Performance Qualification Dose Mapping

July 2022

PANEL ON GAMMA & ELECTRON IRRADIATION

Performance Qualification Dose Mapping

1 Purpose and Scope

The purpose of this document is to provide an introduction and overview of methods of performance qualification (PQ) dose mapping of medical products that are sterilized by ionising radiation. It is based around the requirements found in ISO 11137-1 (ISO 2006), but is written in a narrative style to give a tutorial approach. In this respect, it differs from more formal guidance documents, such as those produced by ISO (e.g. ISO 11137-3 & 4) (ISO 2017, ISO 2020) and ASTM (e.g. ISO ASTM 52303, 2013), although it is entirely consistent with those documents.

ISO 11137-1 gives requirements for performance qualification dose mapping, i.e. determining the magnitude and distribution of absorbed dose in product. Dose mapping is also required in conjunction with a number of other stages of a radiation sterilization process, such as Process Definition (determining the sterilization dose and the maximum acceptable dose) and Operational Qualification (determining the magnitude and distribution of dose in homogeneous reference material). This document concentrates on guidance for dose mapping in Process Definition and Performance Qualification, as guidance on dose mapping for Operational Qualification is covered elsewhere, for example in ASTM OQ Test Methods for Gamma and E-beam Irradiators. It is assumed that the reader is already familiar with the requirements given in ISO 11137-1.

Radiation sterilization of medical products is carried out using both photons and electrons of a range of energies. This document includes guidance on irradiation with photons from isotope sources (^{60}Co and ^{137}Cs), machine generated photons with energies from approximately 100 kV to 7 MV and electrons with energies from less than 100 keV to approximately 10 MeV.

Note: Throughout this document:
Electron and photon energy is expressed in electronvolts (keV, MeV).
X-ray beams are described in terms of the accelerating voltage of the electrons incident on the X-ray target e.g. kV, MV.

Although the guidance given is based around the requirements for medical device sterilization, the concepts can also be applied to other processes, for example the irradiation of foodstuffs.

2 Content of report

A general understanding of photon and electron interaction with matter is a good basis in preparing for performance qualification dose mapping.

Section 3 outlines in separate sub-sections the absorption of high-energy photons from radioisotope facilities based on ^{60}Co and ^{137}Cs and from megavoltage accelerator-based X-ray facilities. In addition, photons generated from lower energy X-ray facilities (up to a few hundred kV) are discussed.

Similarly, there are sub-sections on the absorption of electrons from accelerators using energies at the MeV level, as well as energies at the 100 keV level.

Several textbooks deal with radiation absorption in general, and section 3 only describes a few principles relevant for PQ dose mapping.

Dose measurements made in PQ dose mapping must have measurement traceability to national or international standards, and the measurement uncertainty must be known. Traceability is established through calibration and must be maintained throughout the measurements.

Section 4 discusses calibration requirements and the associated uncertainty estimations, but not in great detail. For more information the reader should consult references such ISO/ASTM 51261 (2013) and CIRM 29 (NPL 2009).

Several dosimetry systems are potentially available for dose mapping. “Potentially”, because not all dosimetry systems are equally well suited for all dose-mapping tasks. Likewise, it is not expected that only one system will fulfil the various needs that a user has.

Section 5 discusses commercially available dosimetry systems and their applicability for PQ dose mapping.

It is not possible to measure everywhere in an irradiation container or on/in all product items in the container. Likewise, not all containers can be dose mapped.

Section 6 discusses limitations and necessities. Where to measure and how much to measure? The use of OQ dose map data to assist decisions regarding dosimeter placement is mentioned. It further discusses how to fulfil requirements on the number of containers to be dose mapped.

When minimum and maximum doses (D_{min} and D_{max}) have been measured and their relationship with dose at the routine monitoring location D_{mon} established, the next step to use these data to determine how the sterilization process can be carried out.

Section 7 shows how the PQ dose map results can be used to determine irradiation facility parameters, including target doses D_{target} that will allow product to be irradiated within specifications. This section refers to ISO 11137-4.

Calculation methods like Monte Carlo and similar techniques can be powerful tools for making estimations of dose distribution.

Section 8 discusses the potential and limitations of calculation methods, as well as the need to validate the calculated results.

3 Radiation absorption mechanisms and implications for dose mapping

The distribution of absorbed dose in material is determined by the interaction of the radiation with the material, and this in turn depends on the type and energy of the radiation and whether it is delivered from one direction, or many directions. A basic understanding of the processes by which radiation interacts with matter can help to give an indication of where minimum and maximum doses might occur and can guide what type of dosimeters to use for dose mapping and where they should be placed. Details of radiation interactions are described briefly below, but more detail can be found in documents such as ICRU Report 80 (ICRU 2008).

Photons from ^{60}Co, ^{137}Cs and MV accelerator-based X-ray facilities

The intensity of photons from these sources reduces as they pass through material both due to loss of energy to the material (i.e. absorbed dose) and due to the photons spreading out as distance from the source increases. For materials of low atomic number (e.g. many polymers) and with a uniform density, this results in an essentially smooth decreasing dose distribution with increasing depth in material. In many radiation processing applications, an appreciable fraction of the photons will travel completely through individual irradiation containers, and radioisotope irradiators are often designed with 2-3 rows

of irradiation containers on either side of the source so that the radiation will pass through several containers to achieve efficient use of the radiation. Containers are usually irradiated from 2 or more sides in order to improve dose distribution. This is shown in Fig. 1 for a product in an 80 cm wide container holding product with density 0.4 g cm^{-3}.

The actual deposition of energy is from secondary electrons liberated when photons interact with atoms of the absorbing material and in the case of photons with energies of one or a few MeV, the secondary electrons will have a range of typically a few millimetres in material with density of 1 g cm^{-3} (Mittendorfer and Niederreiter 2022). The relatively high penetrating power of the photons and the range of the secondary electrons generated by the photons mean that for many medical devices made of low atomic number materials, the distribution of dose within an irradiation container will be smooth, without large changes over small distances. This will not apply, however, if there is local shielding caused by large masses of material in the product. An extreme example of this is the irradiation of metal orthopaedic implants, but significant dose gradients can also occur if there is a large mass of polymeric material.

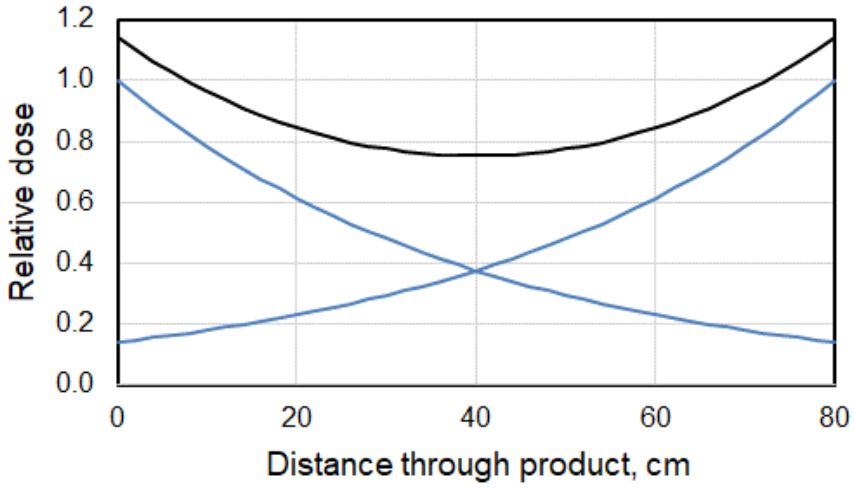

***Figure 1**: Depth-dose distribution for 1.25 MeV ^{60}Co irradiated homogeneous product, with density 0.4 g cm^{-3}. Single-sided irradiation (blue lines) and double-sided irradiation (black line) calculated using an exponential approximation for the absorption.*

Photons generated at a few hundred kV

Photons (X-rays) generated at energies of up to a few hundred keV are increasingly being used for radiation processing and can pose significant challenges in terms of dose mapping. Whilst the fundamental radiation absorption mechanism is similar to that for mega-voltage photons, the increased rate of attenuation through material and the shorter range of the secondary electrons that are produced can result in large local changes in dose over small distances, particularly at surfaces.

Megavoltage electrons

Accelerated electrons travelling through material will lose energy and will be scattered by multiple collisions with the atoms of the absorbing material, until they eventually stop. This results in a finite range though material and a complex dose distribution even in homogeneous materials. Fig. 2 shows typical depth dose distributions for accelerated electrons at various energies in homogeneous material of density 1 g cm^{-3}, where the pronounced initial increase in dose as depth increases from the surface is caused by the scattering of the beam. As with photon irradiations, the dose distribution can be improved by irradiation from more than one direction.

