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Technical Information Report

AAMI TIR29:2002

Guide for process control in radiation sterilization

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AAMI Association for the Advancement of Medical Instrumentation

Guide for process control in radiation sterilization

Approved 16 July 2002 by
Association for the Advancement of Medical Instrumentation

Abstract: This technical information report provides additional guidance for establishing and meeting the irradiator dose mapping, process qualification, and routine control requirements for radiation sterilization as defined in ANSI/AAMI/ISO 11137 for gamma and electron beam sterilization. Although bremsstrahlung irradiation has similar requirements, there is little experience in the design and operation of a bremsstrahlung irradiation facility at the time of this work was initiated, and therefore the requirements for bremsstrahlung irradiation are not included in the scope.

Keywords: irradiator dose mapping, process qualification, routine processing, irradiator validation

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Introduction

This TIR addresses process control in gamma and electron beam irradiators. A critical element in the radiation sterilization process is the dose delivered to product. Processing parameters should be established and then applied by using process control methods to ensure that the dose is obtained in a reliable, accurate, and reproducible manner. This TIR provides guidance on the establishment of processing parameters that include irradiator dose mapping, process qualification, routine processing, and maintenance of validation. Methods of process control may be different depending on the type of radiation technology employed. For this reason, guidance on process control in gamma and electron beam irradiators is treated separately in this document.

For gamma sterilization, the reliability and consistency are ensured by the well-known decay rate of the radionuclide, usually cobalt-60. By ensuring the correct positioning of source and product, and making small, incremental changes in the timer setting to account for the source decay, products can be processed consistently to achieve the same dose. If all product is identical, the only differences in measured dose will be that caused by variability in positioning of product and in uncertainties in dose measurements.

There are several different classes of gamma irradiators. In batch irradiators that only process a single product at a time, the preceding conditions are closely achieved. In multi-pass irradiators that irradiate different products on a continuous basis, changes in intervening products between the source and individual containers can affect dose delivery. The effects of intervening products on dosing conditions should be taken into account when scheduling products and process control.

For electron beam sterilization, the reliability and consistency of the process are ensured by control and monitoring of beam, conveyor, and processing parameters. Once these parameters are established, products processed using the specified parameters will receive the specified doses as long as the product density, characteristics of product packaging, and product orientation are unchanged. With electron beam sterilization, the change from one product to another is relatively simple since the effects of adjacent product are minimal.

Data for determining required processing parameters for both gamma and electron beam sterilization are obtained from dose mapping studies performed during the installation qualification of the irradiator or during process qualification. Data from routine dosimetry may be analyzed using standard statistical process control techniques, and the results used to monitor and maintain control of the process. In addition, calculations using mathematical modeling may be used to estimate dose distributions and effects of varying product densities and distributions. Results of dose calculations can complement experimental measurements of dose to provide a more complete description of the operational characteristics of an irradiator. A properly administered program for process control helps ensure that dose is consistently and accurately delivered to products, which allows for dosimetric release and offers the possibility for parametric release of product.

Suggestions for improving this Recommended Practice are invited. Comments and suggested revisions should be sent to Technical Programs, AAMI, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-5762.

NOTE—This foreword does not contain provisions of AAMI TIR29:2002, *Guide for process control in radiation sterilization*, but it does provide important information about the development and intended use of the document.

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Guide for process control in radiation sterilization

1 Scope

This technical information report (TIR) provides additional guidance for establishing and meeting the irradiator dose mapping, process qualification, and routine control requirements for radiation sterilization as defined in ANSI/AAMI/ISO 11137 for gamma and electron beam sterilization. Although bremsstrahlung irradiation has similar requirements, there was little experience in the design and operation of a bremsstrahlung irradiation facility at the time of the writing of this TIR, and therefore the requirements for bremsstrahlung irradiation are not addressed in this TIR.

NOTE—This TIR is intended to be used in conjunction with ANSI/AAMI/ISO 11137:1994, *Sterilization of health care products—Requirements for validation and routine control—Radiation sterilization*. Since a TIR is considered "informative" and is not subject to the same formal approval process as a standard, the process steps are described in the TIR as "should" rather than "shall." Readers are reminded that many of this TIR's "shoulds" are "shalls" in ANSI/AAMI/ISO 11137:1994.

2 Normative reference

The following normative document contains provisions that, through reference in this text, constitute provisions of this TIR. Subsequent amendments to or revisions of this publication do not apply. However, parties to agreements based on this TIR are encouraged to investigate the possibility of applying the most recent edition. The Association for the Advancement of Medical Instrumentation maintains a register of currently valid International Standards.

ANSI/AAMI/ISO 11137:1994, *Sterilization of health care products—Requirements for validation and routine control—Radiation sterilization*.

3 Terms and definitions

For the purposes of this TIR, the following terms and definitions apply.

3.1 base cycle time: Cycle time selected for processing groups of products.

3.2 center loading: Method of loading the irradiation container in a manner that centers the product in the irradiation container.

3.3 compensating dummy: Simulated product used during routine production runs in process loads that contain less product than specified in the loading pattern or simulated product used at the beginning or end of a production run to compensate for absence of product.

3.4 dose zone: Volume within an irradiation container that receives doses with statistically equivalent values.

3.5 effective density: Bulk density multiplied by the ratio of product width to container width where width is the dimension perpendicular to the source of radiation.

3.6 homogeneous dose map study: Dose map study performed during irradiator qualification or requalification where only materials of the same density and configuration are irradiated without changes to cycle time or conveyor speed during execution of each test.

3.7 irradiation container: Carrier, tote, cart, tray, or other container in which product is loaded to traverse the radiation field during processing. In some instances, this may be the actual product package.

3.8 loading pattern: Geometric configuration of the product in the irradiation container.

