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Guide on the use of low energy electron beams for microbiological decontamination of surfaces

October 2013

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Scope

This Guide describes the validation and routine monitoring of microbiological decontamination of surfaces by low energy electron beams (100-200 keV). The Guide is mainly based on experience gained in connection with installation of electron beam systems for surface decontamination of pre-sterilized containers at several aseptic filling lines at pharmaceutical manufacturers. Its main emphasis is on the dosimetric measurements that should be carried out for the validation of the decontamination process and on establishing the appropriate effective dose. Other aspects such as use of measurement uncertainties and formation of radiation induced by-products are also addressed.

Introduction

Low energy electron beams (100-200 keV) are used to decontaminate the external surfaces of pre-sterilized tubs for vials or syringes before they enter an aseptic filling area where the vials or syringes are filled with pharmaceutical products, e.g. vaccines. Such electron beam systems have also been associated with other material transfers into isolators, such as Restricted Access Barrier Systems (RABS) or other Class A environments (Sadat and Huber, 2002). The reason to use low energy electrons for the decontaminating process is that the accelerated electrons should not penetrate into the volume of the tub occupied by the vials or syringes, and therefore no radiolysis products are formed within that volume.

Penetrating, high energy electron beams have been used for decades to sterilize medical devices; this sterilization process is highly regulated in Europe by the Medical Device Directive (1993, 2007) and supported by European adoption of international standards. The intention of this Guide is to provide a common understanding amongst users of low energy electron beams for surface decontamination, manufacturers of associated equipment and regulators with regard to the definition, validation and routine control of the technology.

Guidelines for radiation sterilization of pharmaceutical products are found in “The rules governing medicinal products in the European Union” (Eudralex, 2009) and in PIC/S “Guide to good manufacturing practice for medicinal products” (PIC, 2009). The international standard, ISO 11137-1 (2006), describes the steps needed to develop, validate and monitor a radiation sterilization process for health care products. The validation principles for pharmaceutical product and for medical device sterilization are similar, although not identical; this Guide draws on the principles described in these documents. The medical device standard ISO 11137 is more detailed than the pharmaceutical guidelines, and using this standard as the template for the current Guide offers the possibility of providing comprehensive guidance to the pharmaceutical industry on important elements of the process of surface decontamination by low energy electron beams.

The Guide describes guidance on characterization and validation of the e-beam process, including the establishment of the absorbed dose required for the process. The facility used for the process comprises subsystems that are subject to Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ). The Guide does not cover all aspects of these activities, but addresses specifically the physical, microbiological and dosimetric aspects of the e-beam process characterization (comparable to OQ and PQ).

Throughout this Guide we consider “product” to be pre-sterilized tubs containing sterile syringes or vials to be filled with a pharmaceutical or medicament in a class A environment filling line. It should be appreciated, however, that the principles embodied in this Guide can be applied to low energy electron beam irradiation of a wide range of products.

Typical process

Figure 1. Filling line in a pharmaceutical facility. Tubs are placed on the conveyor to the left, passed through the e-beam isolator in the middle to the filling area to the right.

The Guide uses as an example lidded tubs containing empty syringes or vials, the whole having been sterilized to a sterility assurance level (SAL) of 10^{-6}, typically with ethylene oxide gas, while packaged in sealed bags prior to being delivered to the pharmaceutical facility. Entry into the filling line is typically in a controlled grade C area where the bags are removed before the tubs are placed onto a conveyor that transports them to the filling line. Bag removal can be a manual or it can be an automated process. By removing the sterile barrier – the bag – in a grade C or D area there is risk of the outer surface of the tub becoming microbiologically contaminated and the purpose of the low energy e-beam treatment of the tubs is to inactivate any such contaminating microorganisms.

Figure 1 shows a typical filling line. Filling lines take different configurations, depending on manufacturer and available space in the manufacturing area. Figure 2a shows schematically a filling line layout and Figure 2b shows how pressure differences must be maintained in order to avoid contamination of the filling line. The pressure differences (pressure cascade) also serve to avoid ozone formed by irradiation of air reaching the area downstream of the irradiation zone and the equipment room.

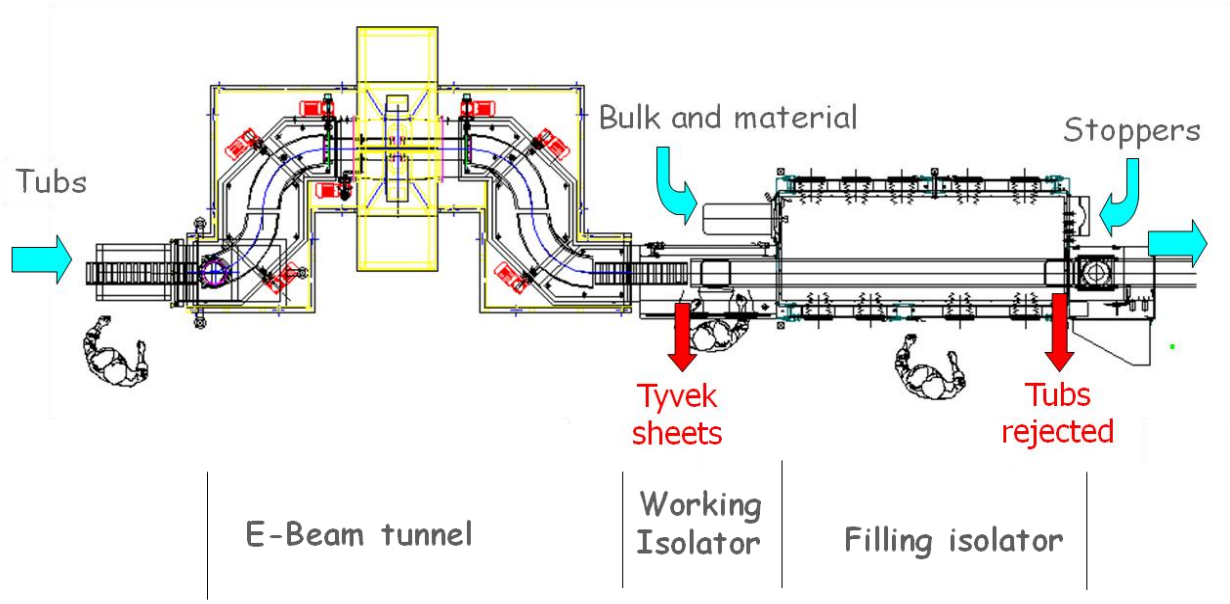

Figure 2a. Schematic of isolator and filling line.

The electron beam (e-beam) system is considered part of the e-beam tunnel (processing equipment) consisting of sub functional groups such as for example electron beam emitters, cooling unit, air handling (exhaust, pressure regulation), conveyor system, debagging, control system, recording, etc.

The low-energy electron accelerators used in the decontamination process use voltages in the range 100 – 200 kV for acceleration of the electrons. Acceleration takes place in vacuum and a thin metal foil – a beam window - separates the vacuum from the atmospheric air. The accelerated electrons penetrate the thin beam window to irradiate the surfaces of the tubs passing the beam on the conveyor. An example of a low energy electron accelerator (called emitter or gun) is shown in Figure 3 and Figure 4 shows how these can be arranged to irradiate product (in this case a tub) from 3 sides, so that the entire surface is irradiated. Because of the low energy of the emitted electrons, they are readily stopped in any material, even in the air between the beam window and the product surface. The accelerated electrons do not behave like a narrow beam. As the electrons penetrate the beam window and air, they are scattered by collision with molecules of these materials, with the effect that a cloud of electrons is formed. This outcome requires careful consideration of particular aspects of dosimetry when the absorbed dose is to be measured, as will be described later.