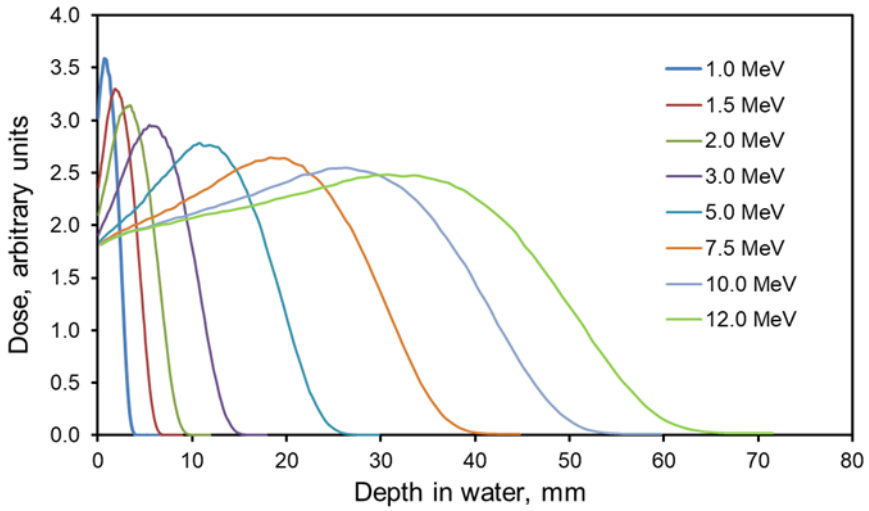

***Figure 2**: Central-axis depth-dose distributions for different electron energies in water calculated using the Monte Carlo code EGSnrc.*

The transfer of energy from accelerated electrons though multiple collisions and scatterings means that dose distributions in products irradiated by electron beams are generally subject to much greater changes in dose over small distances than is the case for MV photon irradiations. This means that detailed dose mapping often using thin film dosimeters is necessary (Mittendorfer and Niederreiter 2020).

Packaged medical devices are often not of uniform density and the representative dose distributions shown in Figs. 3, 4, and 5, arising in uniform, homogeneous materials, might not appear in real dose mappings where there can be voids and variations in density.

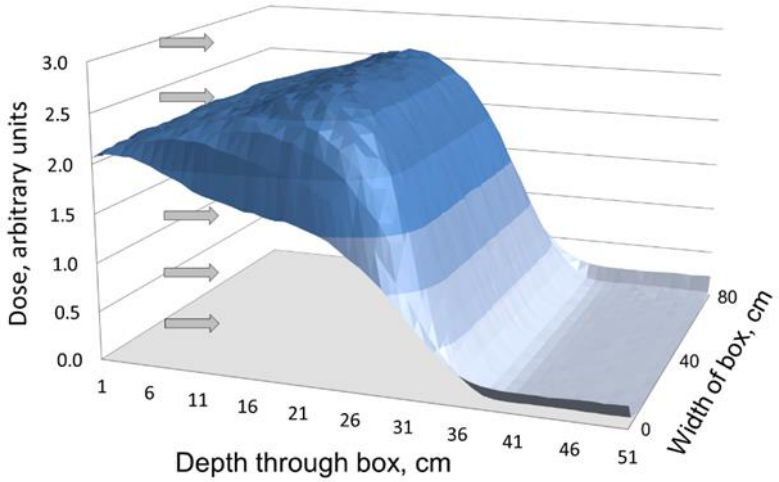

***Figure 3**: Dose distribution through a box of homogeneous polymer-based material of average density 0.125 g.cm^{-3} and depth 50 cm, for a single-sided irradiation with a parallel beam of 10 MeV electrons, calculated using the Monte Carlo code EGSnrc. Here, the electrons enter the material at the left side as shown by the arrows, and the box width is 80 cm. Note the falloff in dose at the sides of the box of material as electrons leave the material and are not scattered back.*

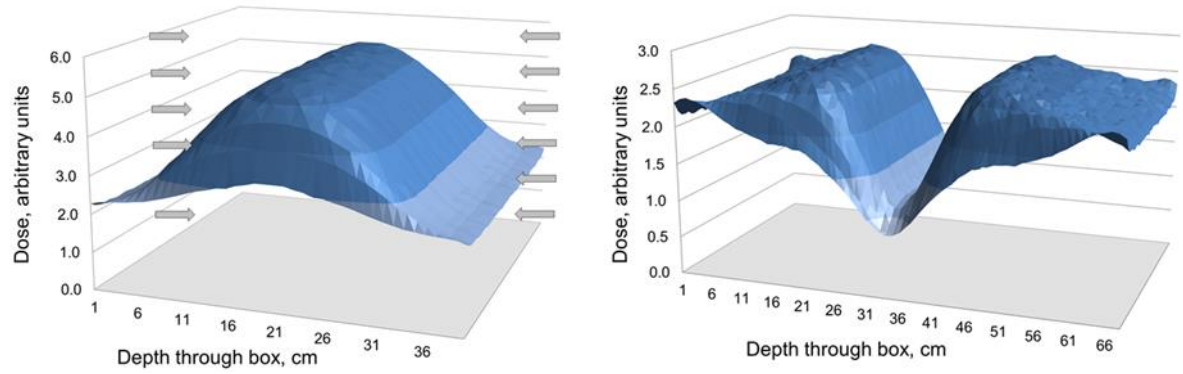

***Figure 4**: Dose distributions through a box of homogeneous polymer-based material, density 0.125 g cm^{-3}, for two material depths of 40 cm (left) and 68 cm (right), in a square box of width 80 cm. These represent two-sided irradiations with parallel beams of 10 MeV electrons, calculated using the Monte Carlo code EGSnrc, with electrons entering from the left and the right sides as shown on the left. Note the peaks in dose corresponding to the maximum in the one-sided depth-dose distributions.*

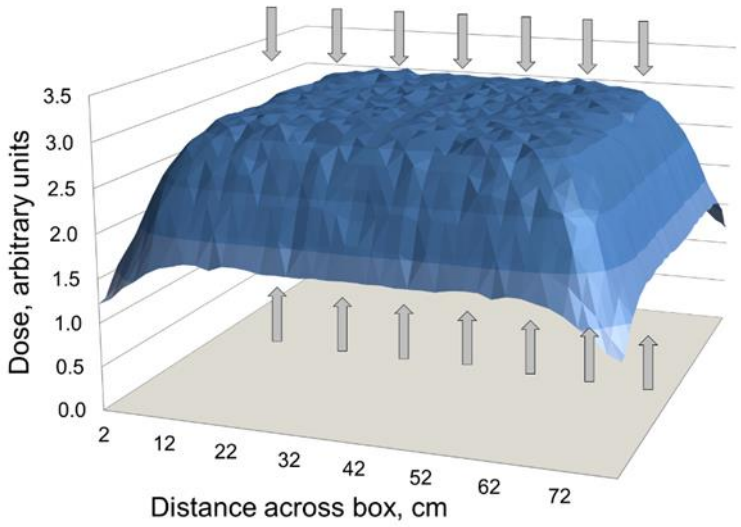

***Figure 5**: Dose distribution in central plane of a homogeneous polymer-based material, density 0.125 g cm^{-3}, depth 60 cm in a square box of width 80 cm, irradiated from two sides (top and bottom in this example, as shown by the arrows) with parallel beams of 10 MeV electron beams, calculated using the Monte Carlo code EGSnrc. Note that the dose falloff at the corners is significantly greater than at the sides alone.*

Product orientation within an irradiation container can have a great effect on dose distribution and this is often greater for electron irradiation than is the case for gamma irradiation. It is important that if different orientations are possible, then the product orientation used during dose map is maintained during actual processing. Complex products, for example, can sometimes be placed with different orientations within the product container, and special packaging arrangements must sometimes be used to ensure that only one orientation is possible. Likewise, even with simple product such as wound dressing it might be possible to align all items either parallel to the e-beam direction or perpendicular to the e-beam direction, resulting in greatly differing dose distributions.

Kilovoltage electrons

Low energy (70 keV to 300 keV) electrons are used in several diverse applications, and also to sterilize some medical products. The ranges of the electrons are of the order of tens to hundreds of micrometres as shown in Fig 6. The treatment is essentially limited to the surface of a product, and it is also highly

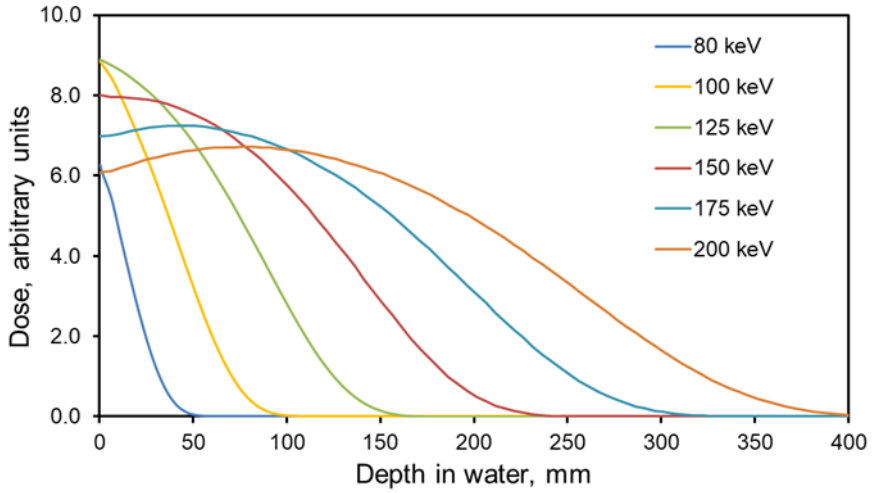

***Figure 6**: Calculated depth-dose relationships for low-energy electrons in water using EGSnrc. These calculations include a 9 µm thickness titanium exit window and a 2 cm air gap.*