3.9 mathematical modeling: Use of mathematical methods to determine dose distribution.

3.10 process load: Volume of material with a specified loading pattern irradiated as a single entity.

3.11 product grid: Dosimeter placement grid used to determine routine dosimeter monitoring locations.

3.12 product path: Path in which the product transverses the cell during the irradiation process.

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3.13 qualification dose map grid: Three-dimensional dosimeter placement grid where dosimeter locations are placed in an array to thoroughly examine the potential zones of minimum and maximum dose during irradiator qualification.

3.14 scaling of dose: Direct relationship between dose and processing parameters such as beam current and conveyor speed for electron beam and source activity and cycle time for gamma.

3.15 statistical equivalent: Doses with magnitudes that differ by less than the statistical uncertainty in the measurement process.

3.16 transit dose: Amount of dose product may receive while the source mechanism is in motion.

4 Installation qualification: Irradiator dose mapping

4.1 General

Prior to performance of the irradiator dose mapping, dosimetry systems with a known level of accuracy and precision should be selected as stated in ANSI/AAMI/ISO 11137. After the completion of the equipment documentation, equipment testing, and equipment calibration in accordance with ANSI/AAMI/ISO 11137, a series of dose mapping exercises should be performed to determine the magnitude, distribution, and reproducibility of dose.

For gamma irradiators, this is carried out by:

a) performing homogeneous dose map studies;

b) determining the qualification dose map grid;

c) performing additional dose map studies that examine the effects of transitions between different product runs, transit dose, partial loads, and center loading;

d) scaling of dose; and

e) reviewing and analyzing data.

For electron beam, this is carried out by:

a) performing homogeneous dose map studies;

b) determining the qualification dose map grid;

c) defining the beam characteristics through scan width uniformity and beam depth dose studies;

d) performing additional dose map studies that examine edge effects, partial loads, process interruption, and number of passes in front of the beam;

e) scaling of dose; and

f) reviewing and analyzing data.

4.2 Gamma

4.2.1 Homogeneous dose maps

To characterize the irradiator with respect to the magnitude, distribution, and reproducibility of dose delivery, dose map studies using homogeneous material, in sufficient quantities to simulate a full irradiator, are performed. The homogeneous dose mapping studies should be performed for each product path to be used for routine processing.

4.2.1.1 Determination of the qualification grid

Dosimeters should be placed in a three-dimensional array sufficient to determine the minimum and maximum dose and to obtain knowledge of the dose distribution. The number of dosimeters and their distribution depends on the spatial resolution desired. Knowledge of the expected dose distribution obtained from mathematical modeling and/or dosimetry data from similar irradiator designs may be used as a guide for selection of the grid. Other considerations in selection of the grid include system design and the range of processing parameters.

4.2.1.2 Selection of materials

Dose mapping should be carried out with homogeneous materials that are within the limits of the bulk density range for which the irradiator is to be used. Typically, densities representing the minimum, maximum and, if applicable, an intermediate density, are examined.

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Some materials commonly used for the dose mapping studies include styrofoam sheets (approximately 0.01 g/cm^3 – 0.03 g/cm^3), corrugated sheets (0.13 g/cm^3 – 0.19 g/cm^3), ceiling tiles (0.25 g/cm^3 – 0.27 g/cm^3), and soft plywood (0.40 g/cm^3 – 0.60 g/cm^3). It may be advantageous to use product for the irradiator dose mapping. The materials selected for the dose mapping studies should allow placement of dosimeters throughout the dose-mapped volume within the irradiation container.

4.2.1.3 Loading the irradiation container

Irradiation containers used for homogeneous dose mapping studies should be filled to their design capacity. Weight limits for the irradiation container need to be taken into account when determining container fill for the homogeneous studies.

While carrying out the homogeneous study, sufficient irradiation containers should be filled with the homogeneous material to simulate a fully loaded system. Often this can be accomplished by filling the irradiation containers where the majority of dose is delivered (e.g., the product path directly adjacent to the source racks). The number of filled irradiation containers depends on the product path.

4.2.1.4 Dosimetry

Dosimeters should be placed in the irradiation containers in the positions defined by the qualification dose map grid. The dosimeters should be located in the irradiation containers that are surrounded by the homogeneous material (i.e., center portion of the irradiation run). To allow statistical analysis of the data and to test for reproducibility in the dose map data, a minimum of three containers should be dose mapped for each density studied.

4.2.1.5 Processing conditions

The homogenous dose map studies should be performed without source interruption, cycle time changes, or other interruptions during irradiation. All unusual events should be documented and investigated. If any event is cause for invalidation, the entire study or portion affected should be repeated.

4.2.1.6 Analysis of data

Statistical analysis of the resulting homogeneous dose map data should be performed to determine the equivalent zones of minimum and maximum dose, as well as those zones that are intermediate in dose. This information is used to select maximum and minimum dose zones and to determine the ratio of maximum to minimum dose. Also, this may serve as a guide in the selection of dose map grid locations for remaining installation qualification dose map studies (e.g., transition and partial load dose maps).

4.2.2 Additional dose map studies

4.2.2.1 Transition dose maps

In those irradiators where different density products are processed at the same time, the effect on magnitude and distribution of dose should be examined. This can be performed by sequentially processing two products with different product densities. To determine the effect on the magnitude and distribution of dose between the products, the last container for the first product density and the first container of the second product density should be mapped. For example, in the case of 12 irradiation containers of 0.02 g/cm^3 product followed by 12 irradiation containers of 0.15 g/cm^3 product, the last container of the 0.02 g/cm^3 product and the first container of the 0.15 g/cm^3 product would be dose mapped. This dose map data should be compared to the dose map data from homogeneous product density runs.