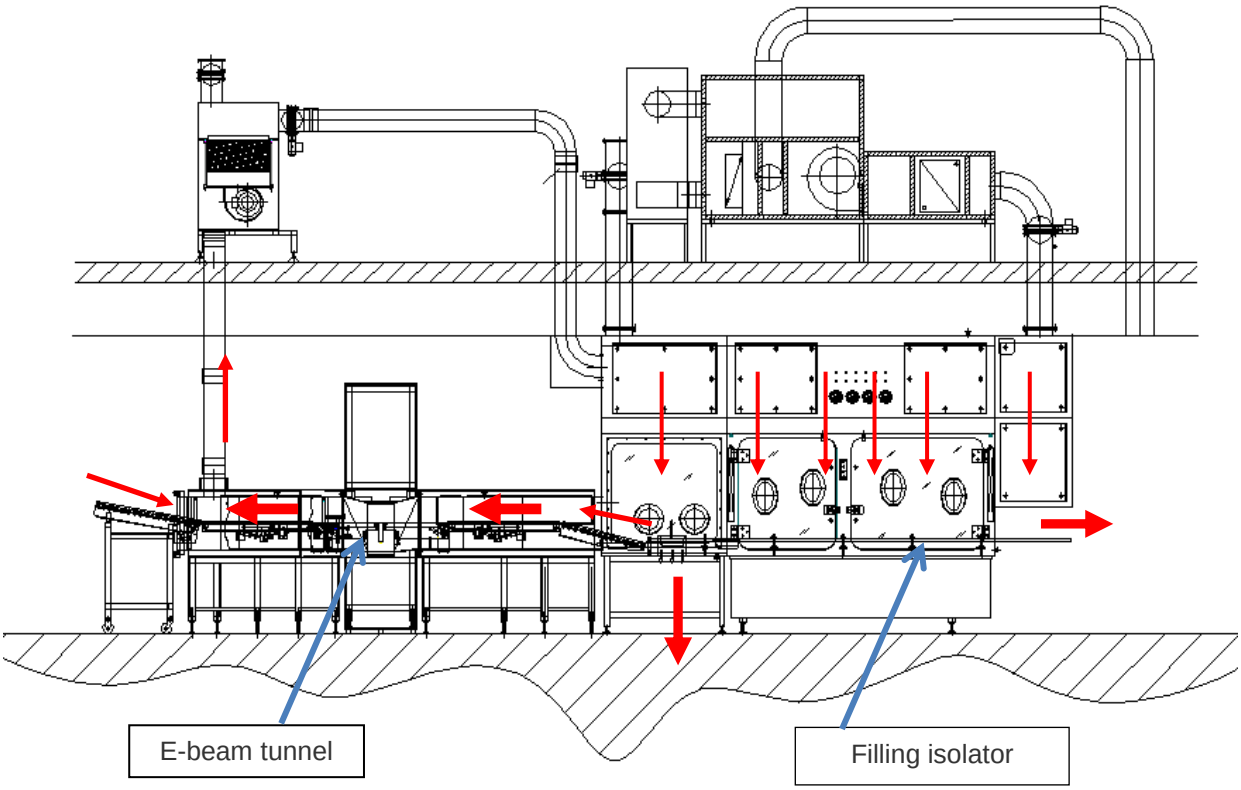

Figure 2b. Schematic of isolator and filler line indicating typical air flow that maintains pressure differences (pressure cascade).

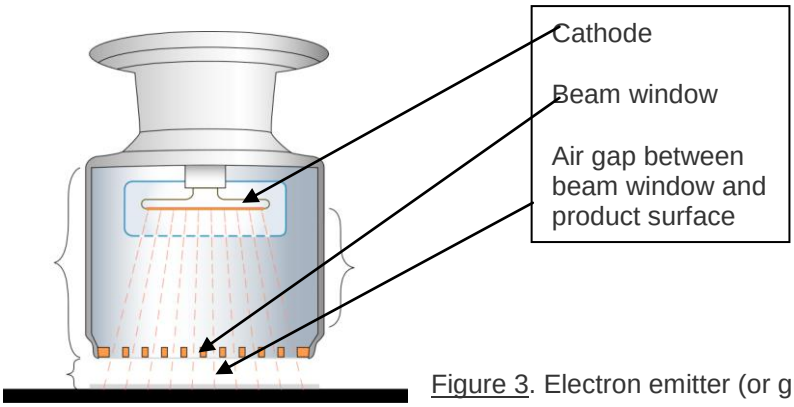

Figure 3. Electron emitter (or gun) unit (Metall and Plastic)

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It should be borne in mind that even if the electrons are stopped readily, stopping leads to formation of penetrating x-rays. The dose provided from the x-rays can be regarded as small when considering the inactivation of microorganisms, but it can be lethal for humans. Therefore, adequate shielding must be provided as part of the electron beam facility in order to prevent any dose to personnel. The shielding is usually provided by lead and tubs are entered through the shielding via a labyrinth or other arrangement that prevents harmful radiation reaching the outside of the isolator. All access doors must be protected by interlocks that prevent operation of the facility if the doors are opened. Radiation protection regulation may differ from country to country, and it must be ensured that the safety aspects of the facility comply with national regulation.

The electron beam must irradiate the entire surface of the tub and it is therefore extended over the tub width. The cathode emitting the electrons can be a point cathode and, in that case, the electron beam is scanned over the width of the tub, or a long cathode can be used that provides a curtain of electrons that covers the tub width.

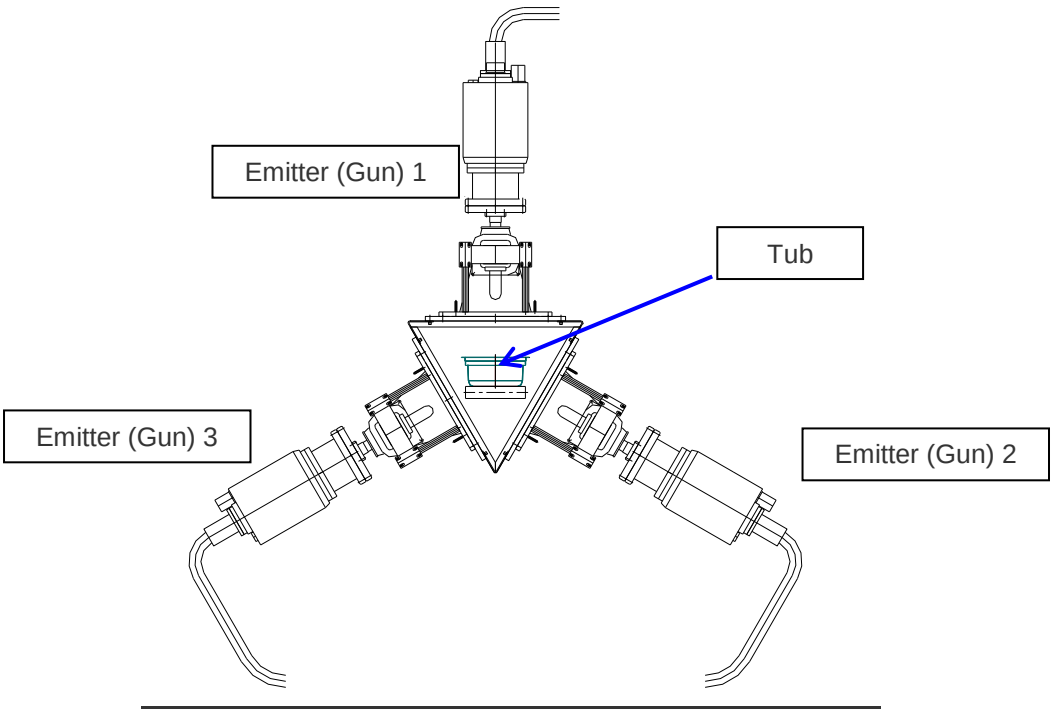

Figure 4a. E-beam system with 3 electron guns (Getinge-Linac)

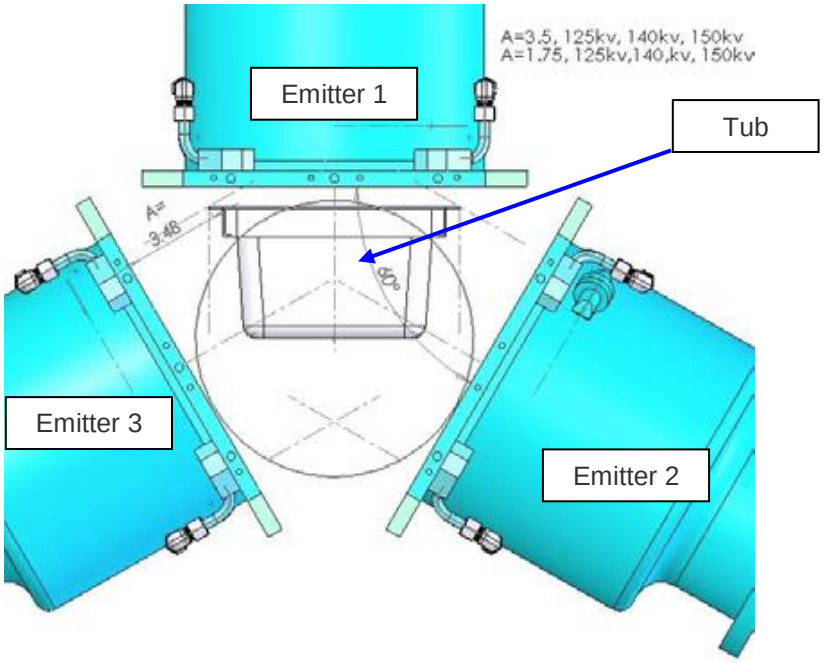

Figure 4b. E-beam system with 3 electron emitters (Metal and Plastic)

Product, process and equipment characterization

Product definition

As a part of the documentation of the low energy electron beam process, the product and its packaging should be described. The description comprises the outer dimensions, the weight, the materials from which the product are made, and the manner in which the product is presented to the irradiation process.

Examples of products are tubs that are shown in Figures 5a and 5b.

Figure 5a. Pre-sterilized tub in its primary packaging.

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Fig. 5b. Open tub with syringes to be filled.

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Process definition

The aim of the irradiation process is to inactivate microorganisms on the outer surfaces of the tub so that contamination of the aseptic filling area by the tub is avoided with a high degree of assurance. At the same time, the properties of the tub material must not be adversely affected by the ionizing radiation. Therefore, a minimum dose that can produce the required degree of decontamination must be established as well as a maximum dose that will not compromise the properties of the materials of the tub or its content.

Establishing of a maximum acceptable dose

When determining a maximum acceptable dose the effects of ionizing radiation on the materials comprising the outer surfaces of the tub must be considered as well as any effects on the materials and products inside the tub.

The physical and chemical properties of polymers are affected by irradiation, and the materials for the tub should be selected so that these irradiation effects are minimized. General information on effects of ionizing radiation on polymer materials can be found in the literature such as AAMI TIR 17 (2009) or Massey (2005), and the manufacturer of the material can often provide test data. Such data might give useful information about radiation effects for the materials used, but testing using the actual irradiation facility might be needed.