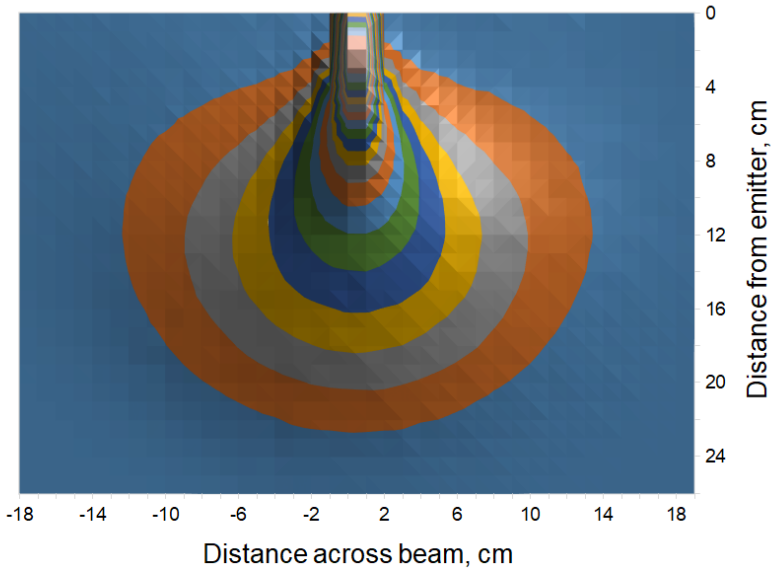

***Figure 7**: 150 keV pencil beam of electrons entering from above. The beam broadens into a "cloud" as it scatters and loses energy in air having passed through a 10 µm titanium exit window, calculated using the Monte Carlo code EGSnrc. The different colours represent 5% dose intervals, so that the outer orange band encompasses dose from 5% to 10% of the maximum value.*

dependent on the properties of the accelerator and the presentation of the product to the beam. After electrons at these energies have passed through the exit window from the accelerator and through a few centimetres of air, they effectively form a "cloud" and reach the surface that is being irradiated from many angles. A typical "cloud" from a 150 keV beam is shown in Fig. 7.

Measurement of dose distribution in these beams is very specialised, since the range (penetration) of the electrons is of the same order or even less than the thickness of the dosimeters. Irradiation using low energy electron beams is described, for example, in "Guide on the use of low energy electron beams for microbiological decontamination of surfaces" (Panel on Gamma and Electron Irradiation, 2013) and in ISO ASTM 51818 (2020).

4 Dosimetry system calibration and measurement traceability

The quality of the dosimetry system calibration and the uncertainty associated with dose measurements during PQ dose mapping will feed through directly to the uncertainty in dose delivered during routine processing (see Sec. 7). The ability to demonstrate measurement traceability, as required in 11137-1, will also depend on the traceability of dose measurements during dose mapping. Traceability in this context is the ability to demonstrate that measurements of dose made during dose mapping and during radiation processing can be related back to the underlying measurement standards held at national and international measurement laboratories through a defined chain of calibrations (see Fig. 8). In order to avoid a break in this traceability chain, the dosimetry systems must have calibrations that are appropriate for the conditions (dose range, environment, type of radiation, etc.) during dose mapping. These conditions might not be the same as those of routine processing.

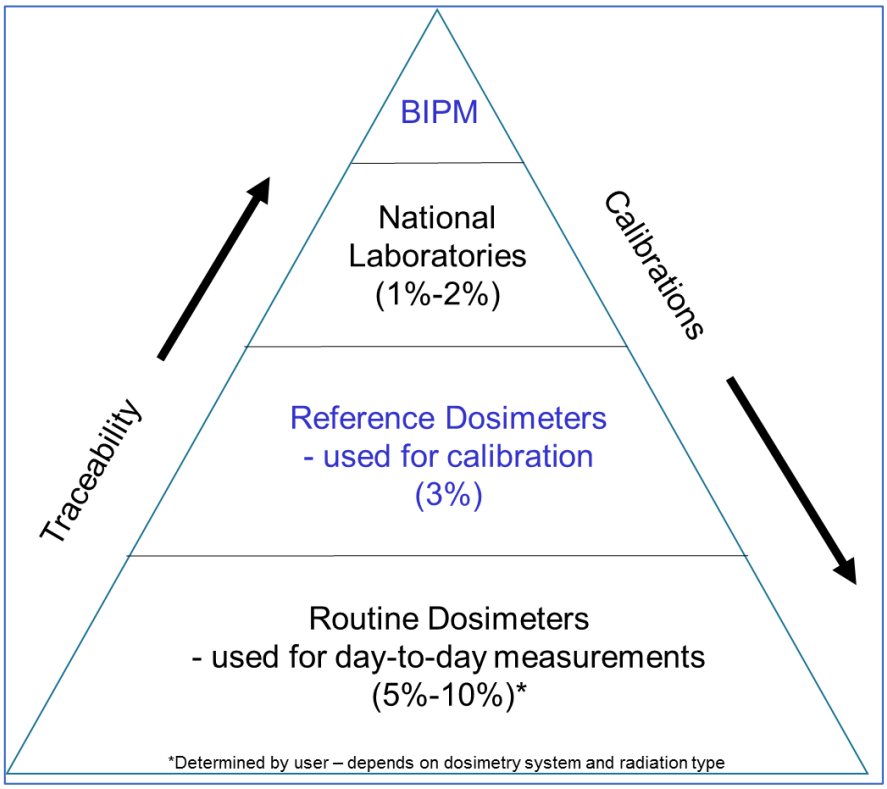

***Figure 8**: Dosimetry Traceability Chain and Typical uncertainties (2σ) shown in brackets. (BIPM: Bureau International des Poids et Mesures).*

Methods of dosimetry system calibration are described in several publications, for example NPL Report CIRM 29 and ISO ASTM standard 51261, and these methods should be followed in detail. The ability to calibrate satisfactorily a system under the conditions of use may be an important consideration in the selection of a dosimetry system (see Sec. 5). General details of dosimetry system calibration will not be given in this document, but several issues specific to the use of dosimeters for dose mapping are given below:

- The range of doses used for dose mapping may be different to the doses used in routine processing. If the same dosimetry system is used in both cases, it is important that the

calibration dose range is wide enough to cover the full range of doses to be measured. Dose measurement involving extrapolation of a calibration curve outside of the range over which it was generated can lead to significant errors and should not be carried out.

- In many situations, for example product irradiated by electron beams or high density (metallic) product irradiated by photons, it can be necessary to use thin film dosimeters without any protective sachet in order to measure as close as possible the dose to the surface of the product. The response of such dosimeters is generally sensitive to their water content and consequently to the ambient humidity. This means that unless some form of verification of the dosimetry system calibration is carried out, there is likely to be a break in the measurement traceability chain. This verification is often accomplished by irradiating the dosimeters without protective sachets alongside reference dosimeters, whose response is known under these conditions. The reference dosimeters could be a different type of dosimeter, e.g. calorimeters or alanine dosimeters, or the same type of film dosimeter contained in protective sachets used to stabilise the water content.

- During the calibration exercise, the measurement reproducibility of the dosimetry system is determined. This represents a first estimate of the obtainable dose measurement reproducibility in a dose map exercise. However, the uncertainties of the measured D_{min} and D_{max} are influenced by product variability, by dosimeter placement variability, and, depending on the design of the dose map exercise, also by machine variability. These components of uncertainty and variability are parts of the total uncertainty associated with dose mapping.

5 Selection of dosimetry system for dose mapping

It is an essential requirement for dosimeters – or more correctly, dosimetry systems – used in performance qualification dose mapping that they must be able to measure the dose in the irradiated product, but it might not be as straightforward as it seems to fulfil this criterion. Understanding what is required to be measured and the conditions under which it is measured is needed, as is understanding the dosimetry system, its properties and limitations.

The main purpose of PQ dose mapping is to determine the relationships between the minimum dose D_{min} and the maximum dose D_{max} in the irradiated product, as well as their relationships with the dose at the routine monitoring location D_{mon}. Using radiation sterilization as an example, D_{min} must during routine processing be greater than the sterilization dose D_{ster}, and D_{max} must be less than the maximum acceptable dose $D_{max,acc}$. This is outlined in the radiation sterilization standards (ISO 11137), but the principle is the same, regardless which irradiation process is considered. The minimum dose to product must be greater than the dose required for the process to be effective, and maximum dose must be less than the dose that might negatively affect the specified functional requirements of the product.

PQ dose mapping must be carried out using product in its final packaged form. This will often be inhomogeneous in nature with local density changes within product and between product units as they are packed in containers, shipping boxes or retail boxes, thus giving rise to local scattering and shielding of the radiation. A product surface represents an interface, where dose can be expected to change as the radiation field changes rapidly. Dose can therefore vary significantly in and around product units, with dose gradients as the consequence. Under such circumstances it can be difficult to select the location for placing dosimeters and to select dosimeters so that there can be confidence that the real D_{min} and D_{max} doses are measured. If individual dosimeters are used for dose mapping, then it can require many dosimeters to obtain reasonable assurance that D_{min} and D_{max} are found and measured, while use of dosimeter film sheets or strips together with appropriate measuring equipment can cover larger areas, where there is a greater probability that the real D_{min} and D_{max} will be found, and their values measured.