The effect of empty containers on the magnitude and distribution of dose may be determined by dose mapping product that is preceded and followed by empty containers. This will provide information on doses received when product is introduced into an empty irradiator, or is flushed out of the irradiator by empty containers.

The dose map grid may be a full qualification dose map grid or portions of the qualification dose map grid. Additional locations may be included due to different attenuation properties of the products.

4.2.2.2 Partially filled irradiation containers

Partially filled irradiation containers may receive higher doses than full containers. The effect of the partial fill on maximum dose may be more pronounced in higher-density products. Dose mapping of these containers will provide information regarding the magnitude and distribution of dose. The highest density product used in the homogeneous dose map study should be used for this study.

Dosimeters should be placed at potential maximum dose zones in the partially filled irradiation containers as well as in full irradiation containers adjacent to the partially filled irradiation containers. To simulate routine conditions,

partially filled irradiation containers should be dispersed in a run of full containers. The number and location of the partially filled containers in the run depend on the irradiator design.

4.2.2.3 Center loading

To satisfy the maximum and minimum dose constraints that may be imposed on a product, it may be necessary to reduce the width of the product load within the irradiation container. A common practice is to center the product in the irradiation container. The magnitude and distribution of dose for center-loaded containers should be examined.

Simulated products that were used in the homogeneous dose map study may be used in this study.

The dose map grid selected for the center loading study should include dosimeter locations defined in the qualification dose map grid, or locations determined to be equivalent minimum or maximum dose zones from a previous homogeneous dose map study.

A minimum of three center-loaded irradiation containers should be placed sequentially in a run of fully loaded containers filled to the design limit with product that has the same effective density as the center-loaded containers. The run should simulate a fully loaded system.

4.2.2.4 Off-carrier processing

Off-carrier processing may be performed in different ways, including special conveyor systems (research loops) that move product into and out of the cell, or product may be manually placed at fixed locations in the cell. At these fixed locations, rotation of product on turntables or manual manipulation of product on processing tables may be used to improve dose uniformity. The cubic volume limitations of the product to be processed off carrier should be defined. Once defined, dose mapping should be performed as defined by 4.2.1 above.

Consideration should be given to dosimetry and the environmental effects of off-carrier processing as these effects may be different from on-carrier processing. For example, dose rate or temperature may be different, which may affect the performance of some dosimetry systems.

4.2.3 Additional tests

4.2.3.1 Transit dose

During the travel of the source rack to and from a safe storage position, product continues to receive dose until the source rack is completely shielded or in its full up position. As source movements are a normal occurrence in gamma processing, the additional dose received by product during source movements should be considered. This increase in dose depends on the position of product at the time of source movement, and usually is a concern only for those products closest to the source.

The transit dose tests may be performed using a product from the homogeneous dose map studies or empty containers. In the case of empty containers, dosimeters may be placed on the walls of the irradiation container.

Dosimeters should be placed at the maximum and minimum dose zones and in locations that cover the vertical height of the irradiation container in the plane closest to the source.

To ensure that the delivered dose is within the calibrated range of the dosimetry system, the sources should be raised and lowered a number of times while the dose-mapped irradiation containers are closest to the source rack to obtain an absorbed dose that can be measured using the dosimeter.

4.2.3.2 Scaling of dose

Dose mapping may be performed at cycle times that are different from those used for actual processing. The timer settings for routine processing may be determined from direct scaling of the dose map data, provided that doses received during the transportation of product into and out of the irradiator and the doses received during the transfer from one irradiation position to another are shown to be insignificant with respect to total dose.

4.2.4 Review and analysis of data

The irradiator dose mapping data is used to determine the magnitude and reproducibility of dose and the locations of the minimum and maximum dose zones within irradiation containers. This data also provides information on the relationship between dose at the minimum and maximum dose zones and the reference monitoring positions, if applicable.

Measurements of dose at a given location or dose map zone will differ due to uncertainties in the measurement process. Replicate measurements in multiple irradiation containers (i.e., at least three) may be used to calculate a mean dose at each dose-mapped location and give an estimate of the standard deviation about that mean. If the

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variability of dose about the mean of each dose map zone is assumed to be similar, the dose map data may be pooled to derive a single value for the standard deviation. This number may be used to calculate a minimum detectable difference in values of mean dose using statistical evaluation. Doses that do not differ by more than this minimum detectable value are statistically equivalent. Data obtained from the various irradiator dose mappings defined in 4.2 should be reviewed and the results used to select the product dose map grids used for characterizing dose distribution in actual product loads. The rationale for the selection or omission of a potential minimum or maximum dose position from the product grid should be documented.

4.3 Electron beam

4.3.1 Homogeneous dose maps

Dose map studies of an irradiation container filled with homogeneous product should be performed to characterize the irradiator with respect to the magnitude, distribution, and reproducibility of dose delivery. The first aspect of this characterization is mapping the surface of the irradiation container (i.e., the plane of the irradiation container closest to the scan horn). This ensures that the dose at all locations of the irradiation container is consistent. The second aspect of irradiator dose mapping is the measurement of dose as a function of distance from the surface of the irradiation container. This is referred to as depth-dose analysis and, in a homogeneous material, is a function of the angle of the incident beam, the density of the material being processed, and the consistency of the beam energy spectrum.

Material interfaces, including the effects of the edge of an irradiation container, can have significant effects on the distribution of dose. Understanding the effect of surfaces and edges during irradiator dose mapping exercises may be valuable in process qualification dose maps. Edge effects are evaluated by analyzing irradiator container dose map data at qualification grid locations near the edge of the container.