The tub itself is usually made from a radiation resistant polymer such as polystyrene that is virtually unaffected by irradiation. The lid, however, is usually made from polyethylene, which might become brittle when irradiated. It might therefore yield particulate contamination if it is torn as it is peeled and removed from the tub in the filling area. One manufacturer of the lid material (Dupont, trade name Tyvek®) indicates that this material has been tested up to 100 kGy for electron beam irradiation (see DuPont data sheet). Unless other data are available, it might therefore be suggested that the maximum acceptable dose for the material of the tub lid (Tyvek®) is 100 kGy.

Another aspect is the peel strength for the lid that might be affected by irradiation as the properties of the sealant used for binding the lid to the tub might be affected. It might be difficult to find published information about this, and the user of the e-beam facility might therefore have to carry out appropriate testing.

Electrons accelerated with voltages up to 200 kV do not penetrate the tub wall, but the tub is usually sealed with a porous material such as Tyvek®, that allows sterilization of the tub and its contents with Ethylene Oxide. The voltage used for acceleration of the electrons can be chosen to limit penetration of electrons through the lid, but Tyvek® has a very inhomogeneous fibrous structure and, in practice, electrons may penetrate some areas while being stopped in others. In order to compensate for the inhomogeneity, a liner (a single or double layer of Tyvek®) is often placed between the lid and the syringes or vials.

In case accelerated electrons do penetrate into the tub volume, then the major effects of irradiation to be considered are formation of gaseous radiolysis product and possibly glass discolouring or irradiation effects on, for example, the properties of rubber stoppers of syringes or vials.
Irradiation of air leads to formation of ozone (O_3), nitric acid (HNO_3), and nitrogen oxides (NO_x) which are highly oxidizing gaseous agents. These gases might affect the properties of the materials that make up the syringes or vials and/or the pharmaceutical product to be filled into the syringes or vials. The amounts of these radiolysis products formed are proportional to absorbed dose and, for a known dose, the amounts formed can generally be calculated. However, with low energy electrons, it is difficult to determine the dose inside tubs making calculation of radiolysis products of the air within tubs problematic. Such radiolysis products are not chemically stable and, normally, they will

decay in minutes. However, it might take only seconds to transfer the tub from the irradiation zone to the filling area and, during this short time, the concentration of radiolysis products might not have changed significantly leaving enough radiolysis products to be harmful to the pharmaceutical product.

Ozone and other radiolysis products are formed in the irradiated air outside the tub and they might penetrate by diffusion through the Tyvek® cover. Under normal process conditions this possibility is remote, because a flow of air is maintained through the tub feed-in tunnel as part of the pressure cascade preventing contamination of the filling area and, moreover, the tubs are moved quickly out of the irradiation zone. However, a process interruption might occur, where the tubs would be stopped in an area with ozone and other radiolysis gasses present. Preventive measures, for example in the form of continued ventilation of the air tunnel, are essential to avoid these gases from affecting the product.

The significance of radiolysis products and the establishment of a maximum acceptable dose within the tub depend on the sensitivity of the pharmaceutical product to the radiolysis products. Not all products are equally sensitive, and validation of the influence of radiolysis products might be needed.

Establishing the dose for an effective decontamination process

The level of potential contamination of the surfaces of tubs is affected by the manner in which the tub is removed from its bag and placed onto the conveyor. In a manual operation in which operators cut open the bag and place the tub on the conveyor, bioburden numbers in the order of 100 cfu per tub have been found (Bachmann and Harper, 2007). In a purely automated process, on the other hand, with no manual involvement, bioburden levels effectively at zero have been found. However, regardless of the initial bioburden obtained in tests, it is necessary to eliminate the possibility of introducing microorganisms into the filling area and therefore a decontamination process is carried out.

For decontamination of material to be introduced into a class A filling area, the concept of log-reduction of the microbiological contaminants is employed. As bacterial spores normally exhibit the greatest resistance towards decontaminating agents such as ionizing radiation, and are generally used as reference microorganisms in decontamination, log reduction is referred to as Spore Log Reduction (SLR) in, for example, FDA (2004). Depending upon the magnitude of the bioburden or the number of bacterial spores found on surfaces prior to the decontamination process or the maximum probability of finding a viable spore after applying the decontamination process, a 4 or a 6 SLR is specified. In this Guide, it is recommended to follow the more conservative FDA recommendation of a 6-log spore reduction, see FDA (2004), appendix 1.

When the required SLR level has been selected, then the absorbed dose required to obtain this level can be set. One rationale for setting the dose can be based on published data for the radiation resistance of standard microbiological preparations, biological indicators (BI), used to assess the effectiveness of radiation sterilization of pharmaceuticals. The commonly used BI microorganism for radiation is *Bacillus pumilus* spores, its resistance to radiation being well characterized.

The radiation resistance of a given microorganism is expressed numerically by its D-10 value, the dose needed to reduce a population of that microorganism to 10% of the initial number. The D-10 value of *B. pumilus* spores irradiated with gamma rays was found to be approximately 1.6 kGy (Tallentire and Khan, 1975), but the value observed will depend on the conditions under which the spores are irradiated. Recent studies involving irradiation at low energy electron accelerators found D-10 values to be 1.8 kGy (Bachmann and Harper, 2007) and 1.58 kGy (Tallentire et al, 2010), respectively.

Taking a D-10 value of 1.8 kGy as a worst case for *B. pumilus* spores for a bioburden having a D-10 value equal to that of *B. pumilus* spores, an SLR of 6 would be obtained at 6 x 1.8 kGy = 10.8 kGy. Since experience of the use of low energy electrons for decontamination is not extensive, it might be reasonable to choose a greater dose than 10.8 kGy for the low energy electron process and, in this Guide, it is suggested to use a treatment dose of at least 15 kGy.

The microbiological contaminants on tubs are likely to be of human origin, and these microorganisms are generally less resistant (have smaller D-10 values) than *B. pumilus* spores. Using a minimum dose of 15 kGy for the decontamination process is therefore likely to lead to a greater log reduction value than 6.

For a given population of microorganisms comprising bioburden on product treated with a particular minimum decontamination dose of radiation, the probability of a microorganism surviving increases with the initial bioburden number. Thus, the probability of introducing microorganisms into the grade A filling area also increases with the initial bioburden number. Therefore, in those circumstances in which bioburden actually occurs, it is essential to determine it in order to assess the desired level of its reduction, and hence the dose required to obtain this goal.

Methods of bioburden determination for medical devices are found in ISO 11737-1 (2006) and these methods might be applied to tubs to be decontaminated by a low energy electron beam process. However, it is not a straightforward exercise to determine the bioburden on the entire outer surface of a tub. It might involve immersion of the whole sealed tub into an eluting liquid, suspension of surface contaminating microorganisms in the liquid, followed by their enumeration. Alternatively, the approach of using a sample item portion (SIP) as described in ISO 11137-2 (2013) might be used to provide the bioburden estimate. A SIP is a selected portion of the product that represents the whole product. If the bioburden is evenly distributed on the product, the SIP may be selected from any portion of the product. That is likely to be the case for pre-sterilized tubs that are un-packed in a grade C or a grade D environment.

The SIP approach assumes that a piece would be cut from the tub, and its bioburden determined. This can be difficult to do in practice and a modified method has been used, namely sampling by contact plate (Rodac) of defined areas of the product (the tub), and using the area of the contact plate as the SIP. It is recognized that this sampling method may not be effective in removing all microorganisms from the test surface, and it requires skilled personnel in order to avoid contamination during the testing. It is therefore important that a thorough validation of the method is carried out.

There are essentially two approaches available for validation of the efficiency of removal of microorganisms from a product (see 11737-2). These are:
- repetitive treatment of the product or,
- inoculation of product with known levels of microorganisms followed by quantitative assessment of the extent of recovery.

One aspect of the validation of the contact plate SIP approach might be carried out by repeating the sampling by contact plate at the same area of the tub, and it is suggested to repeat the sampling at a minimum of 10 tubs in order to gain confidence in the obtained result.

The recommendation of a 6-log spore reduction should not stand alone, but requires that the bioburden of tubs prior to decontamination is low in order to achieve a low probability for introducing microorganisms into the filling area. For a bioburden of 1000 cfu per tub, the probability of finding viable microorganisms on a tub would be equal to or less than 10^{-3} if SLR = 6 has been obtained. This might be judged as an acceptable level for the probability of introducing viable microorganisms into the grade A filling area. In most cases the bioburden is lower than 1000 cfu per tub and hence the probability of introducing viable microorganisms into the filling area would be lower than 10^{-3}.

It is a presumption for a selected minimum dose of 15 kGy to be adequate that the bioburden does not exceed 1000 cfu per tub. The bioburden should therefore be determined at regular intervals, for example quarterly, using 10 tubs for each determination in order to monitor that the number and possibly the composition of the bioburden do not change significantly with time or season. Warning and action limits for the bioburden number should be specified, but the judgment of whether or not significant changes have occurred lies with the competent microbiological laboratory that carries out the testing.

If a minimum dose greater than 15 kGy is selected, e.g. 25 kGy, then the frequency of bioburden determinations might be reduced, because of the greater safety imposed by the greater minimum dose.

Dosimetry

Selection of dosimetry systems

A number of dosimetry systems are commercially available for dose measurement in industrial radiation processes. It is the user's responsibility to select a system that can fulfil the requirements for accurate dose measurement under the special irradiation conditions of the low energy electron beam system and a consideration might be to use more than one system. Dosimeters for dose mapping, for example, may have requirements that are different from dosimeters to be used for routine dose measurements.