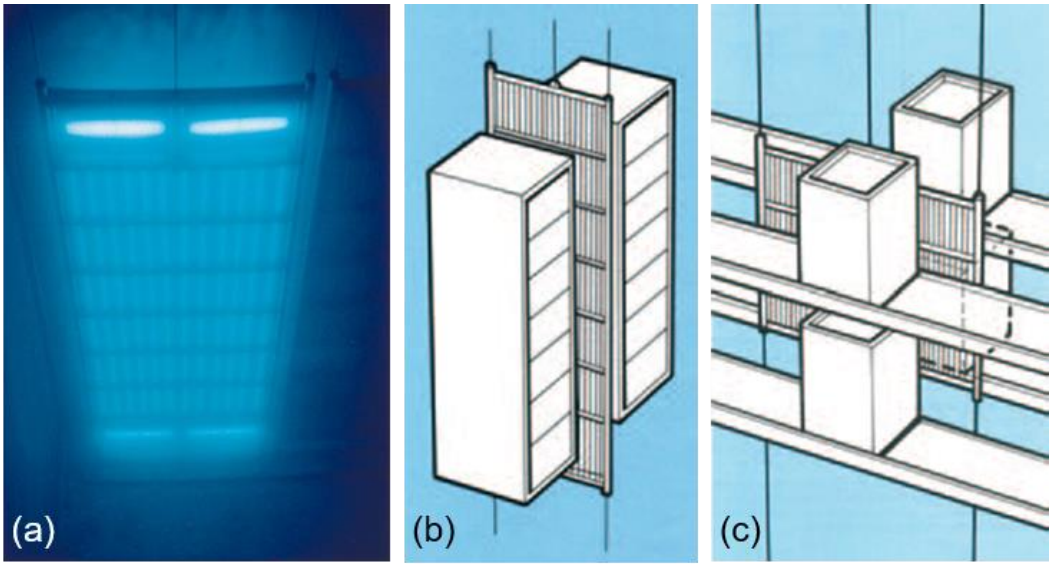

***Figure 9**: (a) view of a ^{60}Co source rack in its storage pond, showing the blue Cherenkov radiation; (b) source rack overlapping product; (c) product overlapping source, on two-layer conveyor system.*

The extent of dose gradients in or at an irradiated product depends very much on the type of radiation used. Product irradiated in an industrial cobalt-60 gamma facility is usually irradiated from two or more sides, and as the product container passes through the facility it is furthermore irradiated from a broad angle by the many individual sources of the source rack, see examples in Figs. 9a, 9b, 9c.

The photons emitted from cobalt-60 gamma sources or X-ray emitters do not deposit energy directly. They produce secondary electrons that effectively irradiate the product in a container, from multiple sides, leading to rather uniform dose distribution. However, dose gradients in the order of several percent per cm can be generated due to absorption of the photons as they pass through the container depending on the properties of the absorbing material, and dose gradients can be generated around individual product units, in particular when these are made from material such as metal, for example in certain types of implants.

***Figure 10**: Layout of high-energy X-ray irradiator based on a Rhodotron electron accelerator.*

X-rays generated by stopping of accelerated electrons in a dedicated target have been used in hospitals for many years for diagnosis and treatment, and recently high and low energy X-rays have also been used industrially for irradiation of product. X-ray facilities for high-volume irradiation of products typically uses electrons accelerated at 5-7 MeV for generation of X-rays, see Fig. 10, but X-ray facilities using much lower energy such as 100-200 keV are also used for irradiation of, for example, blood for transfusion, see Fig. 11.

***Figure 11**: A small low-energy X-ray blood irradiator of the type used in many hospitals, to deliver a dose of a few tens of grays to blood used in transfusions*

The properties of high-energy X-ray photons are similar to cobalt-60 photons, and the same radiation absorption processes lead to energy deposition, but the layout of the X-ray facility results in potential differences in dose gradients, because the photon beam is not isotropic, and possibly also because of differences in energy spectrum between cobalt-60 and X-ray photons. As a first estimate dose gradients similar to those generated in cobalt-60 irradiation could be expected.

Irradiation of product by accelerated electrons will inevitably generate significant strong dose gradients the extent of which depend very much on the nature of the product and of the energy of the electron beam. Radiation processing normally uses electron energies up to maximum of 10 MeV in order to avoid inducing radioactivity in the irradiated product, and this energy level is commonly used for medical device sterilization. The two types of 10 MeV electron accelerators most often used are the linear electron accelerator and the Rhodotron (Fig. 12).

At the low end of the energy spectrum, electrons at 70 or 80 keV (Fig. 13) are used for decontamination of surfaces of food packaging. Over this wide range of electron beam energy – about 70 keV to 10 MeV or more – electron irradiation is used for many different applications.

When electron irradiation is used for product irradiation such as radiation sterilization of medical devices, then it is common to irradiate the product from two or more sides leading to a more homogeneous dose distribution expressed as a smaller dose uniformity ratio DUR = D_{max}/D_{min}, and usually thereby also reducing local dose gradients.

Given the range of conditions described above, what is required of the dosimetry system in terms of being able to measure accurately the dose at locations on product, where dose can change several kGy within short distances? What lateral (or spatial) resolution is required?

***Figure 12**: A high-energy electron linear accelerator (left), and an IBA Rhodotron, used in the generation of 10 MeV electron beams (right).*

***Figure 13**: A low-energy laboratory irradiator supplying electrons from 80 to 200 keV (left), and an industrial facility used in the manufacture of thin polymer films (right).*

For dose measurements for gamma and X-ray irradiation, the required lateral (or spatial) resolution might be limited to a few percent variation over distances in the order of centimetres. In the case of electron irradiation, the required spatial resolution might be in the order of several percent over a few millimetres or less.

The spatial measurement resolution of a dosimetry system is to some extent determined by the physical size of the dosimeter, but possibly more important might be the ability of the measurement system to resolve dose gradients that can be present in the dosimeter itself following irradiation in a dose map exercise. An alanine pellet or alanine film dosimeter (Fig. 14) measured in an EPR spectrometer can only measure the average dose over the volume of the alanine pellet or film, and the same is the case for liquid dosimeters in ampoules (Dichromate or ECB for example) that are measured in spectrophotometers, where the average dose in the irradiated liquid will be measured.

***Figure 14**: Alanine pellet and film dosimeters (left), alanine TapeTab dosimeters (centre) and liquid dichromate dosimeters in glass ampoules (right).*

PMMA (Perspex) dosimeters (Harwell 4034 and Radix, for example) also have limited spatial resolution due to their physical size and measurement in a spectrophotometer.

Thin radiochromic film dosimeters that are measured by optical techniques are available as single dosimeters or as sheets and strips. The single dosimeters are normally packaged in small pouches, see for example FWT-60 and GEX DoseStix (Fig. 15).

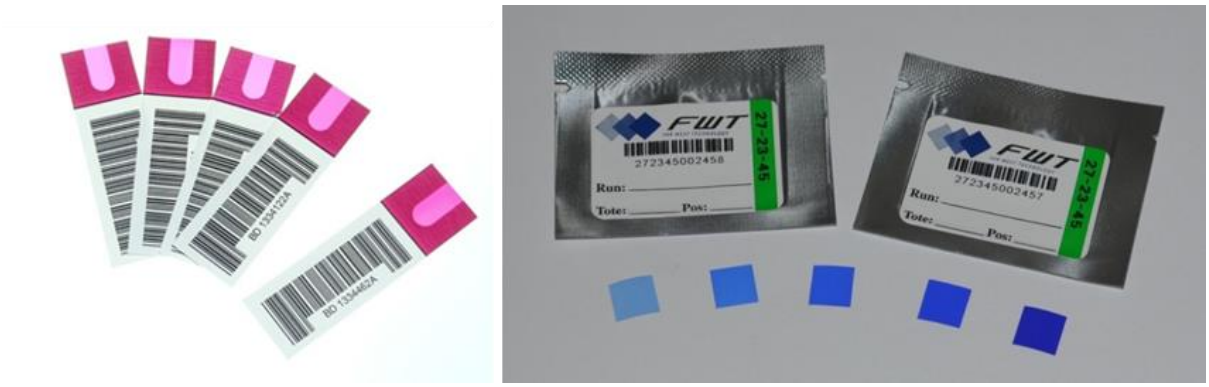

***Figure 15**: GEX DoseStix based on Risø B3 dosimeter film (left), and FWT-60 dosimeter films (right). These dosimeters are normally available in sealed pouches, maintaining a controlled atmosphere and water content.*

Optical thin film dosimeters with thickness in the order of 10 µm – 100 µm such as Risø B3 or CTA (Fig. 16) might have inherent high spatial resolution, but the actual resolution of the dosimetry system depends on the optical resolution of the measurement system. Some spectrophotometers are equipped for analyzing film strips, and the lateral resolution is in that case determined by the size of the analyzing light beam, that typically is in the order of 2 mm × 4 mm. The size of the analyzing light can be reduced by focusing the light beam as in a microscope leading to very high lateral resolution but scanning this analyzing light beam across an irradiated dosimeter film can take a long time.

***Figure 16**: Dosimeter films may also be available as sheets (left: Risø B3) or strips (right: CTA)*

An example of custom-designed dosimetry equipment for measurement of CTA dosimeter film strips is the so-called dosasap® scanner and software. Fig. 17 is an example of a measurement with this system; it is a depth dose curve for a 10 MeV electron beam.