4.3.1.1 Determination of the irradiation container qualification grid

Three dimensions of the qualification grid should be defined and evaluated during the irradiator dose map. As shown in Figure 1, these dimensions include:

a) the direction of conveyor travel (X-direction);

b) the direction the beam is being scanned (Y-direction); and

c) the direction of beam travel (Z-direction).

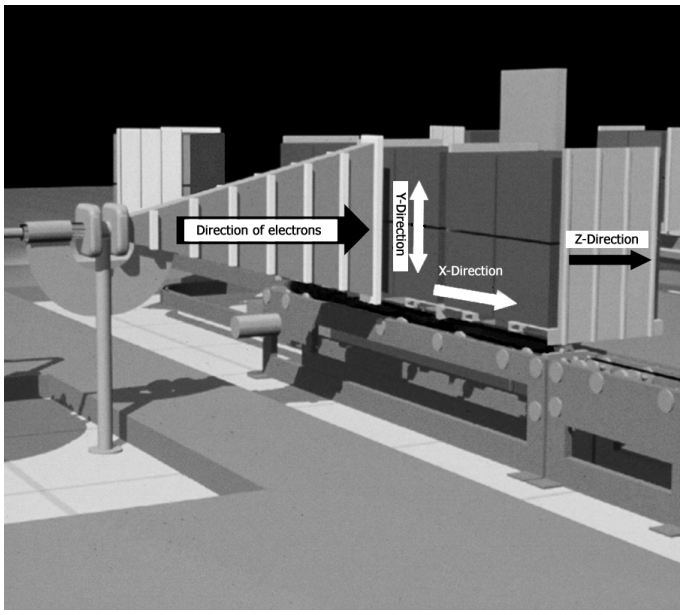

Figure 1—Qualification grid dimensions

4.3.1.2 Selection of materials

Dosimeters for dose uniformity studies should be mounted on a fixture with homogeneous backing material such as a sheet of ethafoam, cardboard, or plastic.

4.3.1.3 Dose mapping in the X- and Y-directions

The uniformity in the dose received over the surface area of the product container should be evaluated. A uniform dose should be maintained in the X- and Y-directions (i.e., the direction of conveyor travel and the direction that the beam is being scanned).

Surface dose uniformity studies should be carried out using dosimeters in both the X- and Y-directions. The dosimeters may be either continuous dosimeter film strips or discreet dosimeters placed adjacent to each other to form strips. The dosimeter resolution should be sufficient to ensure that there are no gaps in dose delivery to the surface. This confirms that combination of beam spot size, pulse width, pulse repetition rate, and scan frequency is adequate to provide continuous dose coverage.

Typically, scan uniformity measurements are performed for the plane of the product container closest to the scan horn. Data should be collected at the extremes of the range of operating conditions to be employed during routine processing, for conveyor speed, beam current, and beam scan.

4.3.1.4 Dose mapping in the Z-direction

Doses should be measured on the surfaces of the homogeneous materials at several depths throughout the irradiation container volume. Dosimeters should be placed in a defined grid pattern at each depth, including the corners and centers. A sufficient number of irradiation containers should be mapped to confirm reproducibility of data. All product paths (e.g., single and double pass) to be used during routine production should be examined.

The irradiator dose map profile provides confirmation of the consistency of beam penetration throughout the irradiation container. It is impacted by the angle of the incident beam relative to the irradiator container, the density of the homogeneous material being processed, and the consistency of beam energy.

Several factors affect the energy of an electron beam, including the accelerating potential of the accelerator, the distance the beam travels through the air prior to reaching the product, and the design and construction of the exit window, as well as the use of scattering foils.

NOTE—The depth-dose analysis is only a secondary confirmation of beam energy. The primary measurement and determination of the beam energy is performed during the accelerator-testing portion of the installation qualification.

4.3.2 Additional dose map studies

4.3.2.1 Partial load

Partial irradiator container loads are common in routine product processing, and should be addressed during process qualification. Certain types of partial loads may be addressed during irradiator dose mapping, and the resulting dose map data used in the process qualification of homogeneous products.

In the direction of conveyor travel, partial containers are typically equivalent to full loads if the irradiator edge effects are taken into account (e.g., no side panels or movable side panels are used to provide a constant edge effect).

In the direction of beam scan, uniformity of dose as a function of beam scan should be evaluated and documented. The edge effects in this direction also should be examined. In the direction of beam travel, the depth-dose uniformity should be addressed. Except for extremely homogeneous product, it is difficult to apply the irradiator dose map data to specific process qualifications.

4.3.2.2 Single and double pass

More efficient throughputs and lower maximum to minimum dose ratios may be achieved by processing irradiation containers from two sides. This can be accomplished by passing the irradiation container in front of the beam with one side facing the beam, rotating the product such that the other side faces the beam, and then passing the irradiation container in front of the beam a second time. Dose delivered to the product from this double pass process is a superposition of dose received from each pass in front of the beam. The effects of double pass irradiation should be evaluated. This may be accomplished by performing additional dose map studies or, with justification, superimposing single-sided irradiator dose map data.

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4.3.3 Additional tests

4.3.3.1 Process interruption

The impact of a process interruption event (a system shutdown and restart while processing is in progress) on dose delivery should be characterized and documented. Process interruption characterization data collected during irradiator dose mapping can be used to evaluate the effect of process interruptions during routine production. Examples of process interruptions include conveyor faults, beam faults, safety system faults, and control system faults. The critical factors that will determine the magnitude of dose delivery variation due to process interruption are the dynamics of beam shutdown and restart in relation to conveyor system shutdown and restart. The source of the system shutdown may impact these dynamics. For example, a shutdown caused by a beam fault may have different dynamics than a shutdown from a conveyor fault.