General guidance for dosimetry system selection can be found in ASTM 2628, but for dose measurement with low energy electron accelerator systems consideration should particularly be given to

- thickness of the dosimeter,
- dose range,
- reproducibility of the response of the dosimeter,
- ability for in-plant calibration,
- influence on response of temperature and humidity.

Dosimetry system calibration

Dosimetry used in development, characterization and validation of the low energy e-beam process must be traceable to national standards, and calibration of the dosimetry system used for the dose measurements is an essential part of establishing traceability, see ISO/ASTM 51261 (2012) and CIRM 29 (2009). Calibration is normally not provided with purchase of the dosimeters, rather it must be established by the dosimeter user. Calibration is, in principle, a straight forward exercise: The user's dosimeters are irradiated to known doses and the response of the dosimeter is measured employing the user's measurement equipment. A calibration function for the dosimeter system is then established based on the known doses and the measured responses.

The easiest way to irradiate with known doses is to send dosimeters to a calibration laboratory that possesses a calibration irradiation source. This would in most cases be a cobalt-60 gamma cell with a dose rate that is traceable to a national dose standard, for example at National Physical Laboratory, UK, National Institute of Standards and Technology, USA, or a calibration laboratory that is accredited in accordance with EN ISO 17025 (2005). Dosimeters can be irradiated with accurate doses in this way, but the calibration function generated on this basis might not be valid when the dosimeters are used at the user's low energy electron facility.

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The response of many dosimeters depends on environmental influence factors such as temperature, humidity and dose rate (ASTM 2701, 2009) and, if these conditions are different for the calibration irradiation and the process irradiation, then the calibration function might not be valid. Therefore, it is recommended that calibration is carried out under the conditions of use, i.e. by irradiation of the user's dosimeters at the user's facility, together with reference standard dosimeters from a calibration laboratory (ASTM 51261 (2012); CIRM 29 (2009)). Calibration is then established as function of the dosimeter response as it would occur under the conditions of use, against the doses measured by the calibration laboratory.

The effects of influence factor variations (in particular temperature and humidity) are reduced, when the irradiation process is carried out in a controlled environment such as it is normally the case for an aseptic filling line.

It must be recognized that irradiation of many dosimeters with low energy electrons (less than 300 keV) may lead to dose gradients through the thickness of the dosimeter, i.e. the dose at the side of the dosimeter facing the emitted electrons might be different from that at the side distant from the emitted radiation because of limited penetration of the electrons. When the dosimeter is measured, this will lead to an apparent dose that is related to the dose distribution through the thickness of the dosimeter. For a given set of irradiation conditions, the apparent dose will depend on the dosimeter thickness, i.e., different thickness dosimeters will measure different apparent doses. One way to overcome this problem is to specify all dose measurements in the first micrometer of the absorbing material. This is given the symbol D_μ and is independent of dosimeter thickness (Helt-Hansen et.al. 2010). The user's dosimeters would be calibrated in terms of D_μ, as dose measurement for the calibration exercise is carried out by the calibration laboratory that issues the reference standard dosimeters, and this dose is given in terms of D_μ. It is therefore an issue that is dealt with by the calibration laboratory that must be able to give calibration doses in terms of D_μ. The user will not have to do calculations for D_μ if the dosimetry system has been calibrated by this method.

It is recommended practice (ISO ASTM 51261 (2012), CIRM 29 (2009)) that for calibration irradiations over a dose range of less than one decade (factor of ten) to use at least 5 dose points distributed arithmetically (e.g. 10, 20, 30, 40, 50 kGy). For irradiations over more than one decade at least 5 dose points per decade should be used, in this case distributed geometrically (e.g. 1, 1.5, 2.3, 3.4, 5.1, 7.6, 11.4, 17, 26, 38, 58, 87 kGy). Using at least four replicate dosimeters at each dose point is recommended (ISO/ASTM 51261 (2012)).

It has been common practice to establish calibration functions by irradiation of dosimeters at a calibration laboratory as mentioned above and, in some cases this may be a practical approach if the doses required for the calibration are not easily delivered by the user's irradiation facility. Nonetheless, it is necessary to verify that the calibration function established in this way is valid for irradiation at the user's facility. Verification can be accomplished by irradiation at the user's facility of the user's dosimeters together with reference standard dosimeters from a calibration laboratory. The irradiation would typically be carried out at a few doses only, and corrections to the calibration function that was initially established would be made as needed based on the results of the verification.

Calibration of the same batch of dosimeters should be verified at least once a year by irradiation at 3 dose points. A complete calibration should be carried out for a new batch of dosimeters.

It is possible that a repeat calibration or calibration verification leads to results that appear to be different from the previous calibration. A decision on whether two calibrations are different or not can be based on a statistical evaluation of the uncertainties of delivered dose and of the response measurement of the dosimeters.

Calibration of the facility and its instrumentation

All measurement equipment used to monitor and record the operation of the irradiation facility should be qualified and calibrated, including measurement equipment for monitoring of the environment of the facility. This is important in order to show that the facility operates consistently and reproducibly within specified limits.

Uncertainties

Dose measurement results must be accompanied by estimates of their uncertainty. To be complete, the measurement uncertainty includes uncertainties involved in calibration and establishment of traceability, as well as the uncertainties involved in the direct measurement. It is advisable to establish an uncertainty budget, i.e. an analysis of all the individual uncertainty components that contribute to the uncertainty of a given measurement. The uncertainty budget analysis is useful for identification of sources of uncertainty and in particular for identifying those components of uncertainty that could be reduced.

The total uncertainty of dose to product will consist in part on the measurement uncertainty and in part on the variability of the product and of dose delivered by the irradiation facility as given by the following components:

Dosimeter calibration uncertainty	σ_{cal}
Dosimeter reproducibility	σ_{rep}
Dose mapping uncertainty, including product variability	σ_{map}
Irradiation facility (Machine) variability	σ_{mach}

Estimates of the individual components of uncertainty for dose to product can be obtained during calibration of the dosimeters (σ_{cal} and σ_{rep}), during OQ (σ_{mach}) and during PQ (σ_{map}).

These uncertainty components are combined “in quadrature”, i.e. as the square root of the sum of the squares of the individual components, to give the total uncertainty of the measured dose:

$$\sigma_{total} = \sqrt{(\sigma_{cal}^2 + \sigma_{rep}^2 + \sigma_{map}^2 + \sigma_{mach}^2)}$$

An example of an uncertainty budget for dose to product in a low energy electron decontamination process is given in appendix 1a. The established uncertainties can be used to specify acceptance limits for variation of dose to product and for routine monitoring doses to (see appendix 1b).

Validation of the electron beam system.

Design Qualification, DQ

For major installations of new equipment such as a low energy electron accelerator system, it is common practice to begin by defining a Qualification Plan and the User Requirements (URS). During the initial stages of the qualification at least one detailed risk analysis (e.g. FMEA, Failure Mode and Effect Analysis) addressing all e-beam sub systems should be performed which might result in amendment of already existing documents (resolve any discrepancies, fine tune requirements, etc.) and which will affect the test program to be defined for the Installation, Operational and Performance Qualifications. When potential suppliers of equipment have been identified, the equipment functional specifications and facility layout are formally reviewed against the user requirements. This process is generally designated Design Qualification (DQ).

Design Qualification is not described in this Guide. It is considered to be part of the qualification of the overall aseptic filling process.

Installation Qualification, IQ

IQ is carried out to demonstrate that the low energy electron beam equipment and any ancillary items have been supplied and installed in accordance with their specification as described in the User Requirements, and the specifications should be assessed against these requirements. IQ documentation should include verification of all drawings and details of construction materials, equipment interfaces, dimensions and tolerances of the equipment, support services, power supplies and calibration procedures.

In order to verify that the low energy electron accelerator system has been delivered in accordance with specifications, a range of dose measurements may have to be carried out. The measurement activities depend on the purchase agreement between supplier and user, and they would include measurement of the characteristics of the electron beam. Typically, the measurements could be the same as the ones carried out during Operational Qualification (OQ). Understanding the OQ measurement requirements therefore can be the basis for IQ specifications. IQ measurements are not described in detail here, but because IQ and OQ measurements can be the same, it might be a useful approach to let IQ measurements be the first of a repeated series of OQ measurements.

Operational Qualification, OQ

The purpose of OQ is to demonstrate that the electron beam equipment, as installed, is capable of operating and delivering appropriate doses within specified acceptance criteria both with respect to distribution of dose to product and with respect to variability of dose, and a series of dose measurement would be carried out with these purposes in mind. It is necessary to repeat each measurement a sufficient number of times to allow determination of the uncertainty of the measurements. In many cases 3 measurements have been considered “sufficient”, but clearly a higher degree of confidence in the measurement result is obtained by using a greater number of measurements.

OQ dose measurements are usually not carried out using actual product, but rather using a reference product designed to have uniform surfaces facing the low energy electron beams so that dose can be measured reproducibly without effects from the dose gradients caused by the more complex geometry of the surfaces of a tub (see Figure 6 for an example of a reference product).