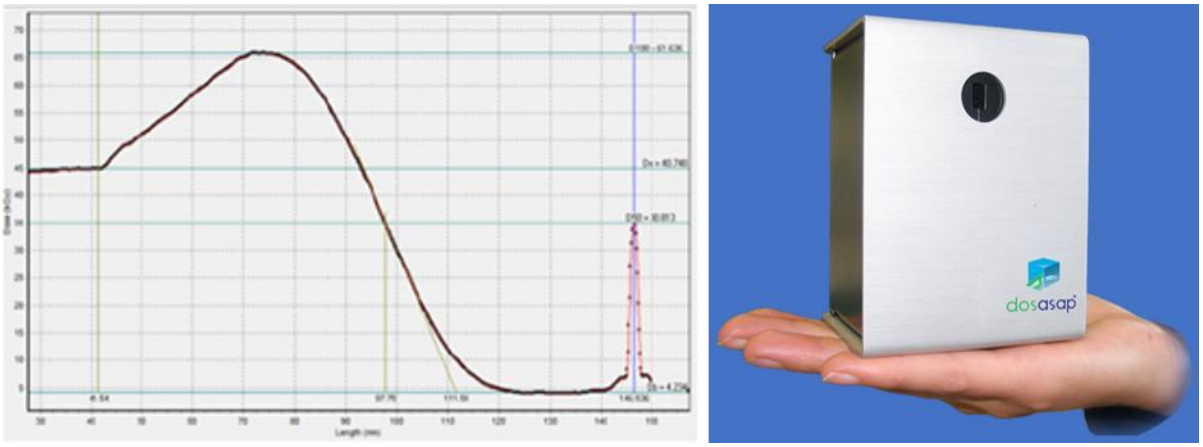

***Figure 17**: Example of an electron beam depth-dose curve measured using CTA dosimeter film placed in an aluminium wedge (left), by the Aerial dosasap® scanner (right).*

Alternative methods for analyzing optical film dosimeters include scanners with associated image analysis software. The scanner might be a relatively simple office scanner. The lateral resolution is determined by the selected scanning resolution such as 200 dpi corresponding to a resolution of 100 µm (Fig. 18)

The location and magnitude of D_{min} and D_{max} must be determined from the many individual dose measurements in a dose map exercise. Single dosimeters, such as alanine pellets, FWT-60, DoseStix or Harwell 4034 will only measure the average dose of the dosimeter. This limits the ability of these dosimeters to measure at locations with dose gradients while a single dosimeter film can measure a wide range of doses depending on the measurement system. The maximum dose and minimum dose on a single dosimeter film can be measured as shown in the example in Fig. 18, where a Risø B3 dosimeter film is measured using a scanner and analysed by the software RisøScan.

***Figure 18**: Example of use of RisøScan software in analysis of scanned image of B3 dosimeter film (left), and desktop scanner with scanned dosimeter image (right).*

The dosimeter for dose mapping should not interfere with the dose to be measured. This can be a particularly important issue when dose to surface of the irradiated product is to be measured, which is often the case for dose mapping for radiation sterilization. Product surfaces represent interfaces, and at an interface, dose is likely to change through the thickness of the product due to lack of secondary electronic equilibrium at the surface. Thin film dosimeters attached to product surfaces can effectively be considered part of the surface and can therefore measure the surface dose, while the dose measured by a thicker dosimeter might differ significantly from the dose to the product surface. This aspect is most important in the case of e-beam irradiation, and often less so in gamma irradiation, where the radiation is highly scattered leading to reduced interface effects.

Dose mapping for low energy e-beam irradiation is one situation where thin film dosimeters are used. Fig. 19 shows Risø B3 dosimeters on the surface of a so-called “tub” that is used at pharmaceutical aseptic filling lines. The surface is irradiated in order to prevent microbiological contaminants from entering the aseptic filling area.

Medical devices that are sterilized using high energy e-beam irradiation can also need thin film dosimeters for detailed dose mapping. This applies in particular to complex devices with metal parts, such as the one shown in Fig. 20. A thin dosimeter film (Risø B3, size 19 mm × 32 mm) was wrapped around the small metal part, and the device was irradiated from two sides at a 10 MeV electron accelerator.

***Figure 19**: Tub irradiated with low energy electrons (110 – 150 keV) where Risø B3 film dosimeters are used for dose mapping.*

***Figure 20**: Medical device with small metal part marked. Length 20 mm, diameter 6 mm. Reproduced with permission from Cochlear Bone Anchored Solutions AB.*

The dosimeter film was scanned and analyzed using image handling software (RisøScan), and the measurement of minimum dose is shown in Fig. 21. The left side shows the scanned image of the irradiated dosimeter film, and to the right is shown the dose measurement. Very strong dose gradients are apparent with dose changing from 14 kGy to 22 kGy over a few millimetres. In this image a measurement of minimum dose 14.4 kGy is made at the position of the crosshair.

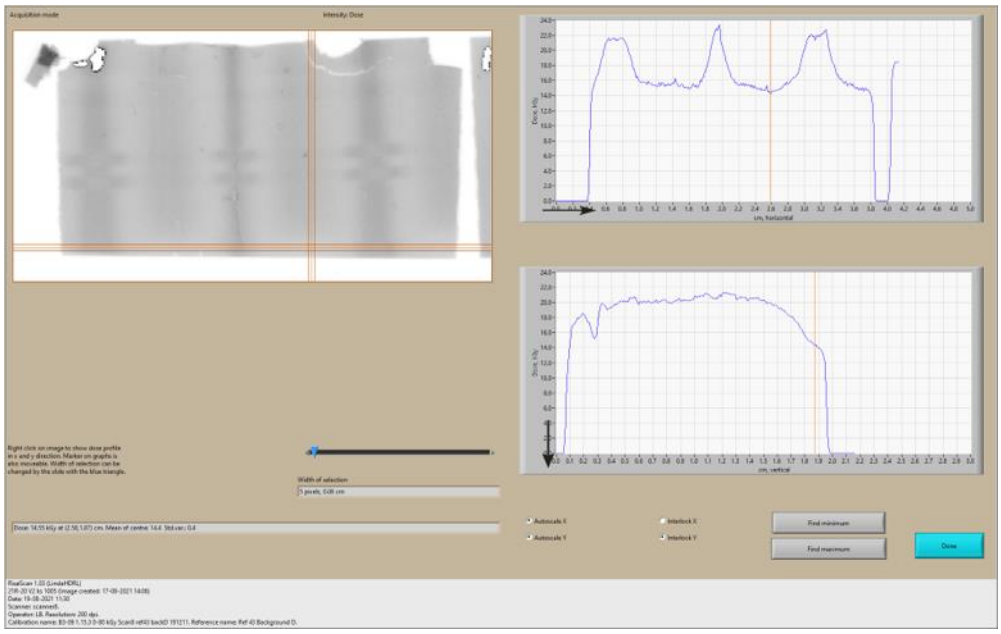

***Figure 21**: Dose measurement using B3 dosimeter film and Risøscan software. The dosimeter film was placed around a small metal object and irradiated at 10 MeV electron accelerator. Reproduced with permission from Cochlear Bone Anchored Solutions AB.*

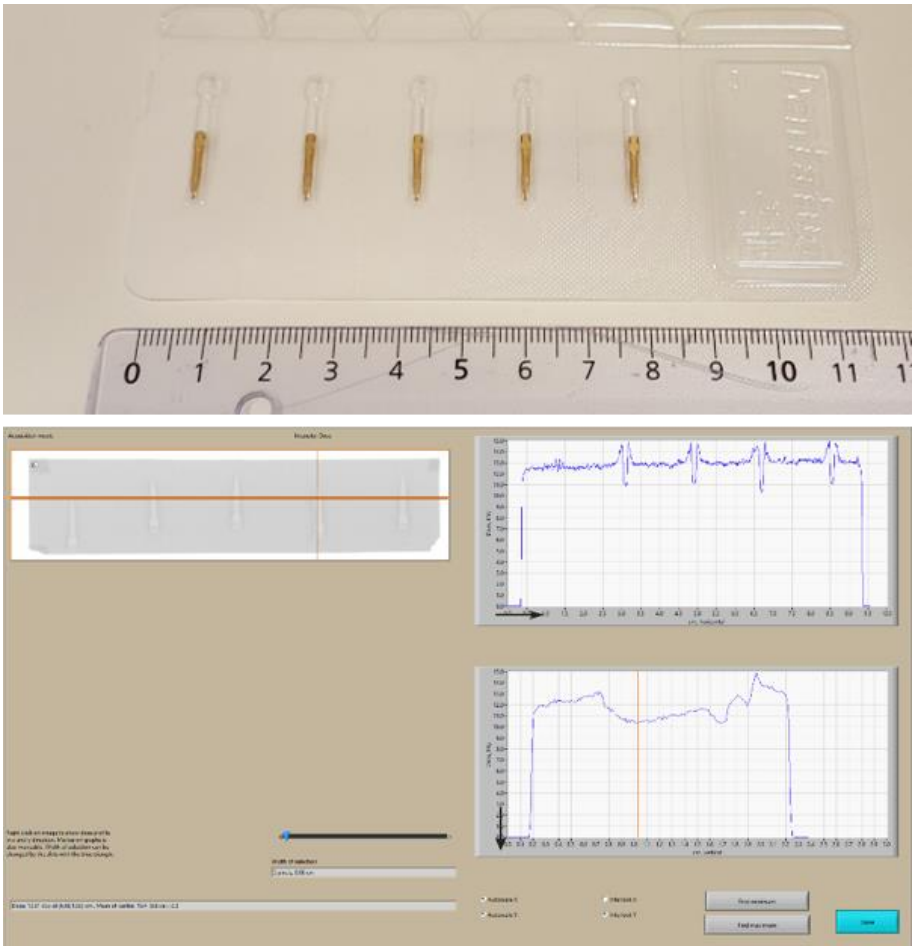

***Figure 22**: Risø B3 dosimeter film was placed over the small metal objects (upper figure) and irradiated at a 10 MeV electron accelerator. Dose measurement of the B3 film using the Risøscan software (lower figure). Reproduced with permission from Cenova AB.*

Figs. 21 and 22 are examples of situations in which a dosimeter that effectively averages dose over its volume, such as an alanine pellet, would not be able to detect the extremes of dose that it is necessary to measure. Similar gradients might also occur in low energy electron beams and kV X-rays, but are less likely in cobalt gamma or MV X-rays.