There are two categories of process interruptions that should be considered. The first is an interrupt initiated by a system fault (e.g., a safety fault, cooling system fault, or power fault) that triggers the shutdown of both the beam and the conveyor system. The second category of interrupt results from a mechanical fault of the conveyor, which triggers the beam and conveyor system to shut down. In both cases, relationships between the time required for the beam and the conveyor to stop and restart should be characterized and understood. For example, with a system fault, the distance the irradiator container travels after the beam is de-energized and the time required for the irradiator container to begin travel again once the system is re-energized should be determined. The impact of these dynamics on dose delivered to product in an irradiation container in front of the beam during such an incident should be characterized and documented.

Dose variation typically is most severe at the irradiator container surface closest to the scan horn. Therefore, this surface should be used for process interruption studies unless other depths from the container surface are justified. Data should be collected at the extremes of the range of operating conditions that can be impacted by processing interruptions (e.g., at the minimum and maximum of process conveyor speeds).

4.3.3.2 Scaling of dose

Dose delivered to product may be changed by varying conveyor or beam parameters such as the conveyor speed, beam current, pulse length, pulse repetition rate, or scan width. The parameters that can be varied depend on the type of accelerator and the design features. Doses from irradiator dose mapping studies may be different from doses selected during routine processing of product. In the event that parameters used during the irradiator dose mapping differ from those to be used during routine processing, testing should be performed to determine the relationship between the dose map parameters and those to be used for routine processing. The parameters for routine processing may be determined from direct scaling of the dose map data, provided the beam spot size and beam scan frequency are sufficient to provide continuous dose coverage and scan width is not varied.

4.3.4 Review and analysis of data

The irradiator dose map data is used to evaluate the uniformity of dose delivered to the surface of the irradiation container, as well as distribution of dose within the homogeneous product. Dose map data from multiple containers also is used to assess the reproducibility of dose delivery. Statistical analysis of the data as discussed in 4.2.4 may be used to determine dose locations that are statistically equivalent and serve as a guide in selection of dose map grids in process qualification studies.

5 Process qualification

5.1 General

Process qualification deals with the actual products processed in the irradiator. The loading pattern of each product should be established and maintained during the irradiation process. For electron beam irradiation, orientation of product to the beam also should be taken into account. This also may be a consideration for processing some types of products with gamma. For each irradiation path and load configuration, dose mapping studies should be performed to identify the zones of minimum and maximum dose. For gamma irradiators, product loads that exhibit the same dose distribution characteristics (e.g., density, load configuration) as those used in the qualification dose mappings have met the product dose mapping requirements for process qualification.

For health care products, requirements for determining minimum and maximum doses are specified in ANSI/AAMI/ISO 11137.

5.2 Gamma

5.2.1 Product loading pattern

Prior to selection of a loading pattern for a new product, the carton weight and size should be confirmed by measurement of representative samples and, from those measurements, product density should be calculated. Several factors other than optimizing fill efficiency may affect selection of a loading pattern. For example, these factors may include weight limitations of the irradiation container, ease of loading, dose uniformity requirements, or compatibility with other product runs. The allowable variation in the product-loading pattern, including the minimum number of packages in a partial load and any requirements for use of compensating dummy product to fill voids, should be documented.

5.2.2 Product dose mapping

Dose mapping should be carried out for representative irradiation containers sufficient in number to determine the variability of dose between representative containers, particularly at the expected maximum and minimum dose zones and routine monitoring position. Dose mapping exercises should be carried out at the limits of the density ranges of product categories to be processed, irrespective of dose. Each product path through the irradiator in which the product load is to be processed should be dose mapped.

5.2.2.1 Process families

Different products with similar dose and dose absorption characteristics (e.g., density and loading pattern) may be grouped into families to reduce the amount of dose mapping required. The number of families will depend on the characteristics of the products to be processed. A first estimate of the products that may be grouped together into families may be obtained from the irradiator dose mapping data. In general, for routine processing using gamma, families are based on dose requirements of products. Products within a single family should consist of those products that can be processed at the same timer setting without exceeding the specified dose limits for any product in the family.

To simplify the transition between families, families should be chosen so that products of one family can be processed with products of the next family without exceeding the specified minimum and maximum dose limits for either family. Representative products from each family should be dose mapped.

5.2.2.2 Mixed density within the irradiator

Where products of significantly different densities are processed together in the irradiator, the effect on dose magnitude and dose distribution in the respective products should be determined. These studies may be performed during irradiator qualification. Where such studies have not been performed, irradiation containers in the transition zone between the products should be dose mapped (i.e., first and last irradiation containers in the runs).

5.2.2.3 Mixed density within the irradiation container

Where products with significantly different densities are processed within the same irradiation container, dose mapping studies should be performed to determine routine dosimetry locations for the product load. This should be accomplished by performing a dose mapping study(s) that covers the range of densities to be mixed within the irradiation container and the configuration(s) that has the greatest effect on the values of minimum and maximum dose.

5.2.2.4 Heterogeneous

For most health care products, orientation and location of devices within the shipping cartons do not significantly affect dose magnitude and dose distribution. However, for products with localized areas of high density such as metal implants or water bottles, dose mapping at internal locations within the product may be necessary. When dense objects are contained in the shipping carton, it may be necessary to place dosimeters inside the shipping carton during the dose mapping exercise. The number and location of dosimeters depends on the type and location of these objects in the package.

5.2.2.5 Partially filled irradiation containers

The minimum and maximum dose zones in partially filled irradiation containers may differ from fully loaded containers. These differences may be eliminated by filling the container with simulated product that is representative of the product being processed or adding shielding such as metal or cardboard. Either method may require additional dosimetry to determine the location of the minimum and maximum zones.