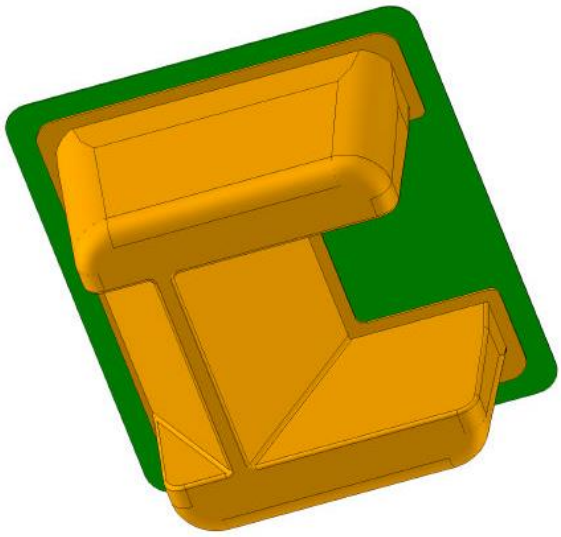

Figure 6. Example of a reference product used at an electron beam isolator for an aseptic filling line

The purpose of OQ dose measurements is to characterize the electron beam facility and they would therefore include measurement of beam width, beam penetration and measurement of dose as function of the key parameters (beam width, beam current and conveyor speed). In addition, the effects of a process interruption should be investigated. OQ dose measurements should be carried out over a range of parameters representing the typical range of operation of the electron beam system. The measurements will depend on electron beam energy and, if different energy levels are to be used for the process, separate measurements should be carried out at each energy level.

Beam width, W_b. The electron beam is made to operate in a wide mode in order to irradiate the product as homogeneously as possible as it passes through the radiation zone. This can be achieved by scanning a small diameter beam over the width of the product or by utilizing extended or multiple cathodes (or emitters) in the electron accelerator. Extended or multiple cathode systems offer possibility for producing a constant beam width profile for the life of the cathode, although changes in emitting efficiency over the length of the cathode might happen with time. Scanning systems, on the other hand, offer the possibility for shaping the beam width profile, but the beam scanning profile depends on the electronic control system of the beam scanner, and it might therefore require additional verification that this system works correctly.

Beam width and beam width profile are measured by placing strips of dosimeter film over the width of the reference product, or by placing individual small dosimeters over the width with a specified distance between the dosimeters. An example of a beam width profile measurement is shown in Figure 7.

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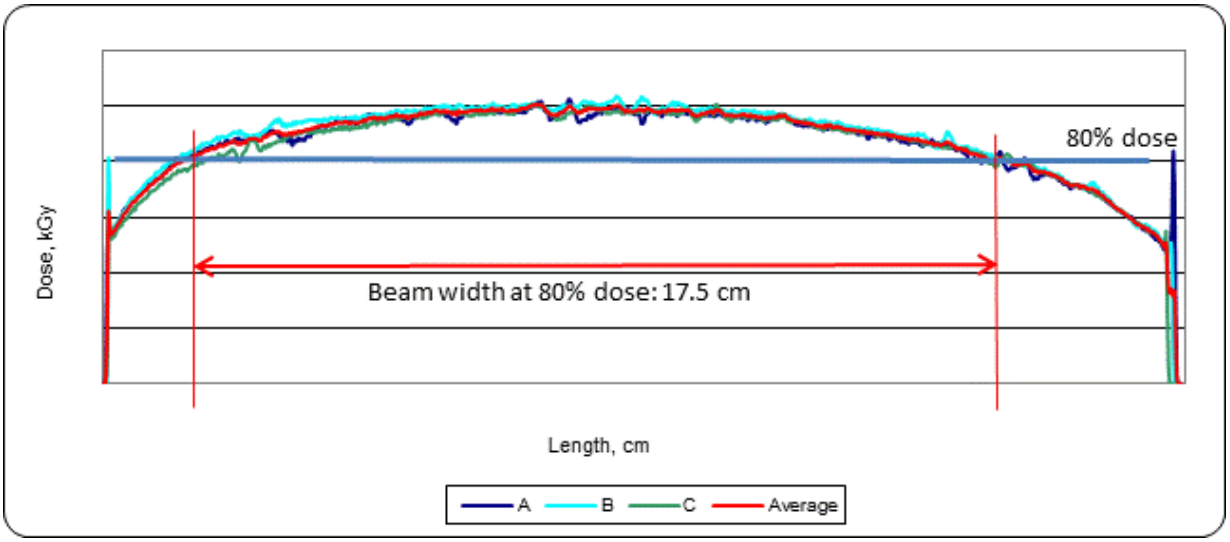

Figure 7.
Example of beam width measurement (3 measurements A-B-C and their average are shown).
Beam width is in this example measured to be 17.5 cm at 80% dose level.

Beam penetration. Penetration of the accelerated electrons into absorbing material depends on the energy of the emitted electrons which, in turn, depends on the acceleration voltage, on the beam window thickness and on the distance between the beam window and the absorbing material. The penetration might even depend on the composition of the gas in the beam zone (which might not be atmospheric air) and on the temperature of the gas.

Beam penetration for low energy electrons can be measured by placing dosimeter films in a stack or by placing dosimeters under increasing layers of thin plastic (see Figure 8a). Examples of measured penetration curves (or depth dose curves) for different accelerating voltages are shown in Fig. 8b.

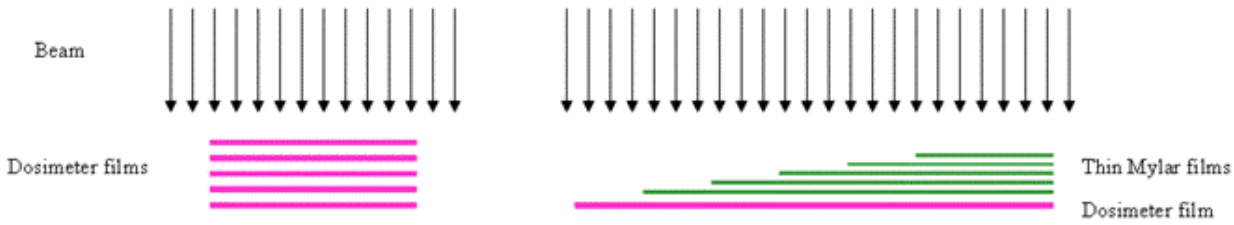

Figure 8a
Methods for measurement of beam penetration.
Left: A stack of thin dosimeter films.
Right: A dosimeter film under increasing layers of thin plastic (Mylar) films.

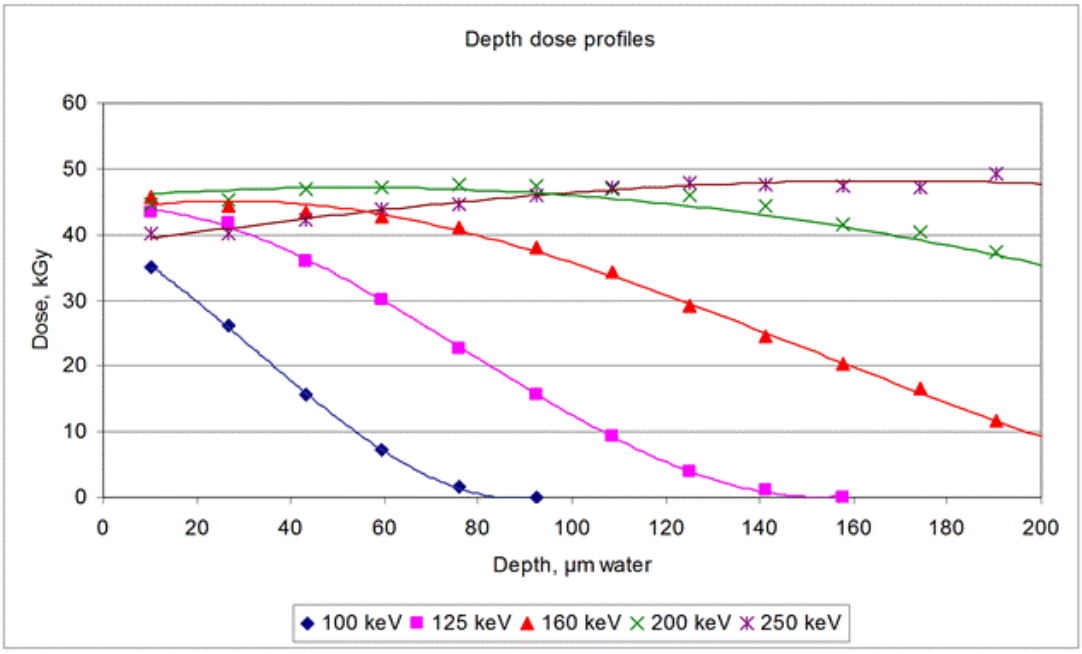

Figure 8b.
Measurements of beam penetration (depth dose) at the same electron accelerator, but at different electron beam energies.

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Dose as function of key parameters. At a given accelerating voltage, the dose delivered by the electron accelerator system depends on 3 key parameters: Beam width W_b, beam current I and conveyor speed V_l. The dose is proportional to current and inversely proportional to beam width and speed, expressed as:

$$\text{Dose} = k * I/(W_b * V_l) \qquad \text{eq. (1)}$$

This simple relationship is represented by a straight line through (0,0), and "k" is then the slope of the line. The relationship in eq. (1) is a calibration of the electron beam system at a given energy, and if different beam energies are used for different products, then it should be calibrated for each energy to be used. In low energy electron beam systems dose can be selected by changing beam current or conveyor speed according to eq. (1), and all dose measurements must always fall on this line – within specified limits. Beam width is usually kept constant in low energy electron beam systems, regardless of whether the beam width is produced by extended or multiple cathodes or by scanning of the beam.

An example of dose measured as function of the three key parameters is given in Figure 9.

It should be mentioned that "dose" in this context must be measured at fixed locations on product or reference product. The selected locations should exhibit minimal dose gradients in order to ensure reproducibility of the measured dose. This is often best obtained using a reference product.