Table 1, adapted from ISO ASTM 52628, gives characteristics for several dosimetry systems that are relevant for PQ dose mapping.

For sterilization, in most cases the dose on the surface of the product must be determined, but for determination of maximum acceptable dose, sometimes the dose to the bulk of the material making up the medical device needs to be determined. It might therefore be necessary to insert dosimeters into the material of the device.

Table A1 from ISO/ASTM 52628 edited for applicability to PQ dose mapping.

Note: Each "Yes" and "No" in the table are given as suggestions, but selection of a dosimetry system for a given dose map task depends on several factors, such as energy of the radiation, complexity of the product and requirement for spatial resolution.

Dosimeter	Description	Radiation Type	Dose Range	PQ dose mapping			
				Gamma + X-ray		Electron	
				Homogeneous product	Inhomogeneous product	Homogeneous product	Inhomogeneous product
Alanine/EPR see ISO/ASTM Practice 51607	Tablets or small rods of 3 to 5 mm diameter and various lengths, consisting primarily of α-alanine and a small amount of binder.	Electron, gamma and X-ray	1 to 10^5 Gy	Yes	Yes	Yes	No
	Film dosimeters on a polymer substrate.	Electron, gamma and X-ray	1 to 10^5 Gy	Yes	Yes	Yes	No
Calorimeter see ISO/ASTM Practice 51631	Dosimetric absorber and thermal sensor held in thermal insulation. The dimensions depend on the energy of the electron beam.	Electron	10^2 to 10^5 Gy	No	No	No	No
Cellulose Acetate see ISO/ASTM Practice 51650	Films, usually as 8 mm wide rolls.	Electron, gamma and X-ray	$5x10^3$ to 10^6 Gy	Yes	Yes	Yes	Yes
Ceric-Cerous Sulfate see ISO/ ASTM Practice 51205	Aqueous solution of $1.5x10^{-2}$ mol dm^{-3} $Ce(SO_4)_2$,$Ce_2(SO_4)_3$ and 0.4 mol dm^{-3} H_2SO_4. The dosimeter is usually irradiated in sealed 2-mL glass ampoules of 10-mm inner diameter.	Electron, gamma and X-ray	$5x10^2$ to 10^5 Gy	Yes	No	No	No
Ethanol Chlorobenzene see ISO/ASTM Practice 51538	Aerated solution of ethanol, chlorobenzene and water, sometimes with a small amount of acetone and benzene added. The dosimeter ampoules are typically 2 to 5 cm^3 in volume and useful dose range depends on the concentration of chlorobenzene.	Electron, gamma and X-ray	10 to $2x10^6$ Gy	Yes	No	No	No
Fricke Solution see ISO/ASTM Practice 51026	Aerated aqueous solution of 10^{-3} mol dm^{-3} ferrous sulfate, and 0.4 mol dm^{-3} sulfuric acid. Sodium chloride, 10^{-3} mol dm^{-3}, is sometimes used to reduce the effect of trace organic impurities.	Electron, gamma and X-ray	20 to $4x10^2$ Gy (upper limit) can be extended to $2x10^3$ Gy	Yes	No	No	No
Potassium/Silver dichromate see ISO/ASTM Practice 51401	Aqueous solution of $2x10^{-3}$ mol dm^{-3} potassium dichromate plus $5x10^{-4}$ mol dm^{-3} silver dichromate in 0.1 mol dm^{-3} perchloric acid. If $5x10^{-4}$ mol dm^{-3} silver dichromate only is used, it can be used for a lower dose range from 2 to 10 kGy.	Electron, gamma and X-ray	$2x10^3$ to $5x10^4$ Gy	Yes	No	No	No

Polymethylmeth acrylate (PMMA) see ISO/ASTM Practice 51276	PMMA strips, with or without radiation sensitive dyes.	Electron, gamma and X-ray	10^2 to 10^5 Gy	Yes	Yes	No	No
Radiochromic liquid see ISO/ASTM Practice 51540	Organic or aqueous solutions of leuco (colorless) dyes that become intensely colored upon irradiation.	Electron, gamma and X-ray	$5x10^{-1}$ to $4x10^4$ Gy	Yes	No	No	No
Radiochromic Film see ISO/ASTM Practice 51275	Polymer films containing leuco (colorless) dyes Film thicknesses vary from a few micrometers to about 1 mm.	Electron, gamma and X-ray	10^0 to 10^5 Gy	Yes	Yes	Yes	Yes
Radiochromic Optical Waveguide see ISO/ASTM Practice 51310	Organic solutions of leuco (colorless) dyes held in flexible plastic tubes that are sealed at both ends by glass or plastic beads or small rods.	Electron, gamma and X-ray	10^0 to 10^4 Gy	Yes	No	No	No
Thermoluminesc ence dosimeters (TLD) see ISO/ASTM Practice 51956	Crystalline material in the form of powder, pellets, single crystals, Most commonly employed materials for TLD are LiF, CaF_2, $CaSO_4$, and $Li_2Bi_4O_7$.	Electron, gamma and X-ray	10^{-4} to 10^3 Gy	Yes	Yes	Yes	No

6 Where to measure and how many measurements

It is a requirement in PQ dose mapping to characterize the minimum dose D_{min} and maximum dose D_{max} (magnitude, location, variability) for the defined load configuration in an irradiation container and a specified pathway through the irradiator. In addition, the relationship between these doses and the dose at the routine monitoring location D_{mon} must be determined.

Number of dosimeters per irradiation container

The number of dosimeters in each dose mapped irradiation container is not specified in standards. The number has to be selected by the dose map practitioner, and it should primarily be based on the expected ability to measure dose in the container at locations where dose gradients are likely to happen. A relative high number of dosimeters should be placed in such areas, while fewer dosimeters can be placed at areas where dose distribution is expected to be uniform. The selection often has to be based on the dose map practitioner's prior knowledge and experience.

Note that using sheets or strips of dosimeter film effectively increases the number of dosimeters as one strip of dosimeter film can measure both minimum and maximum dose, and any dose in-between.

Calculation of dose distributions based on Monte Carlo (MC) and similar methods can be very useful tools when decisions about dosimeter location have to be made. The calculated dose distributions shown in Figs. 4 and 5 for homogeneous product irradiated at 10 MeV e-beam are examples on how MC calculations can be used to identify expected D_{min} and D_{max} zones where particular attention should be given to placing of dosimeters. The MC methods are well established, particularly in medical dosimetry, and they are being more and more used also in radiation processing dosimetry. Different methods are described in ASTM E2232 (2021), and their applicability are discussed in section 8 in this report.

In cases where little prior knowledge and experience exists due to, for example, special product configuration or unusual irradiator design, the best advice might be, in an initial experiment, to place dosimeters at locations uniformly distributed throughout the irradiation container. Based on the initial measurement results from this exercise, a more detailed dose map plan can be specified.

Symmetry arguments can be used to reduce the total number of dosimeters in the irradiation container. Such arguments can typically be based on OQ dose map data, where, for example, left-right symmetry at an electron accelerator facility has been consistently demonstrated. It might then suffice to place dosimeters in only half of the irradiation container, provided that product packaging within the product box is also symmetrical.

Number of dose mapped containers

Dose mapping of several irradiation containers is needed in order to be able to determine sample averages as well as sample standard deviations for D_{min} and D_{max}. "Several" is often interpreted as three irradiation containers, but this number is the absolute minimum for any statistical analysis to be carried out. Dose mapping of a greater number of irradiation containers clearly gives a better basis for determining the average values of D_{min} and D_{max}, and their standard deviations.