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5.2.2.6 Off-carrier processing

Dose mapping should be carried out to determine maximum and minimum dose zones and routine monitoring position(s). The product to be processed may be small in cubic volume and require a minimal number of dosimeters. In such instances, it is common for any product thus processed to have the same dosimeter map. In situations where the product cubic volume warrants a dose map grid to justify a reduction in dosimeters for routine off-carrier processing, dose mapping exercises should be carried out at the limits of the density ranges of product categories to be processed, irrespective of dose. Off-carrier dose mapping should include process capability for various dimensions, densities, and rotation or inversion schemes; describe grid and minimum monitoring for “non-standard paths”; and establish routine process control.

5.2.3 Review and analysis of data

Results of the process qualification studies are used to establish loading patterns and select locations for routine monitoring of dose. Irradiator dose map data and statistical analysis of that data may be used as a guide in grouping products with similar loading patterns into dose map families. Results of the product dose maps also are used to determine the adjustment factors that are applied when a reference location is selected for routine monitoring of dose. An important part of this analysis is an estimate of uncertainty in the measured values of dose, and use of this information for selecting process parameters to ensure (with a high level of confidence) that all measurements of dose fall within acceptable limits. Examples are given in annex A.

5.2.4 Selection of routine monitoring positions

Routine monitoring positions should be determined from the dose map data. The routine monitoring positions should be selected in one of the three following ways:

a) Locations of absolute minimum and maximum doses.

b) Locations of doses determined to be statistically equivalent to the absolute minimum and maximum doses. Any statistically equivalent location may be selected.

NOTE—Dose mapping often generates two or more dose zones or dosimeter monitoring locations with approximately the same values of dose. In these cases, statistical analysis of the dose map data should be used to determine if the differences in values of dose are significant, or are a result of statistical variations in the measurements. For values of dose found to be statistically equivalent, selection of minimum and maximum dose zones for routine monitoring may include any of these locations.

c) Reference locations may be selected for reasons of ease and reproducibility of dosimeter placement or due to the inaccessibility of the actual minimum and maximum dose locations. Reference monitoring positions are fixed locations where the relationships between the actual minimum and maximum doses are known. These relationships are commonly called adjustment factors (AF). The AF for minimum dose is given by

$$AF_{min} = D_{ref} \div D_{min} \qquad \text{(Equation 1)}$$

and the adjustment factor for maximum dose is given by

$$AF_{max} = D_{ref} \div D_{max} \qquad \text{(Equation 2)}$$

where:

D_{ref} = reference dose

D_{min} = minimum dose

D_{max} = maximum dose

Once established, adjustment factors can be used to calculate and report the minimum and maximum dose in the product by applying these adjustment factors to a dose measurement at the reference location. Examples are given in annex A.

5.2.5 Documentation requirements

Documentation of a process qualification study should include:

a) the results of dose map data as it relates to each product or group of products;

b) the date the dose map study was performed;

c) the product path;

d) the loading pattern, including number of cartons and their configuration per irradiation container;

e) product container weight, dimensions, and density; and

f) material used for center loading the product or shielding the irradiation container.

5.3 Electron beam

5.3.1 Product loading pattern

A loading pattern should be established for each product type. This loading pattern should include a description of the orientation of the product within the package material and secondary packaging, as well as a description of the product orientation to the sterilization process. A typical way of defining the orientation to the sterilization process is by using the direction of the conveyor travel (the X-direction), the beam scan (the Y-direction), and the direction of the beam travel (the Z-direction).

Prior to selection of a loading pattern for a new product, the carton weight and size should be confirmed by measurement of representative samples, and product density should be determined. Several factors affect selection of the loading pattern. These factors may include but are not limited to:

a) maximum depth of penetration of the electrons in the Z-direction (results of the depth dose studies performed during the installation qualification or empirical relationships may provide guidance relative to this thickness);

b) product and packaging materials;

c) number of product units per shelf pack;

d) number of shelf packs per shipper;

e) number of “devices” per packaged unit;

f) orientation of materials within the shipper;

g) dimensions, mass, and density of shipper, product, packaging, shelf packs, and devices;

h) product quantity and orientation of the product units within the shipper; and

i) product family groupings.

5.3.2 Product dose mapping

Dose mapping should be carried out for representative irradiation containers sufficient in number to determine the variability of dose between representative containers, particularly at the expected maximum and minimum dose zones and routine monitoring position. Dose mapping exercises should be carried out at the limits of the density ranges of product categories to be processed, irrespective of dose.

To facilitate measurements and observations, it may be appropriate to cut or section the shipping container, product, or packaging materials, and to use photographs. Permission of the product manufacturer should be obtained prior to initiating any such action.

5.3.2.1 Process families

For electron beam irradiation, each product typically is dose mapped. However, to reduce the amount of dose mapping required, product may be grouped into process families. Grouping of products into process families is only appropriate if the product, packaging, and loading pattern are equivalent from a density perspective. The following should be considered:

a) orientation of product in both the shipping container and inner containers;

b) density and distribution of mass;

c) size and shape of package; and

d) item count and distribution of product units within the shipping container.

Based on the dose map results, products may then be grouped for processing under the same conditions.

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5.3.2.2 Dosimeter placement

Product units should be reviewed for areas that might result in local dose gradients. This may be due to localized heterogeneities within the product that could result in enhanced or diminished dose due to shielding or scattering effects. This can result in dose gradients within a small volume. More extensive dosimetry measurements should be made in these areas. Examples include material heterogeneity (e.g., metal vs. plastic) or randomized product geometry (e.g., plastic cylinders randomly situated in a carton).

Historical data, literature-based references, and user knowledge may all be employed to aid in the determination of dosimeter placements for product dose mapping using dosimeters. The location of dosimeters should be documented.