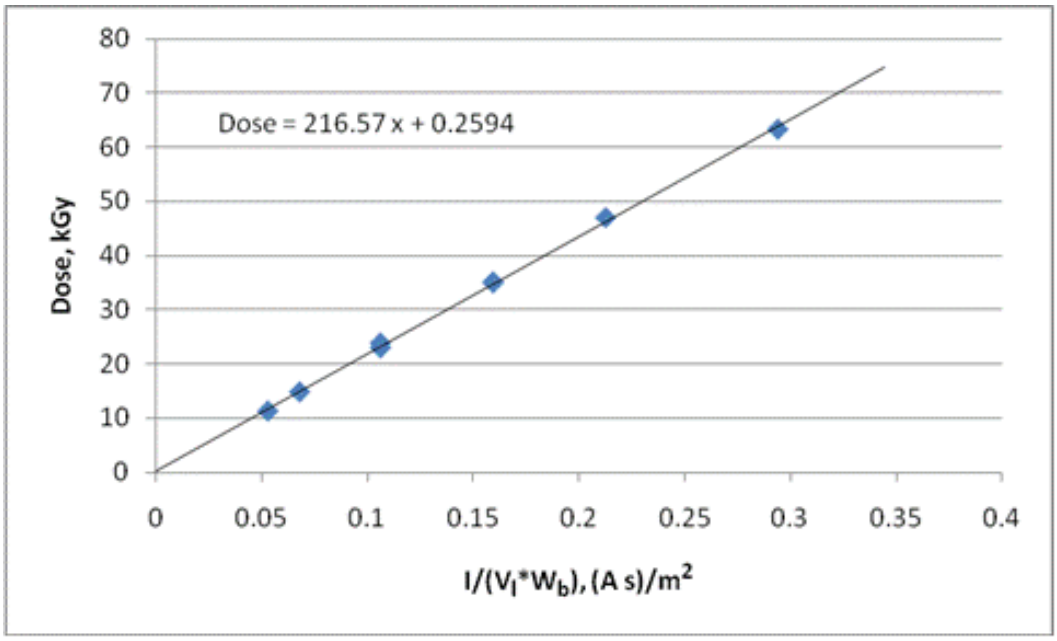

Figure 9
Example of measurement of dose as function of beam current I, conveying speed V_l and beam width W_b.
Measured at an electron accelerator with beam energy 110 keV.

$$k = 216.57\ (\text{kGy} * \text{m}^2) / (\text{A} * \text{s})$$

Note: Small deviations from the straight line passing at (0,0) is often seen in practice.

Process interruption. The electron beam process may be stopped for a variety of reasons. A number of parameters are monitored and, if any of these fall outside specified limits, the process may be designed to stop by automatically switching off the beam current(s). The system is normally designed to stop the conveyor if the beam currents stop (and vice versa). With high-energy systems for medical device sterilization, it is often possible to re-start the beam without product being affected, but, with low energy systems that are integrated parts of an aseptic filling system, this is normally not the case and product must be discarded if a process interruption occurs while a tub is in the irradiation zone. It is necessary to demonstrate during OQ that this will indeed happen in case of a process interruption and that affected tubs can be identified.

Irradiation process interruptions may be planned. This can be the case if, for example, the filling process is interrupted, and tubs with syringes or vials should under these circumstances be prevented from entering the filling area. The electron beam process is stopped so that tubs are not irradiated during the waiting time until the filling process is resumed.

A special case of “process interruption” might occur because of sparks in the high voltage system. Sparks can occur in the power supply, in the high voltage cable and connectors or in the accelerator itself. During the spark condition the high voltage may be reduced to zero and no electrons are accelerated. The spark condition might only last for a fraction of a second, but its effect on dose to product is very difficult to measure, because nobody wants to force a spark! However, the effects of sparks on dose to product should be considered during OQ, and if the effect is judged to be significant, it might lead to tubs being discarded if sparks occur during their irradiation.

For multiple beam systems, such as those used for decontamination of tubs, OQ measurements must be carried out for each beam. This would normally be done with all electron accelerators operating simultaneously, but it could also be done for each electron accelerator operating individually.

Details of the measurements to be considered during OQ are givenabove. Further guidance can be found in ISO ASTM 51818 (2012).

Other aspects of the OQ testing program- include, but are not limited to

- verification of the pressure cascade between the relevant equipment parts of a filling line
- air flow visualization (smoke studies)
- functional testing and alarm testing as well as integrity testing (filter and e-beam),
- verification of safety control
- operator panel testing

These OQ aspects are not covered in this Guide.

In order to demonstrate consistent operation of the facility, the OQ dose and dose distribution measurements should be repeated at intervals specified by the operator of the facility, and when changes are made that might affect dose or dose distribution. The intervals for repeat OQ should be chosen to provide assurance that the facility is consistently operating within specifications.

Repeat of OQ dose measurements is typically carried out on an annual cycle, but specific parts of the repeat of OQ might be carried out at shorter time intervals within this cycle.

Activities that might affect the OQ status of the irradiation facility include, but are not limited to

- replacement of accelerator window,
- replacement of window support grid,
- replacement of conveyor parts,
- change in accelerator energy,
- change in distance of accelerator window to product surface.

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The most common cause for repeating OQ, or parts thereof, is the replacement of a complete accelerator unit, also called the emitter unit. Electron accelerators for use in aseptic filling lines are usually made as integrated units that require replacement of the complete unit in case of failure of a sub-component such as cathode or window. It is important to be able to demonstrate that the new unit can deliver the same dose and dose distribution as the unit being replaced, and that the OQ status of the facility has not changed. This might require, for example, that the beam current of the new unit is adjusted to deliver the same dose, and a measurement procedure for this purpose must be in place. Appendix 2 gives a suggested procedure to be followed in case of accelerator unit replacement.

If repeat of OQ dose measurements show that the OQ status of the irradiator has changed, then Performance Qualification (PQ) should be repeated.
In most cases one voltage only is used for each electron accelerator in these facilities. However, if different voltages are used, then separate OQ measurements must be carried out for each voltage.

Performance Qualification, PQ

PQ concerns measurement of dose to product and the establishment of the facility parameters that will allow the product to be irradiated with at least the dose required for decontamination while not exceeding the maximum acceptable dose for product. The locations and magnitudes of minimum and maximum doses should be determined, the dose at a routine monitoring position should be measured, and the ratio between the measured minimum and maximum doses and the dose at a routine monitoring position(s) should be established. Having established these relationships allows prediction of the minimum and maximum doses during processing, when only the dose at the routine monitoring position is measured.

ISO 11137-3 (2006) and ASTM 2303 (2011) provide general guidance on dose mapping, but it is no simple matter to carry out dose mapping of a tub that is irradiated by low energy electrons. The complex geometry of the outer surface of the tub coupled with the low energy of the electrons leads to strong dose gradients that can occur over very short distances. For PQ dose mapping, thin film dosimeters have to be used that can be placed at all critical locations on the surface, bearing in mind that the low energy electrons are stopped readily, so even a thin layer of plastic acts as a shield for the radiation.

Figure 10

Example of dose map dosimeters on a tub after irradiation.

It is not possible to place dosimeters all over the outer surface of the tub, and instead locations for placing dosimeters must be selected so that it is likely that minimum and maximum doses are found and measured. Personnel that carry out this dose mapping task must have the necessary competence to make qualified decisions about placing dosimeters and about choosing dosimeter systems that are suitable for the task. Some commercially available dosimeters might be prepared in sealed pouches in order to protect them against ultraviolet light and to minimize influence from changes in relative humidity. The packaging may prevent dosimeters from being placed in critical locations and it is therefore recommended to use thin film dosimeters without protective packaging that can be placed at all selected locations. Figure 10 shows an example of thin film dosimeters placed on a tub for dose mapping. It might be added that the packaging material of dosimeters in many cases would effectively stop the low energy electron beam and thus render a packaged dosimeter useless for measurement under these conditions.

