

Guidance Notes on the Dosimetric Aspects of Dose-setting Methods

Publication of The Panel on Gamma & Electron Irradiation – Working Group on Microbiology

1. Introduction

The implementation of the European Union Medical Devices Directive and its associated technical standards has increased the interest within Europe in methods of determining sterilization dose based on bioburden data (commonly called "dose-setting methods"). The most widely applied methods are those originally developed by AAMI and now incorporated as an informative annex to ISO Standard 11137 "Sterilization of health care products - Requirements for validation and routine control- Radiation sterilization"¹. The Methods as published contain little information on dosimetric aspects, and the Panel on Gamma and Electron Irradiation felt it would be useful to produce practical guidance based on the experience of Members. This document is intended to be read in conjunction with Annex B of the ISO standard and expands on the information given there.

2. Definitions

The terminology used in this document is the same as that used in ISO Standard 11137¹. For convenience, some relevant definitions are reproduced below:

Reference standard dosimeter - Dosimeter, of high metrological quality, used as a standard to provide measurements traceable to and consistent with measurements made using primary standard dosimeters.

Product unit - Health care product, collection of products or components within a primary package.

Sample item portion (SIP) - Defined portion of a health care product unit that is tested.

3. Selection of Dosimetry System

The dosimetry system used to monitor verification and incremental doses must be capable of providing accurate and precise results over the entire dose range of interest (e.g. 2 to 18 kGy in the case of a typical Method 2A experiment, and 1 to 8 kGy in the case of Method 2B). In general, the dosimetry system used for final sterilization dosimetry will not be suitable for the lower doses of the dose-setting methods. More detailed guidance on the selection of dosimetry systems can be found in Annex C of ISO Standard 11137¹ and in ASTM Standard E1261².

4. Calibration

4.1 Preparation of the Calibration Curve

The dosimetry system must be calibrated over a dose range wider than that of its intended use. This is achieved by means of a calibration irradiation, which can either be carried out at the irradiation facility, or at a calibration laboratory. The number of dose points chosen will depend on the range of doses required, but, as a guide, at least five dose points should be used for each decade, and at least four dose points should be used if the range is less than one decade. The calibration doses should be evenly spread over the range being used. At least four replicate dosimeters should be irradiated at each dose point.

Further guidance on calibration procedures is given in ASTM Standard E1261².

4.1.1 Calibration at the Irradiation Facility

This method involves performing a set of calibration irradiations in the same irradiator that will be used for dose setting purposes. This minimises the likelihood of systematic errors, which can arise if the conditions of the calibration irradiation do not match those of actual use. Dosimeters from the batch to be calibrated must be irradiated in close proximity to reference dosimeters (for example alanine or dichromate) supplied and measured by an officially accredited calibration laboratory. Care must be taken to ensure that both the dosimeters being calibrated and their accompanying reference dosimeters receive the same dose. The dosimeters from the batch being calibrated are then measured on the instrument, (normally a spectrophotometer) that will be used for all subsequent measurements, and a calibration curve prepared relating dosimeter response to the absorbed dose (as determined by the reference dosimeters).

4.1.2 Irradiation at a Calibration Laboratory

With this method, a number of dosimeters from the batch in question are irradiated to a series of known doses at an officially accredited calibration laboratory. These dosimeters are then measured on the instrument (normally a spectrophotometer) that will be used for all subsequent measurements, and a calibration curve prepared relating dosimeter response to absorbed dose. In order to compensate as fully as possible for the effects of environmental factors, the calibration irradiation should be carried out under conditions of dose rate, temperature and humidity that are as close as possible to those that will be experienced in use.

Having prepared the calibration curve, a calibration verification experiment must then be performed to establish the magnitude of any systematic errors that may arise due to differences between the conditions of the calibration irradiation and the conditions that will occur during dose setting irradiations. Calibration verification is achieved by irradiating dosimeters from the batch being calibrated alongside reference dosimeters supplied and measured by an officially accredited laboratory. Irradiations must be performed at several (at least three) doses using the irradiator, and the operating conditions, that will be employed for dose setting purposes.

The difference between the doses measured by the two dosimetry systems should be calculated for each nominal dose value. If differences greater than 5% are found at any dose, the entire calibration procedure should be systematically examined to determine if there are any influencing factors, such as temperature, humidity or dose rate, that have not been properly taken into account. The orientation and position of the dosimeters during the verification irradiation should also be checked to ensure that both dosimetry systems were exposed equally to the radiation field.

After correction of the calibration for identified deficiencies, the results should be examined to determine if any significant bias exists between the dose readings of the system being calibrated and the reference dosimetry readings. If a significant bias is apparent, the calibration curve of the dosimeters being calibrated should be adjusted to bring the measurements into agreement with the doses measured by the reference dosimeters.