5.3.3 Review and analysis of data

Results of the product dose maps should be used to:

a) select routine monitoring location(s) which may be on the surface of the irradiation container or at a reference location;

b) determine a statistically based relationship between dose at a reference location and the minimum and maximum doses in the product; and

c) define dose specification for the routine monitoring location(s), if used.

The data should be analyzed to ensure that minimum and maximum product specifications will be achieved. Due to the sensitivity of dose to location of product units within the irradiation container and high dose gradients that often exist in heterogeneous products irradiated by electron beams, uncertainty in the dose measurement process should be taken into account when setting process parameters. Examples are given in annex A.

5.3.4 Selection of routine monitoring position

Routine monitoring positions should be determined from the dose map data. The minimum or maximum dose location may be chosen for monitoring dose during routine processing or, alternatively, a reference location selected for ease and reproducibility of dosimeter placement may be used. The reference location may be on the surface of the package or a position located off the product (e.g., dosimeter holder affixed to an irradiation container or a stand-alone dosimeter processed next to the irradiation container). The relationship between the actual minimum and maximum doses to the reference position must be known. The AF for minimum dose is given by

$$AF_{min} = D_{ref} \div D_{min} \qquad \text{(Equation 3)}$$

and the adjustment factor for maximum dose is given by

$$AF_{max} = D_{ref} \div D_{max} \qquad \text{(Equation 4)}$$

where

D_{ref} = reference dose

D_{min} = minimum dose

D_{max} = maximum dose

Once established, adjustment factors can then be used to calculate and report the minimum and maximum dose in the product by applying these adjustment factors to a dose measurement at the reference location. Examples are given in annex A.

5.3.5 Documentation requirements

Documentation of the process qualification study should include:

a) the results of dose map data as it relates to each product or group of products;

b) the date the dose map study was performed;

c) the product path;

d) the loading pattern, including number of cartons and their configuration per irradiation container;

e) product container weight, dimensions, and density;

f) type of materials used to center load the product or shield the irradiation container; and

g) machine settings such as voltage, beam current, and scan width.

6 Routine monitoring and control

6.1 General

Routine process controls should be administered to ensure that products are processed to the requirements specified in ANSI/AAMI/ISO 11137. Process controls during routine processing include proper receipt of product at the irradiator, scheduling, product loading, irradiation, dose monitoring, unloading, product release, and shipment of product. For some of these items, the elements that need to be considered are common to both gamma and electron beam, while other items possess elements that are unique to gamma or electron beam.

6.2 Receipt of product

Upon receipt of product at the irradiator, it should be verified for the correct lot or batch, processing specifications, and product count, including number of samples and product damage, in accordance with written procedures.

6.3 Scheduling of gamma irradiators

Scheduling of product runs requires knowledge of the dose delivery characteristics of the irradiator and the physical characteristics and prescribed irradiation conditions for the product. This information is used to select cycle timer settings, product flow through the irradiator if more than one product flow is allowed, and grouping of products that are processed sequentially. In addition, this information is used to determine if the product run requires special processing conditions due to minimum dose requirements, dose range constraints, product weight and density, or allowed time for completion of the irradiation.

6.3.1 Irradiator characteristics

This information is obtained from installation qualification studies, requalification studies, and physical attributes of the irradiator. The information includes:

a) internal dimensions of the irradiation container;

b) available flows of product through the system;

c) dose rates and partition of dose in various segments of the system;

d) dose uniformity as a function of product density and size of product unit;

e) relationships governing process cycle time and dose delivered to product; and

f) weight constraints of the system.

6.3.2 Product specifications

Product specifications or standard operating procedures should be developed from information generated during product and process qualification studies and the physical properties of the product. Special processing conditions such as temperature constraints during irradiation are included in this body of information. The information includes:

a) product identification;

b) special handling requirements;

c) loading configuration;

d) maximum dose to be delivered to the product;

e) minimum dose to be delivered to the product;

f) frequency and location of dosimeters used for routine monitoring;

g) case/product density and size;

h) special processing conditions (e.g., temperature, products that support microbial growth); and

i) maximum allowable time from manufacture to sterilization, for products with this specification.

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6.3.3 Scheduling of single product runs

6.3.3.1 Single product runs

In some batch irradiators, products are processed individually in single product runs. In addition, product specifications may require processing of single product runs in irradiators that are capable of multiple product runs.

6.3.3.2 Steps in scheduling single product runs

The following steps apply to processing of single product runs:

a) Product should be loaded into the irradiation containers based on a validated loading pattern. Dose range constraints or product density may require loading the containers to less than optimum fill efficiency (e.g., center loading or shimming of product in the irradiation containers).

b) Product runs should be scheduled to satisfy the allowed time constraints for completion of the irradiation.

c) The cycle timer should be set to deliver the required minimum dose without exceeding the maximum dose.

d) Possible effects on the magnitude and distribution in dose in the first and last irradiation containers of the run should be taken into account. This may require addition of compensating dummy product at the beginning and end of the run.

6.3.4 Scheduling of multiple product runs

6.3.4.1 Grouping of products for multiple runs

The first step in scheduling different product runs in the irradiator is to group together runs having similar cycle times. The cycle times for individual products are determined from results of the irradiator dose commissioning study and process qualification studies. Runs can be grouped together even though they may not have the same process cycle time, as long as all products within the group are dosed within their validated dose limits and dose distribution is not significantly affected by the mix of the product runs. The degree to which different runs can be grouped together depends on the irradiator design and its dose delivery characteristics. Also, compatibility with a group of runs may be possible by center loading the product or placing shields on the outside of the irradiation containers.