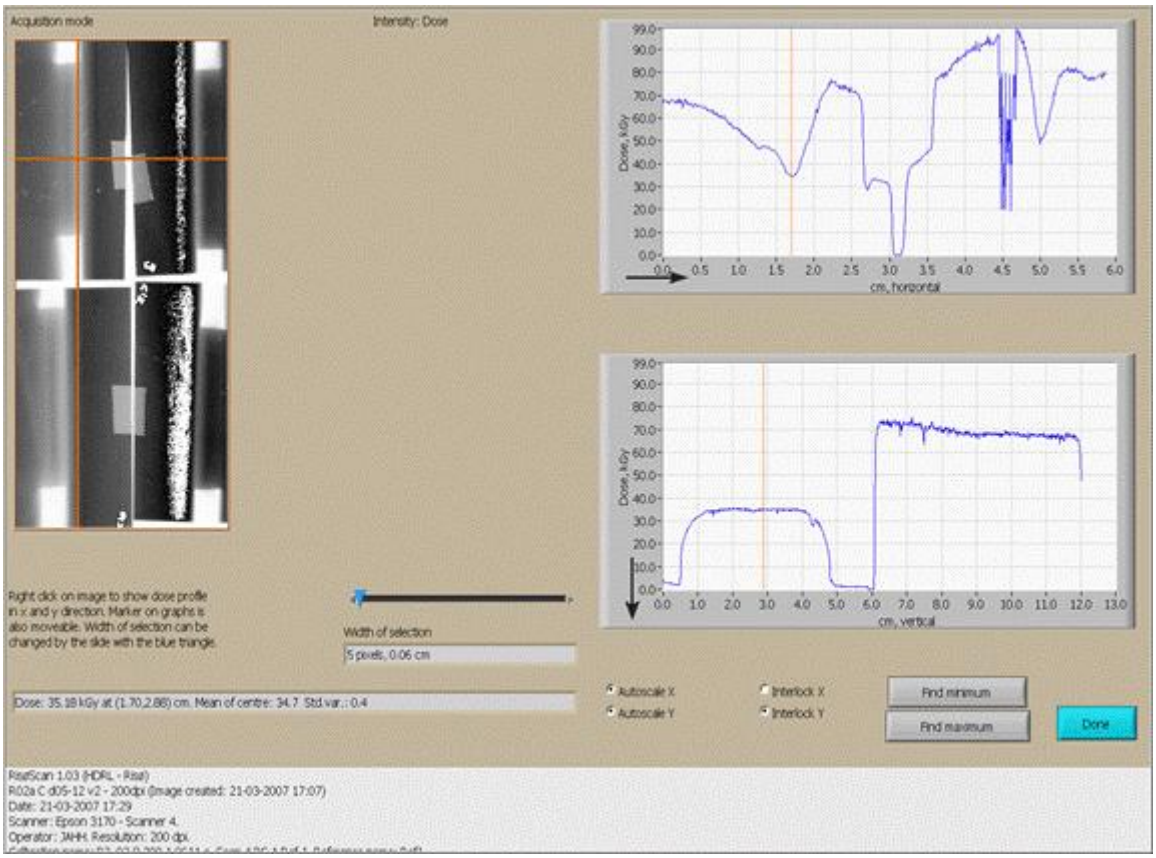

Figure 11. Example of dose map measurement. Four dosimeters films are shown on the image. Measurement of minimum dose is shown for dosimeter 1.

Measurement 1: Dose along horizontal axis on image
Measurement 2: Dose along vertical axis on image
Two white areas on the dosimeter films are caused by holders for the dosimeter film

The dosimeter measurement system must be capable of resolving the dose gradients detected by the dosimeter. Dose measurements made, for example, using a standard spectrophotometer that measures only at a single point of a dosimeter are not likely to measure the dose extremes correctly. Scanning measurement systems, on the other hand, improve the possibility for detecting the real minimum and maximum doses on a sheet of dosimeter film. Figure 11 shows an example of dose measurement using a scanning system.

In addition to measurement of dose on the outer surface of the tub, the dose under the Tyvek® lid and liner should be measured. The accelerating voltage may in some cases be chosen so that effectively no dose can be measured under the Tyvek® liner, but because of the inhomogeneous nature of Tyvek® it cannot be predicted whether dose occurs locally under the Tyvek®. Dose gradients might be observed that vary over short distances. Therefore sheets of thin film dosimeters and a scanning measurement system are useful for this type of measurement (see Figure 12 for a measurement example).

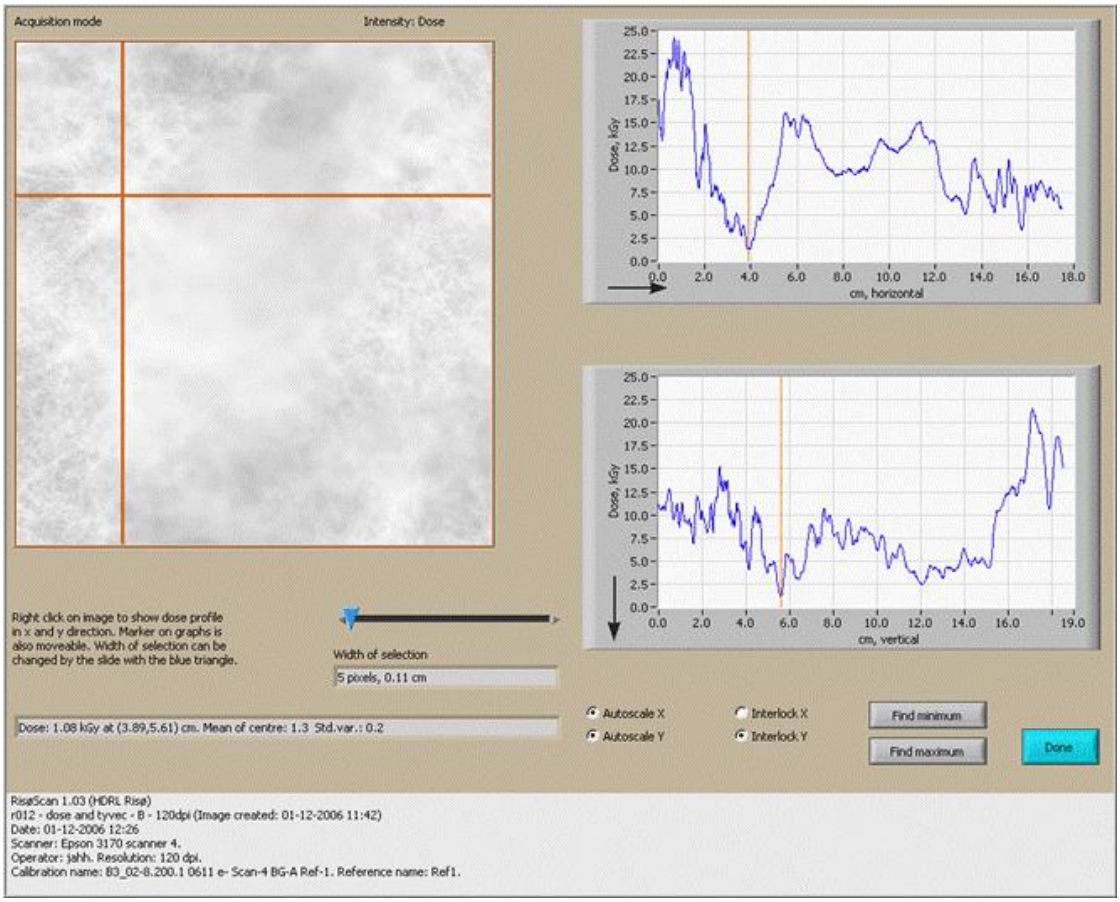

Figure 12.
Example of dose measurement under Tyvek®.
The inhomogeneous nature of Tyvek® gives rise to an uneven dose distribution.

During the dose mapping exercise, the positions where routine monitoring of dose can take place are identified. These positions should be easily accessible and should be selected to be at areas with no or only minimal dose gradients. The relationship between minimum dose, maximum dose and the dose at the routine monitoring position is determined during the dose mapping exercise. Therefore, during processing, measurement of the dose at the routine monitoring position can be used to predict the minimum and maximum dose to the product.

For e-beam systems with multiple electron accelerators, positions for routine dose monitoring must be selected so that the performance of each accelerator can be monitored. Thus, for systems with 3 e-beams, 3 routine monitoring positions are selected either at normal tubs or at reference tubs. The use of reference tubs for routine dose measurement has the advantage that these can be designed to exhibit less dose gradients than usually found on real tubs.

The PQ dose mapping measurements should be repeated a sufficient number of times to allow determination of measurement uncertainty of dose to product and of dose at routine monitoring positions. The same consideration concerning “sufficient” that was discussed under OQ applies here. In many cases 3 measurements have been considered “sufficient”, but a higher degree of confidence in the determination of uncertainty is obtained by using a greater number of measurements. Based on the measured uncertainties, acceptable limits for variation of the routine dose can be determined that will ensure that the minimum dose on the tub exceeds the selected required minimum dose with a specified level of confidence.

Repeat of PQ dose mapping should be considered if product is changed in a manner that might affect dose or dose distribution on the tub, or if the OQ status of the irradiation facility is changed.

Process specification

A process specification should be established for the irradiation process and includes description of the product, mode of loading onto the conveying system, maximum acceptable dose, decontamination dose, position of routine monitoring dosimeters and key operating parameters for each electron accelerator of the facility: accelerating voltage, beam current, beam width, conveyor speed, and routine dose that are required in order for the irradiation process to deliver the specified minimum dose to the product surface without exceeding the acceptable maximum dose.

The process specification should take into account the uncertainty of dose to product, so that the average minimum dose exceeds the required minimum dose at a specified “safety level”. This “safety level” might be selected at 2 standard deviations, corresponding to approximately 97.5% confidence that the required minimum dose to product is always exceeded at all locations at the outer surface of the tub. Appendix 1 gives an example of calculation of limits of routine doses based on an established uncertainty budget and on doses measured during PQ dose mapping.

Routine dosimetry

It is recommended in ISO 11137-3 to measure dose at a routine monitoring position at the beginning and end of a product batch being irradiated, and at suitable intervals for large batches. The frequency of dose measurement should take into account the risk associated with dose measurements exceeding specified limits, and the possible need consequently having to discard or recall product.

It might be thought desirable to measure the dose for each product (tub) for the low energy electron beam decontamination process but, in practice, this is not possible. The dosimeters have not been sterilized prior to use, and they might introduce microbial contamination into the filling area. If dosimeters were placed on the tub surface, they might shield areas of the tub under the dosimeter from the required radiation. Furthermore, using a reference tub for routine dose measurements will introduce un-sterile components into the filling area. The routine dose measurement would therefore normally be carried out at the beginning of a production batch prior to a vapourized hydrogen peroxide (VHP) cleaning cycle of the filling area with the first measurement of a batch being considered as the last measurement in the previous batch for multiple batches; this means that the interval between dose measurements can be large. Consideration should be given to the risk and consequence of having product irradiated with doses outside specifications, if a routine dose measurement gives results outside specifications. Such consideration might lead to choosing a greater safety level than 97.5% as mentioned above.