Note: The extent of the adjustment may not be constant across the entire dose range. In such cases, caution must be exercised in applying correction factors derived from a small number of dose points, and consideration should be given to performing a full “in-facility” calibration, as described in 4.1.1

4.2 Effect of Post-irradiation Instability

Dosimeter readings may not be stable and may vary with time after irradiation. In order to minimize errors from such effects, the time between irradiation and readout of the calibration dosimeters should ideally be the same as the time between irradiation and readout of dosimeters in normal use. If this is not possible, then additional studies will need to be carried out to determine the magnitude of any instability, and corrections applied if necessary.

Note: The storage conditions, eg temperature and humidity, of the dosimeters can have a significant effect on the magnitude of post-irradiation changes.

5. Dose Tolerance Limits

The dose tolerance limits in the dose-setting methods refer to the maximum, and in some cases minimum, doses that can be delivered to any point on a given product unit or "sample item portion" (SIP). Implicit in this requirement is the fact that the dose distribution on a product unit is known; this may require detailed dose mapping of individual product units, particularly in the case of electron beam irradiations. The configuration of the product units during irradiation should be chosen to achieve the minimum practical variation in dose, both on each individual unit, and between different units. This may necessitate the irradiation of product units individually. In exceptional cases, it may be necessary to dismantle and repackage the product in order to achieve an acceptable range of doses on the unit. If this is done, then care must be taken not to compromise the microbiological aspects of the dose setting method (see, for example Note 21 in Annex B of ISO 11137).

For a Method 1 verification dose experiment, the "*actual dose may vary from the verification dose by +10%*". This means that the maximum dose on a product unit or SIP must not exceed the required verification dose by more than 10%. There is no minimum tolerance limit set for Method 1 verification doses, but the option is given to repeat the experiment "*if the delivered dose is less than 90% of the calculated verification dose*".

Note: The term *delivered dose* is not defined in ISO 11137. For the purpose of determining whether or not a Method 1 verification dose experiment may be repeated, it is recommended that *delivered dose* is taken to be the arithmetic mean of the highest dose and the lowest dose received by product units in the experiment. This interpretation is consistent with the use of the term *delivered dose* in ISO TR 13409 "Sterilization of health care products - Radiation sterilization - Substantiation of 25 kGy as a sterilization dose for small or infrequent production batches"³.

For Method 2A incremental doses the "*doses shall be delivered independently and may vary at random from the nominal dose by ± 1.0 kGy or $\pm 10\%$, whichever is greater. If the delivered dose is less than the stipulated range, the incremental dose may be repeated. Individually monitor each of the doses delivered to product units with dosimeters.*" The requirement to deliver doses independently means that separate dose measurements must be made for each incremental dose level. Ideally, the maximum and minimum doses on each product unit or SIP should be within the stated tolerance band. In practice, however, this may not be

achievable, particularly in the case of electron beam irradiations. In such circumstances the maximum dose on the product unit becomes the important parameter, and this must be kept below the maximum of the tolerance band. The irradiation geometry should be chosen to minimise the maximum to minimum dose ratio, even though the minimum may fall below the tolerance band.

Similar considerations apply to Method 2B incremental doses, although here the tolerance bands are tighter at “ ± 0.5 kGy or $\pm 10\%$, whichever is greater, with the exception that at 1.0 kGy the dose may vary by only ± 0.2 kGy”.

For Method 2 verification doses only a maximum tolerance limit is set at “+1.0 kGy or +10%, whichever is greater” above the required dose. The maximum dose on a product unit or SIP must not exceed the tolerance limit. An option to repeat the experiment is given if the delivered dose is less than 90% of the required dose for Method 2A and if the delivered dose is less than the stipulated range for Method 2B.

Note: There are a number of errors in the 1995 published version of ISO 11137¹ in the sections dealing with Method 2A and Method 2B verification dose experiments (Sections B3.4.2.2.3 and B3.4.2.4.3, respectively). In both of these sections the last two sentences should read: *The actual dose may vary from the D^* kGy dose by +1.0 kGy or +10%, whichever is greater. If the delivered dose is less than 90% of the D^* kGy dose, the test may be repeated.* There is uncertainty about the precise meaning of the terms DD^* , *actual dose* and *delivered dose*, but for the purpose of determining whether or not a Method 2 verification dose experiment may be repeated, it is recommended that *delivered dose* is taken to be the arithmetic mean of the highest dose and the lowest dose received by product units in the experiment. The DD^* dose to be used in subsequent calculations should be taken to be the highest dose received by product units in the experiment.

6. Dose Monitoring

In general, some form of dose mapping exercise has to be carried out to determine the range of doses delivered. This will often involve determining the relationship between the dose received by individual product units and the dose received by a dosimeter at a

standard monitoring location. The dose mapping must be carried out in sufficient detail to identify the maximum and minimum dose positions on the product units being irradiated. Significant dose gradients can occur on individual product units and this fact must be taken into account when positioning dosimeters. Each case needs to be assessed individually, but some general guidance on dosimeter placement is given below.

For small low density product units being irradiated by gamma rays, it is usually sufficient to place dosimeters on the outside of the sterile barrier, as there will not be a significant dose gradient on the product unit. Typical examples are product units made up of elements of low atomic number (i.e. non-metallic) that, in addition, do not contain any blocks of material large enough to cause local radiation shielding of adjacent areas.

