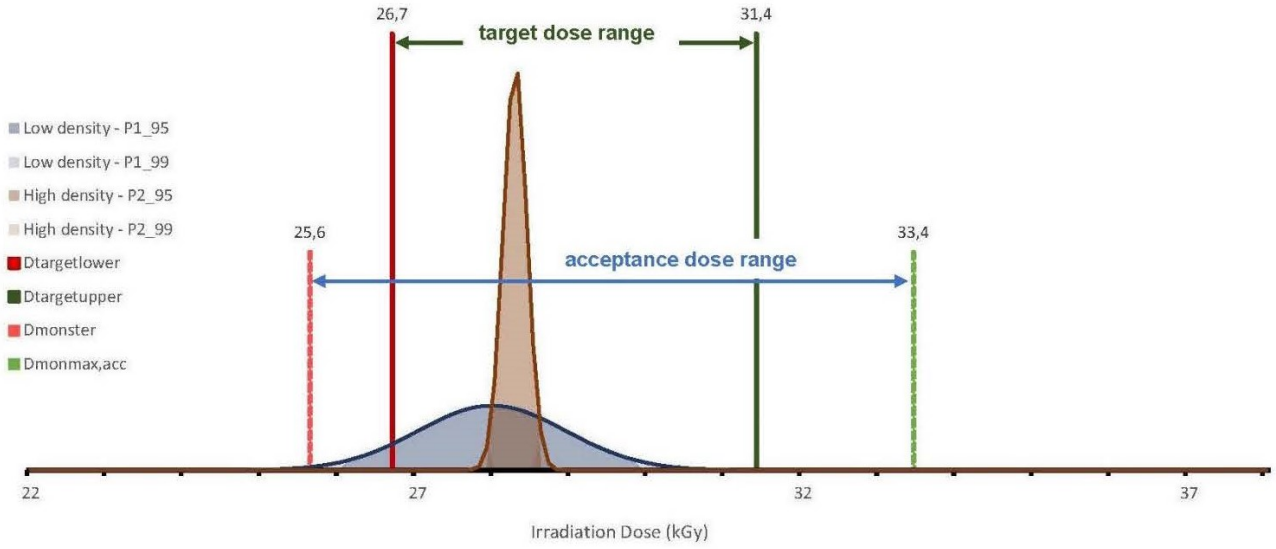

The figure shows the process and release specifications in relation to the statistical distribution of the measured dose at the routine monitoring position. The correlations and derivations of the different values are shown below:

Legend		
D_{ster}	**Product specification**	Sterilization dose: lower limit of the product specification
$D_{max,acc}$		Maximum acceptable dose: upper limit of the product specification
D_{min}	Minimum dose	(absorbed) minimum dose means the lowest radiation dose occurring at a defined irradiation container. The minimum dose must not be lower than the sterilization dose.
D_{max}	Maximum Dose	(absorbed) maximum dose means the highest radiation dose occurring at a defined irradiation container. The maximum doses must not be higher than the maximum acceptable dose.
DUR	$=D_{max} / D_{min}$	Dose uniformity ratio: the relative dose window is characteristic for a specified packaging configuration
D_{mon}	REF or RMP	Reference dose or routine monitoring dose (measured at routine monitoring position)
AF_{min}	$= D_{min} / D_{mon}$	Adjustment factors: The dose measured at the routine monitoring position is proportionally correlated to both the minimum dose and the maximum dose
AF_{max}	$= D_{max} / D_{mon}$	
$(AF_{min})_{corr}$	$= mean(AF_{min})-k*sd(AF_{min})$	To account for measurement uncertainty, the adjustment factors (mean values) must be corrected by the amount of two times the standard deviation (k=2) from at least three measurements
$(AF_{max})_{corr}$	$= mean(AF_{max})+k*sd(AF_{max})$	
D_{mon}^{ster}	$= D_{ster}/mean(AF_{min})$	**Acceptance dose range; release specification:** Assuming a controlled process, release limits for routine irradiation can be determined from the measured minimum and maximum doses by converting the product specifications to the routine monitoring position.
$D_{mon}^{max,acc}$	$= D_{max,acc}/mean(AF_{max})$	
D_{target}^{lower}	$= D_{ster}/(AF_{min})_{corr}$	**Target dose range; process specification:** The corrected adjustment factors and the product specifications are used to determine process specifications, which determine the target dose range at the routine monitoring position.
D_{target}^{upper}	$= D_{max,acc}/(AF_{max})_{corr}$	

Figure 1 *together with the legend shows the relationships between the various specifications (product specification, process specification and release specification) and their relation to the statistical distribution of the reference dose values (D_{mon}) using the example of two different packing densities of a planned processing category.*