It is advantageous to plot measured routine monitoring doses in a process control chart in order to monitor how the facility is operating, and to observe possible trends. It is recommended to set warning limits for the measured routine dose, for example at 2.5 standard deviations and to select 3.5 standard deviations as action limit, see report by Panel on Gamma and Electron Irradiation (Panel 2006).

Routine monitoring of process parameters

For routine doses monitored at relatively large intervals as indicated above, it is important that the key process parameters (i.e. beam current, accelerating voltage, beam width, conveyor speed) are

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monitored and recorded continuously during processing, or at intervals as specified by the operator. These intervals should be chosen to provide assurance that the irradiation facility is consistently operating within specifications. In this context it should be borne in mind that beam energy, beam current and beam width are usually not measured directly, but as derived parameters and understanding the relationship between monitored values and the actual parameters is important.

Warning and action limits should be specified for each parameter in order to ensure that all products are irradiated within specified limits. It is recommended that the same considerations are used for setting these limits as for setting the limits for the routine monitoring dose.

Maintaining process effectiveness

Maintenance

General maintenance responsibilities should be described as part of the quality management system.

Calibration – including dosimetry

Requirements for instrumentation and dosimetry calibration and frequency of recalibration should be described as part of the quality management system in order to maintain measurement traceability.

Requalification

Requalification (OQ) of the low energy electron beam equipment should be carried out at specified intervals in order to demonstrate that the facility operates consistently within specified limits.

Assessment of change

Any change in the irradiator which could affect dose or dose distribution should be assessed, and possible repeat of IQ, OQ and PQ should be considered. Changing of operating characteristics of emitter or replacement of an emitter might be considered as such a change, and procedures should be in place in order to provide assurance that the facility continues to operate within specifications after an emitter change. Typically, a complete OQ might be carried out, but it is possible to set up procedures that include only part of a complete OQ.

A change in product, its package or the presentation of product to the electron beam process should be assessed for its effect on the appropriateness of the process.

Microbiology

Monitoring of the bioburden of product should be carried out at a frequency specified by the user (the primary manufacturer) who should specify a bioburden limit. It is suggested in this Guide that the limit might be set at 1000 cfu per tub.

Appendix 1a Example of uncertainty budget for dose to product

Numbers are used as examples only. The actual values should be developed for individual facilities.
In this example, two separate dosimetry systems are used for measurement of minimum dose and routine dose, respectively.

Measurement of minimum dose D_{min}		%	
Calibration of dosimeter	σ_{cal1}	7.2	
Measurement reproducibility of D_{min}	σ_{map}	7.1	
Measurement of routine dose D_R			
Calibration of dosimeter	σ_{cal2}	6.0	
Measurement reproducibility of D_R	σ_{rep}	4.3	
Overall uncertainty of dose to product	σ_{total}		12.5

σ_{map} represents combined effect of dosimeter reproducibility and product variability

σ_{cal1} and σ_{cal2} are calibration uncertainties of the two dosimetry systens, respectively

During the decontamination process, the dose delivered by the irradiation facility might vary.
The variation is caused by variation of the parameters below.
The limits of the variability of these parameters are known.
Their standard deviations are taken as the limit value divided by SQRT(3) (GUM, 1995, 2008)

Facility variability			
	Limits, %	s.d., %	
Energy	5	2.9	
Beam current	5	2.9	
Conveyor speed	3	1.7	
Beam width	3	1.7	
Total facility variability		σ_{mach}	4.8

Reproducibility of routine dose during process		%	
Facility variation	σ_{mach}	4.8	
Measurement reproducibility of D_R	σ_{rep}	4.3	
	σ_{exp}		6.4

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Appendix 1b

Accept limits for routine dose measurements

Example based on average routine doses D_R measured for emitters 1, 2 and 3 during PQ dose mapping

Selected accept limit, st. dev. 2.5

	D_R(ave) kGy	Reproducibilty σ_{exp} %	Limits Upper kGy	Limits Lower kGy
Emitter 1	57.0	6.4	66.1	47.9
Emitter 2	90.9	6.4	105.5	76.3
Emitter 3	88.9	6.4	103.2	74.6

$D_R(lower) = D_R(ave)*(1 - k * \sigma_{exp}/100)$

$D_R(upper) = D_R(ave)*(1 + k * \sigma_{exp}/100)$

Assurance that required dose is exceeded

D_{min} (lower limit)	kGy	15
D_{min}(ave) measured during PQ	kGy	23.7
σ_{total}	%	12.5
z =		2.9

$z = (1 - D_{min}(lower\ limit)/(D_{min}(ave))/\sigma_{total}*100$

"z" is a measure for the degree of assurance that the 15 kGy limit will be exceeded when the routine doses are maintained at the levels specified above (Luko, 2011).

For z = 2 there is approximately 97.5% probability that the minimum dose will exceed the 15 kGy limit.

For z = 3 there is approximately 99.5% probability that the minimum dose will exceed the 15 kGy limit.

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Appendix 2 – Replacement of Emitter (Gun)

This appendix describes suggested actions to be taken when emitters (or guns) are replaced in the electron accelerator equipment of an isolator for aseptic filling of vials or syringes.

The appendix is based on the assumption that baseline data for the complete facility and for each emitter were generated during Operational Qualification (OQ).
The emitters that were installed during OQ are considered as references, and all emitters installed later are compared against these OQ reference emitters.

k-value

During OQ, measurements of routine dose (D_R) as a function of the equipment parameters that are known to influence dose, namely conveyor speed V_I, beam current I and beam width W_b were made for each emitter. Beam energy will also influence dose, but energy is considered constant.

Plots of routine dose D_R as function of beam current I divided by conveyor speed V_I and beam width W_b should be a straight line that passes through the origin (0,0):

$$D = k \times (I/V_I * W_b)$$

k is the slope of the straight line.

Beam width

Beam width profiles were measured during OQ for the individual emitters by dosimeters placed on the surfaces of the reference product. The surfaces of the reference product do not cover the complete width of the beams, and a measure of the full beam width cannot be obtained during OQ. However, the measured profiles should be reproducible when repeated measurements are carried out.

Emitter replacement

It is assumed that the same emitters were installed for OQ and for PQ.

During PQ the average routine doses required $\mathbf{D_{req}}$ for each emitter that assure the necessary minimum dose to the product was determined. Uncertainty and acceptable limits for variation of the routine doses were also determined. The required routine doses were determined with all three emitters operating simultaneously.

When an emitter is replaced, the routine dose delivered by the new emitter must be the same as the routine dose delivered by the emitter used during OQ-PQ. In that way it is assured that the necessary minimum dose to the product is maintained.

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Suggested procedure when an emitter (Gun) is replaced:

Routine dose

1. Set the beam current of the new emitter to the same value I_{OQ} as the one used for the reference OQ emitter. Set the beam currents of the two other emitters at the values used prior to the emitter replacement.

2. Maintain the conveyor speed at the value used prior to the emitter replacement.

3. Irradiate routine dosimeters placed at the normal routine dosimeter positions with all three emitters operating.

4. Measure the dosimeters using the normal measurement procedures.

5. Accept the measured dose $\mathbf{D_{meas}}$ for the new emitter if it deviates less than one standard deviation of $\mathbf{D_{meas}}$ from $\mathbf{D_{req}}$.

6. If the measured dose $\mathbf{D_{meas}}$ for the new emitter deviates more than one standard deviation of $\mathbf{D_{meas}}$ from $\mathbf{D_{req}}$, then the beam current for the new emitter should be adjusted in accordance with:

   $I_{new} = (D_{req}/D_{meas}) \times I_{OQ}$

7. Re-measure the routine dose in order to verify that the change of beam current was effective.

Beam width profile

8. Set the beam current of the new emitter and the conveyor speed to the same values that were used during OQ for measurement of beam width. Set the beam currents of the two other emitters at the values used prior to the emitter replacement.

9. Place dosimeters at the same positions on the reference product as was used for measurement of beam width profile during OQ.

10. Irradiate the reference product with all three emitters operating.

11. Measure the dosimeters using the normal measurement procedures and compare the beam width profile with the beam profile measured during OQ.

12. Accept the result if the measured doses of the beam width profile deviates less than 1 standard deviation from the doses of the beam profile measured during OQ.

13. If the measured doses of the beam width profile deviates more than 1 standard deviation from the doses of the profile measured during OQ, then a repeat of PQ must be considered. In order to judge if a repeat PQ is needed, the degree of safety of obtaining the required irradiation process should be taken into account.

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Appendix 3 – Glossary of Terms

Bioburden	population of viable microorganisms on or in product and/or a sterile barrier system
Biological indicator	test system containing viable microorganisms providing a defined resistance to a specified sterilization process
D value / D10 value	time or radiation dose required to achieve inactivation of 90% of a population of the test microorganism under stated conditions
Dosimeter	device having a reproducible, measurable response to radiation that can be used to measure the absorbed dose in a given system
Dosimetry system	interrelated elements used for determining absorbed dose, including dosimeters, instruments, associated reference standards and procedures for their use
Reference standard dosimetry system	dosimetry system, generally having the highest metrological quality available at a given location or in a given organization, from which measurements made there are derived.
Requalification	repetition of part of validation for the purpose of confirming the continued acceptability of a specified process
SAL	Sterility Assurance Level probability of a single viable microorganism occurring on an item after sterilization
SLR	Spore Log Reduction
Uncertainty budget	statement of a measurement uncertainty, of the components of that measurement uncertainty, and of their calculation and combination.

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