Some products can be difficult to dose map and actions might be needed to increase confidence in the measured doses. This could apply to products having a small difference between maximum acceptable dose $D_{max,acc}$ and sterilization dose D_{ster}, or products where random packaging makes it difficult to place dosimeters at the same location from container to container. Confidence in the measured D_{min} and D_{max} doses can be increased when, for example, the following actions are taken:

a) More than one dosimeter is placed at defined positions. Using the measured average dose for a dosimeter location then improves the reproducibility of the measurement by $1/\sqrt{n}$ (n = the number of dosimeters at the position).

b) The sample size can be increased by considering symmetrical parts of the irradiation container as individual containers and placing dosimeters in all these symmetrical parts.

c) More than 3 irradiation containers are mapped, possibly with the irradiation containers #4 and beyond having dosimeters placed mainly at the locations of D_{min} and D_{max}, as determined from the results of the first 3 containers. This will increase the sample size. Increased sample size will reduce the width of the confidence interval around the obtained sample average $\bar{X}$ and sample standard deviation s, $\bar{X} \pm \frac{s}{\sqrt{n}}$ where n equals the sample size.

It is generally advisable to place an adequate number of dosimeters throughout the dose mapped volume of an irradiation container in order to obtain a more complete measure of the dose distribution, even if it is expected that several of the dose measurements will not contribute to the measured D_{min} or D_{max} doses. This can provide objective evidence as to where the dose extremes are and are not located.

7 Interpretation and use of measured D_{min} and D_{max} doses

Requirements for PQ dose mapping for radiation sterilization are given in ISO 11137-1:2006, with the main requirements found in clauses 9.3.1 and 9.3.5:

> ***9.3.1*** *Dose mapping shall be carried out using product loaded in irradiation containers in accordance with a specified loading pattern in order to*
>
> *a) identify the location and magnitude of the minimum and maximum dose and*
>
> *b) determine the relationships between the minimum and maximum dose and the dose(s) at the routine monitoring position(s).*
>
> ***9.3.5*** *Dose mapping shall be carried out on representative irradiation containers sufficient in number to determine the variability of dose between containers.*

Detailed guidance on the use of dose mapping data to establish processing parameters is given In ISO 11137-4. This section provides a summary of the methods in ISO 11137-4 and uses the same terminology.

The PQ dose mapping experiment should be designed to measure as a minimum the combined effect of reproducibility of the dose map dosimetry system, the dose variability caused by product variation between containers, and effect of differences in placing dosimeters for measurement of D_{min} and D_{max}.

The dose map experiment can be designed to also include measurement of the effect of irradiator parameter variation. For this experiment dose mapping containers must be irradiated with time intervals that are great enough so that irradiation parameters can be expected to vary within their specifications during irradiation of the dose map containers.

Alternatively, the dose map experiment can be carried out by irradiating containers in direct succession after each other in such a way that the irradiation parameters can be assumed not to vary during irradiation of the dose map containers. This is sometimes called irradiation in a “quiet system”. However,

during actual processing it is expected that the irradiation parameters of the facility will vary, albeit within specifications and this variability must be taken into account when determining the total variability of dose between containers.

In the first case the ratios D_{min}/D_{mon} and D_{max}/D_{mon} should be determined for each container during dose map irradiation, and the acceptable dose range for D_{target} can be determined based on the various ratios and their measured variability.

In the second case – the quiet system – the relationship between D_{min} and D_{max} and the dose at routine monitoring position D_{mon} can be also determined using the ratios as above, and the acceptable range of routine monitoring doses D_{target} for obtaining the required product dose specifications can be calculated taking into account the additional anticipated variability of the irradiation facility (σ_{mach}).

The location and magnitude of D_{min} and D_{max} must be determined from the many individual dose measurements in a dose map exercise. Individual dosimeters, such as FWT-60, DoseStix or Harwell 4034 will each measure one dose only, while dosimeter films or strips can on a single dosimeter film or strip measure a wide range of doses depending on the measurement system.

One approach for determining D_{min} and D_{max} is to identify the single minimum dose and the single maximum dose in each dose mapped container (product box). The average D_{min}, D_{max} and their uncertainties are then determined from measurements in several containers as required in ISO 11137-1.

Regardless of the dosimetry system used, a single dose measurement might not be adequate to determine location and magnitude of D_{min} or D_{max}. Instead, the approach of defining *dose zones* can be adopted (see ISO/ASTM 52303).

Definition from ISO/ASTM 52303:

> ***3.1.6*** *dose zone—a volume or discrete point(s) within a process load that receives the same absorbed dose within the statistical uncertainty of the irradiation process and absorbed dose measurement(s).*

Different approaches can be used to define the dose zones for D_{min} and D_{max}. In ISO/ASTM 52303 three methods are given for defining statistical equivalent dose zones that are based on doses measured by single dosimeters at specific locations within a process load.

Only the dose zones for D_{min} and D_{max} are of interest for establishing process parameters, and if it is assumed that all measured doses within a dose zone are not distinguishable from each other within specified uncertainty limits, then the average doses and their uncertainties characterize the given dose zones and represent D_{min} and D_{max}, respectively.

The outcome of the dose mapping is somewhat different when doses are not measured using single dosimeters, but using sheets or strips of dosimeters film. A dosimeter sheet – large or small – can contain measurements of a large range of doses, and both D_{min} and D_{max} can be measured on the same dosimeter (see example on Fig. 18 in section 5). D_{min} or D_{max} measured on any dosimeter sheet regardless of location in the process load can be part of the respective dose zone, but not all measured D_{min} and D_{max} values belong necessarily to the D_{min} and D_{max} zones. A first choice for the uncertainty to be used for determination of valid dose zones can be obtained from calibration of dosimetry system used for the dose mapping, where reproducibility is determined. This uncertainty that is obtained under well characterized irradiation conditions is the smallest uncertainty to be expected. Historical information for the uncertainties of D_{min} and D_{max} from other dose maps obtained under similar conditions can also be used as first estimates of standard deviations for the selected group of measurements representing a dose zone.

In this report it is suggested that in order to determine the D_{min} dose zone, the measured minimum doses are ranked from smallest to largest dose. In order to determine the dose zone at 95% confidence, the smallest measured dose is taken as the lower 95% confidence limit. The higher 95% limit for the

D_{min} dose zone is taken as the lower limit plus 4 standard deviations. The average D_{min} is taken as the average of all doses within this band assuming a normal distribution for these doses. The actual distribution might not be strictly normal, and therefore the actual standard deviation should be calculated for the D_{min} zone.

The D_{max} dose zone can be determined in a similar way, this time with D_{max} data ranked from greatest to smallest dose.

The selection of the initial standard deviation estimate for defining the dose zones is not critical when the average D_{min} and D_{max} and their standard deviations are used for determination of target doses D_{target} for the radiation process, as described below. Selecting, for example, a smaller initial standard deviation for the D_{min} dose zone will lead to a smaller $D_{min,average}$, and the resulting lower target dose D_{target}^{lower} will practically be unchanged.

Uncertainty and variability budgets and their use for determining D_{target}.

A table describing the components of measurement uncertainty and sources of variability related to PQ dose mapping should be established (uncertainty budget). The major components are:

σ_{cal}: Calibration uncertainty, comprising

uncertainty of calibration doses,

curve fit uncertainty

uncertainty due to influence quantities.

σ_{map}: Dose map measurement reproducibility, comprising

dosimetry reproducibility,

product variability.

Separate values of σ_{map} apply to measurements of D_{min} and D_{max}, respectively.

$\sigma_{mach,comb}$: Measured variability of irradiation facility

machine variability,

reproducibility of routine dose measurement.

Note: The dose map experiment can be designed to measure a combined value of σ_{map} and $\sigma_{mach,comb}$ in the same experiment. This involves dose mapping of the individual containers with sufficient time between containers to justify that $\sigma_{mach,comb}$ has been captured in the experiment.

Alternatively, the dose map experiment can be carried out using stable irradiator conditions. In this case $\sigma_{mach,comb}$ should be estimated from OQ or historic data.

These components are combined to one process standard deviation that is used to determine conditions for process irradiation.

$$\sigma_{process} = SQRT (\sigma_{cal}^2 + \sigma_{map}^2 + \sigma_{mach,comb}^2)$$

D_{min} and D_{max} are measured together with the routine monitoring dose D_{mon} and the following ratios can be determined:

$$R_{min/mon} = D_{min}/D_{mon}$$

$$R_{max/mon} = D_{max}/D_{mon}$$

Further, following the principles of ISO/TS 11137-4, the so-called process factors UF are determined:

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

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

$\sigma_{process}^{min}$ and $\sigma_{process}^{max}$ are the process standard deviations associated with D_{min} and D_{max}, respectively, that include all significant sources of uncertainties and process variabilities.

k is the coverage factor that is selected according to the desired confidence level, e.g. *k*=2 for approximately 95% confidence level.

The highest acceptable average dose at the maximum dose location (or for the maximum dose zone) is designated D_{max}^{limit}, and the smallest acceptable average dose at the minimum dose location (or for the minimum dose zone) is designated D_{min}^{limit}. They are determined as:

$$D_{max}^{limit} = D_{max,acc} \times UF_{upper}$$

$$D_{min}^{limit} = D_{ster} \times UF_{lower}$$

$D_{max,acc}$ is the maximum acceptable dose and D_{ster} is the sterilization dose

The range of acceptable target doses – the dose at the routine monitoring location to be measured routinely – is then between these limits:

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

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

The actual value of D_{target} can be selected to be any dose between D_{target}^{upper} and D_{target}^{lower}.

ISO 11137-4 gives examples of applications of these calculations.

