BBF Sterilisationsservice GmbH
Dosimetry
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Explanations for the performance of Dose Distribution Mappings

The performance of dose distribution mappings serves (beside the microbiological establishment resp substantiation of the sterilization dose) for the development and validation of irradiation sterilization. The goal is to prove that the required sterilization dose has been achieved and that the maximum acceptable dose (which does not affect the integrity and functionality of the product) 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 arrangement of the products within the product carton and the irradiation container must be specified.

Note: The specifications and the packing arrangement are QM documents which are subject to document and change management within the scope of the client's QM 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 further discussion, some definitions are given here make the following explanations a little more understandable.

Dose Limits	Are given by the sterilization dose and the maximum acceptable dose
Dose window	The dose window indicates the range from minimum to maximum dose that can occur in an irradiation unit at different locations within the container. In some cases, the term dose window is also equated with the target values defined by the dose limits (i.e., sterilization dose and maximum acceptable dose).
Sterilization dose	Minimum dose that must be achieved at all points of an irradiation unit to ensure that sterility is achieved
Maximum acceptable dose	The highest dose at which a product can be irradiated without suffering loss of integrity or functionality over its intended lifetime.
Reference dose	The dose measured during routine irradiation at a defined location on the irradiation container, which is proportionally related to the sterilization dose and the maximum acceptable dose.
Routine measuring point (RMP)	Specifies the location within the radiation container at which the reference dose is measured.
RMP Minimum dose	Specifies the lower procedural limit of the reference dose, which must not be fallen below in order to comply with the sterilization dose.
RMP Maximum dose	Specifies the upper procedural limit of the reference dose, which must not be exceeded in order to comply with the maximum acceptable dose.
Coverage Factor k	This 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 procedural limits is based on a one-sided confidence level, since the requirement is to comply with the dose limits and not to exceed them.

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Packaging Arrangement

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

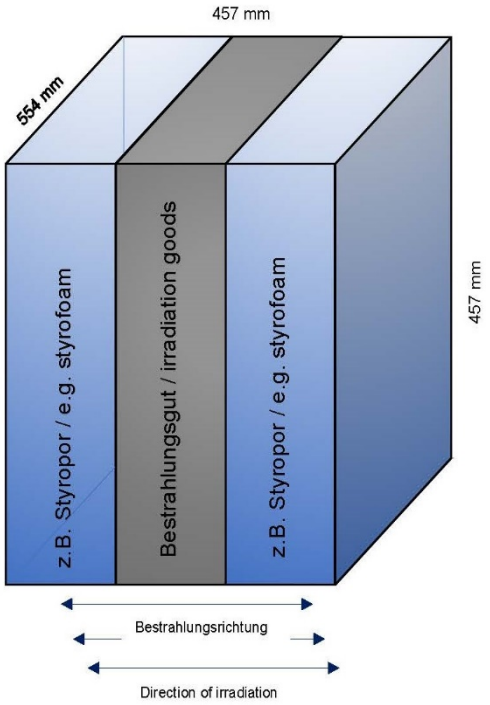
This results in irradiation units with low packing density generally receiving higher irradiation doses than units with high packing density. In addition, products with a high packing density show a larger dose window than products with a low packing density

In our continuously operating irradiation facility, where 2 irradiation units are always placed in the beam path one behind the other in alternating configurations, this also has further implications. 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 in total, 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 preparation of the packing arrangement:

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

At this point, it should also be noted that the packing density does not simply correlate with the weight of the cardboard. Rather, it is crucial that the weight is uniformly distributed over the volume of the box. Empty areas within the box should be avoided. If empty areas cannot be avoided (e.g. because the mass of the product packaging does not allow an uniform filling or because not enough products are available), these should be filled with dummy material of the same or at least a similar density.



For products with a high density, Styrofoam 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 cardboard (and thus perpendicular to the direction of radiation) is strongly preferred because this arrangement usually results in smaller dose windows (see adjacent illustration of a standard box).

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

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

[1] *For orientation: the density of 0.2 g / cm³ corresponds to a maximum cardboard weight of 22 kg. The dose mapping must show whether the required minimum dose (= sterilization dose) can actually be achieved with this density. If in doubt, we recommend maintaining a lower density.*

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Processing categories

The relevant standards allow the creation of processing categories. These are groups of different products that can be sterilized together. Such processing classes are usually based on a comparable (homogeneous) packing density of the irradiation boxes. Corresponding dose mapping studies must ensure that all products belonging to a processing category can be successfully sterilized with the same cycle time (= irradiation time) and within a common RMP dose window.

As a rule, the products with the lowest packing density and the products with the highest packing density are dose mapped three times each 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 density limits for the RMP dose window, which the often cannot be met.

Validation / Basic validation:

For a successful validation of the packing arrangement and a reliable sterilization, two points are ciritcal in the context of dose distribution measurements:

A) The definition of a acceptable dose window for the routine measuring point

B) A statement as to whether, or with what reliability, this dose window can be met in routine operation.

Definition of an acceptable dose window for the routine measuring point

In future we will evaluate the dose distribution measurements according to the example in Annex A.4 of AAMI TIR29. Accordingly, 3 irradiation units must be checked, which should be irradiated on different days. Taking into account the measurement uncertainty, the RMP minimum dose and the RMP maximum dose are calculated from these 3 measurement series on the basis of k = 2, which correspond to the respective sterilization dose and the maximum acceptable dose (e.g. 25-50 kGy). Furthermore, to ensure that the reference dose is reliably above the RMP minimum dose, the variability of the measured reference dose must be taken into account. Using k=2, the expanded measurement uncertainty of the reference dose is determined from its standard deviation and added to the determined RMP minimum dose.

If, during routine irradiation, the RMP 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.

Note: Alternatively, we can transitionally and at the express request of the customer perform the evaluation without taking into account the statistical measurement uncertainty. The evaluation will then be based merely on the mean values of 3 measurement series. However, this will be set out in the corresponding dose mapping reports. Statements on process reliability (i.e. on the probability with which the determined RMP dose limits can be complied with) are not possible in this case.

Reliability of compliance with the determined dose window

The decisive factor for the reliability of the process is whether the reference dose falls within the determined target range of the RMP dose window, taking into account its measurement uncertainty. To check this, the expanded measurement uncertainty of the routine or reference dose is determined. We prefer to use a coverage factor of k = 3, which, considering a two-sided confidence interval, corresponds to a probability of 99% (according to the relevant standards, however, a factor of k = 2 is sufficient with a probability of approx. 95%).

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

Revalidation:

While the PQ has to be carried out once with at least three irradiation units, it is recommended to repeat the dose distribution measurement at least annually with one irradiation unit in order to ensure that the product-specific irradiation process continues to run within the determined limits. Accordingly, the assessment is made against the RMP dose window determined in the baseline validation.

In future, for the sake of clarity, we will show the validation history in the dose mapping reports by a reference to the basic validation and the previous revalidation.

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Single batch validation

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

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

1. the indication of the report number of the underlying baseline validation (this can be found in the upper right corner of each page of the Dose Mapping Report).
   alternatively, the indication that no basic validation is available.
2. if you intend to combine several single batch validations into one base validation at a later stage: the report numbers of all single batch validation reports that have already been generated to date.
3. the reference to the tested packing configuration (including revision level);
4. For basic validations, the submission of the packing configurtation (as well as its brutto weight).

We hope to contribute to a better understanding of the dose mapping exercises with these explanations.