For product units that contain blocks of material large enough to cause local shielding when being irradiated by gamma rays, and for all product units being irradiated by electrons, it will normally be necessary to place appropriately sized dosimeters on the product itself in order to establish the true maximum and minimum doses. This usually entails dosimeter placement inside the sterile barrier, in which case the dosimetry must be carried out on additional samples of the product, in order to avoid contamination of the product units being used for microbiological testing.

Note: If additional product loads are being used for dose mapping, it may be possible to improve accuracy by using either a different type of dosimeter and/or higher doses than employed for the actual dose setting irradiations.

7. Statistical Treatment of Dosimetry Uncertainties

7.1 Introduction

Uncertainties in dosimetry are not discussed specifically in the dose-setting methods, but will obviously have an impact on the validity of the sterilization doses determined. Uncertainties in delivered dose may be significant in comparison to the dose tolerances demanded by the dose-setting methods, and must be considered from the outset when undertaking such exercises. Further general guidance on the treatment of dosimetry uncertainties can be found in ASTM Standard E1707⁴.

7.2 Calibration Uncertainties

Provided the dosimeters have been calibrated in accordance with the methods outlined in Section 4, it is a reasonable assumption that uncertainties due to dosimeter calibration will not be large in comparison to the overall uncertainty of the dose setting method and will not significantly influence the final result. Full documentation of the dosimeter calibration procedure must be regarded as an essential part of the dose setting method.

7.3 Precision of Dose Measurements

In addition to the accuracy of the dosimeter calibration, the precision of individual dose measurements will also have an effect on the validity of the dose-setting exercise. In order to ensure that dosimeter precision does not adversely affect the results, the coefficient of variation (the standard deviation expressed as a percentage of the mean) between the readings of dosimeters irradiated to the same dose should ideally be less than 2%. If the inherent precision of the system being used is significantly worse than this, then more than one dosimeter should be used for each measurement and the results averaged.

7.4 Determination of Dose at Monitoring Position

The process of dose mapping to determine the relationship between the maximum and minimum dose on the product and the dose at a monitoring position is a statistical one and the ratios determined will be subject to uncertainty. This uncertainty will feed through directly to the uncertainty in the delivered dose and must be taken into account when performing

irradiations for the dose setting methods. In order to avoid compromising the dose setting method, dose mapping to determine these ratios should be carried out with sufficient accuracy to ensure that uncertainties in the ratio do not result in the dose tolerance limits of the dose setting methods being exceeded. A suggested approach is to perform several (at least three) replicate dose maps and to determine from them the 95% confidence limits on the ratio of the maximum dose to the dose at the monitoring position. The upper 95% limit should then taken as the ratio to be used in subsequent irradiations, thus ensuring that any uncertainties in dose mapping result in under-dosing rather than over-dosing. A similar approach can be used in respect of the minimum dose, although in this case the lower 95% limit should be taken. An example of this calculation for the maximum dose is given below:

where D_{max} is the maximum dose and

D_{mon} is the dose at the monitoring position

Run No.	Ratio D_{max} / D_{mon}
1	1.066
2	0.988
3	1.040
Mean	1.031
Std Dev	0.040

Using Student's t distribution tables for 3 samples, 2 degrees of freedom calculate the 95% confidence interval on the ratio $D_{max} / D_{mon} = 1.031 \pm (0.040 / \sqrt{3} * 4.3) = 1.031 \pm 0.10$

In order to avoid possible overdosing, the ratio D_{max} / D_{mon} used for dose setting irradiations should be the upper 95% limit ie $1.03 + 0.10 = 1.13$

Note: The uncertainty in the ratio D_{\max}/D_{mon} in the above example ($\pm 10\%$ at 95% confidence) is high compared to the dose tolerances demanded by the dose setting methods and use of the upper 95% limit as recommended would have a significant effect on the outcome of the dose setting exercise. In such cases, it is recommended that the number of replicate dose maps is increased in order to reduce the uncertainty .

Note: This guidance applies only to dose mapping calculations for dose setting experiments. Different statistical analysis should be applied to dose mapping calculations for routine processing.

8. References

1. **ISO Standard 11137**, "Sterilization of health care products - Requirements for validation and routine control - Radiation sterilization", International Organisation for Standardization, Case Postale 56, CH-1211 Geneve 20, Switzerland, (1995).
2. **ASTM Standard E1261**, "Guide for Selection and Calibration of Dosimetry Systems for Radiation Processing", American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, PA 19428, USA, (1994)
3. **ISO Technical Report 13409**, "Sterilization of health care products - Radiation sterilization - Substantiation of 25 kGy as a sterilization dose for small or infrequent production batches", International Organisation for Standardization, Case Postale 56, CH-1211 Geneve 20, Switzerland, (1996).
4. **ASTM Standard E1707**, "Guide for Estimating Uncertainties in Dosimetry for Radiation Processing", American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, PA 19428, USA, (1995)