8 Mathematical modelling for PQ dose mapping

General

Mathematical modelling techniques can help to give information in many situations. The techniques can be used, for example, to

- determine dose in PQ dose mapping in complex products at locations where it is not possible to place dosimeters,
- to predict changes in dose distribution after source change in a gamma facility,
- to predict changes in dose distribution in product after re-arranging packaging geometry.

There are several different approaches that can be taken, ranging from simple empirical approximations all the way to very detailed Monte Carlo calculations, which directly model the scattering, absorption, and other interactions of ionizing radiation in materials. In all cases, understanding what is being modelled and interpreting the results from a calculation are important parts of the process. These require knowledge of the behaviour of the different types of radiation as they interact with materials, as well as knowledge of the characteristics of the radiation delivered by the irradiator.

The Panel on Gamma and Electron Irradiation document on Monte Carlo codes (Panel, 2010) gives a good summary of the capabilities of some of these codes and the requirements for using them, and the report Radiation Technology Series 1 (IAEA 2010) discusses “Use of Mathematical Modelling in Electron Beam Processing”.

It should be noted that these tools require a high degree of knowledge and experience to be used successfully. In this context it is noted that codes that are easier to use, in particular for setting up the dose calculation, might allow wider use of the mathematical modelling methods.

Different methods

The Point kernel method

Point kernel methods (Shultis et al 1996) are used in gamma irradiators, for example in calculations of the optimal arrangement of source pencils in the source rack. These codes have the advantage of speed and give good results, especially for the calculation of doses in materials of uniform density. In these methods, doses at the points of interest are summed over the contributions from the distribution of sources. They are not useful for calculations with electron beams and also not in calculations for gamma irradiations with complex geometries with a great variation in density.

The Monte Carlo method

Monte Carlo methods can in principle deliver arbitrarily precise results, limited only by the level of detail in the input geometry, material information, source spectrum and distribution and selected interaction mechanisms, cross sections, energy cut-off etc. They work by following many (from thousands to many billions or even more) individual particle histories and summing the effects of each particle history to calculate the absorbed dose (or other required dosimetric quantities) in a given location. It is this ability of Monte Carlo calculations to simulate the passage, scattering, and absorption of radiation in arbitrarily complex geometries, which makes the technique so potentially useful regarding PQ dose mapping. The required number of particle histories depends on the required statistical significance of the calculated result.

Absorbed dose is a quantity built up from the incremental energy deposited by vast numbers of individual photons or electrons. The Monte Carlo technique mimics this process. The calculations simulate the actual physical scattering and other events that affect those particles as they pass through the materials making up a product.

Calculations in support of OQ measurements which make use of simple geometries and homogeneous materials can be straightforward to carry out and interpret. Figures 2 to 7, for example, in section 3, were obtained via the use of Monte Carlo calculations with the EGSnrc code (Kawrakow et al 2020), simulating the dose deposited in large volumes of low-density, homogenous material. The EGSnrc code, which is designed for calculations involving high-energy electrons and photons, offers some advantages: It is free to the end user, and it can calculate with great precision the dose each side of boundaries between two materials. This consideration might be particularly important where particle transport around geometrically very small regions is being investigated. Other Monte Carlo codes also freely available include Geant4 (Agostinelli et al 2003) and Fluka (Ferrari et al 2005), both of which can handle many different particle types, and MCNPX (2007) although this and some related codes can be difficult to obtain.

In PQ, products being irradiated are very rarely uniform and homogeneous. Even if the product is arrayed very regularly, there will be some variation between product items. In some routinely irradiated product, however, the arrangement of product items can be effectively random, in both position and orientation. This can make the use of a Monte Carlo model difficult, both in its setup, and in the interpretation of the results.

The figures below are examples of output from a Monte Carlo code tailored for radiation processing (www.rayxpert.com, 2021). The output can be visualized interactively by mapping grids (see Figs. 23a and 23b) and tabulated results.

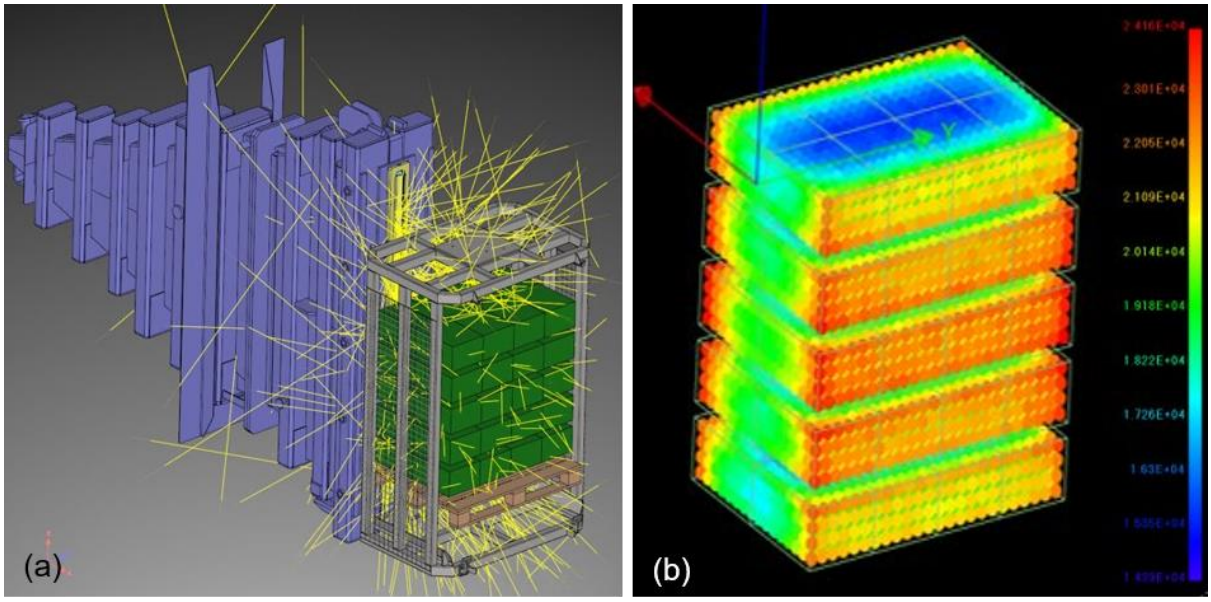

***Figure 23**: (a) Visualisation by RayXpert of an X-ray scanner irradiating a product pallet. (b) Graphic representation by RayXpert of dose distribution in a product pallet.*

With modern computers, the speed of calculations is such that limitations based on the numbers of particle histories followed are far less of a problem now than was the case even ten years ago. Some calculations can be performed (after the initial setup) in just a few minutes, while others might still require a few days to deliver results with statistics appropriate for the situation under investigation.

However, the calculations are still often technically challenging, and care needs to be taken in:

- The choice of the code used (including understanding of that code's own limits)
- Setting up the geometry to be simulated whether this is done in the code itself (which might then need compiling before being run), or whether the geometry is input as a separate file with the information presented as 'cards' or in macros. It should also be considered if materials nearby which might contribute to scattering and absorption, are included in the model.
- Setting up the parameters used in the calculation, including the composition, density, and minimum and maximum energies with which particles are generated and tracked.
- The nature of the source: Is it isotropic? Is it mono-energetic, or is there a broader energy spectrum?
- The nature of the quantities calculated: Dosimetry systems are normally calibrated in terms of dose to water, and this is usually slightly different from the dose to the materials being irradiated (including the materials comprising the dosimeters themselves). In some codes, the quantity output might be, for example, energy in MeV deposited in each region, and this might need to be translated into dose to water in kGy. However, many calculation results can be presented as percentages of a reference dose, so that relative dose and dose distribution are obtained.

Validation

Model calculations should always be verified and validated against measurements in order to be of value to the user. This will give assurance that the desired quantities were calculated without being affected by any errors, necessary compromises in the calculation (simplified geometry and source, for example), or biases caused by, for example, selection of a high value of low-energy cutoff in the tracking which might affect the resulting calculated doses. Validation can also confirm that input parameters were selected correctly.

Validation cannot always be carried out by measurement of the same conditions that were used for the calculation. This can be case when dose is calculated for locations that are not accessible for measurement. Instead, calculation and measurement should be compared using conditions and geometries that can be both calculated and measured, and which are as close as possible to the conditions in question. If agreement is obtained, then it can be concluded that the calculated results are valid, although such conclusions should be made with care.

Complete agreement between measurement and calculation results might not be obtained in several real situations due to inherent uncertainties of both. Analysis of these uncertainties should be carried out to determine if the results agree within the stated uncertainties.

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10 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.

The main contributors to this document are:

Arne Miller, DTU Health Tech, Technical University of Denmark Risø Campus, Roskilde, Denmark

Peter Sharpe, National Physical laboratory, Teddington, Middlesex, TW11 OLW, UK

Mark Bailey, DTU Health Tech, Technical University of Denmark Risø Campus, Roskilde, Denmark

Bart Croonenborghs, Sterigenics, EMEAA, B-3018 Leuven, Belgium

Florent Kuntz, Aérial, 67400 Illkirch, France

Hervé Michel, Radiation Technology EMEA-A, Applied Sterilization Technologies, STERIS

4658 Däniken, Switzerland

David Pymer, Harwell Dosimeters Ltd, Didcot, Oxfordshire OX11 7HP, UK

Enquiries should be addressed to *enquiries@irradiationpanel.org*