6.3.4.2 Steps in scheduling multiple product runs

The following steps apply to scheduling of multiple product runs:

a) Product should be loaded into the irradiation containers based on a validated loading pattern. Product should be scheduled to satisfy prescribed time constraints for processing.

b) The cycle timer should be set to deliver the required minimum dose without exceeding the maximum dose for all products within the product grouping.

c) Possible effects on the magnitude and distribution in dose in the first and last irradiation containers of a product run in a grouping of runs should be taken into account.

d) Mid-process changes in cycle time to go from one base cycle time to another base cycle time may be employed in continuous irradiators. In these cases, product groups may need to be separated by empty containers or buffer product. The effect on the magnitude and distribution in dose in irradiation containers at the beginning and end of a product group from the presence of empty containers or buffer product should be taken into account.

e) The possible effect on the magnitude and distribution in dose in buffer products from mid-process changes in cycle time should be taken into account.

6.3.4.3 Separation of product runs

In continuous irradiators, product runs with significantly different cycle times may need to be separated by empty irradiation containers, dummy product, or buffer product. The number of such containers will depend on the irradiator design. In the extreme, it may be necessary to flush out the entire irradiation cell before the new group of runs is introduced into the irradiator. The effect on dose, particularly maximum dose, should be taken into account when products are introduced into an empty cell. Buffer products, which typically have a wide range of allowable doses between the minimum and maximum dose limits, also can act as product fill between the different groups of runs. The possible effect on dose distribution in these buffer products from mid-process change in cycle time should be evaluated.

6.3.4.4 Change in cycle time between product runs

Mid-process change in cycle time to go from one base cycle time to another base cycle time may be employed in continuous irradiators. The effect on dose distribution and dose magnitude should be evaluated.

6.4 Scheduling of electron beam irradiators

Electron beam sterilization processing facilities typically only process product from a single process qualification dose map in any given irradiation container at any given time. This is due to the relatively small irradiation volume actually being processed by the beam at any given time. Since only one irradiation container is processed at any given time at typical electron beam sterilization facilities, the product from one irradiation container has little or no impact on adjacent irradiation containers from the perspective of dose delivery.

NOTE—If products from different dose map exercises are mixed within an irradiation container, factors similar to those outlined for gamma in 6.3 should be considered.

The only potential impact that scheduling may have on an electron beam facility relates to throughput efficiency. This is driven by two factors that depend on the design of the facility. The first factor is the time required to change from one set of beam parameters to another. The second factor relates to routine dosimetry requirements. If either of these factors has a significant effect on process time, it may be desirable from an efficiency perspective to group product with the same beam parameters together. Such grouping also minimizes the number of transitions between different processing parameters, which minimizes the potential for product to be processed incorrectly.

6.5 Loading of product

When loading product at gamma and electron beam irradiators, one should consider the following items:

a) Product should be loaded into the irradiation containers in accordance with the designated product-loading pattern.

b) Product count should be documented. Test samples should be included in the counts; however, this should be noted in the processing records.

c) Partial containers should be noted in the processing records.

d) Any discrepancies identified during loading should be addressed per established specifications.

6.6 Processing of product

6.6.1 Introduction

Products should only be processed using a qualified irradiator system. This includes documented procedures that ensure that established process specifications are met. The dose delivered to the product should be monitored using a calibrated dosimetry system. This system should be calibrated using established procedures, and be traceable to national or international standards. The overall uncertainty in the measurement of dose should be estimated and documented.

6.6.2 Gamma

6.6.2.1 Processing parameters

Several parameters should be monitored and documented during the gamma irradiation process. These include position of the gamma sources, cycle timer settings, changes in the cycle timer setting, process interruptions (if any), and location of irradiation containers in the irradiator.

6.6.2.2 Location of dosimeters

Dosimeters should be placed in the locations previously selected based upon dose mapping studies. These locations should be documented.

6.6.2.3 Frequency of dosimeters

It is recommended that the dosimeters be placed in or on irradiation containers at the beginning, midpoint, and end of a run. Reference location dosimeters should be placed at equivalent locations in a run. At least one irradiation container with a dosimeter should be in the irradiator at all times while the run is being processed.

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6.6.2.4 Partial containers

The maximum dose should be measured in partially filled containers if the dose mapping study showed that the maximum dose in such studies exceeded the maximum dose in fully loaded containers.

6.6.2.5 Off-carrier processing

Dosimeters should be placed in the locations previously selected based upon dose mapping studies. These locations should be documented.

6.6.2.6 Process interruption

The effect of process interruption on the magnitude and distribution in dose should be taken into account. If interruption involves manual movement of carriers, the corrective action and the positioning of specific carriers when processing was interrupted and resumed should be documented.

For products capable of supporting microbial growth, the process specification should include the maximum interval of time that may elapse between the completion of manufacture and the completion of sterilization processing, and the conditions of storage and transportation to be applied during the time interval, including irradiation.

For products not capable of supporting microbial growth, the effect of radiation dose on microorganisms is cumulative; thus, the interruption of the process in the irradiator generally does not necessitate action.

6.6.2.7 Analysis

ANSI/AAMI/ISO 11137 (7.4.3.3) provides requirements for the analysis of dosimeters relative to process specifications that were defined during the product qualification process.

6.6.3 Electron beam

6.6.3.1 Processing parameters

In meeting the requirement of ANSI/AAMI/ISO 11137 (7.4.1) for control and monitoring of the electron beam process, it is important to differentiate critical beam parameters from secondary parameters. Critical beam parameters may be defined as those that, if they deviate from the specifications, would result in an inappropriate dose being delivered to the product. Secondary parameters may be monitored and controlled, but they do not necessarily impact critical parameters (and, hence, dose delivered to the product) if they deviate from the specification.

The ability to monitor, control, and document the state of control of critical beam parameters is an important factor in defining routine processing requirements. If such control is validated as part of the electron beam control system, then the operating procedures become relatively simple. If such control is not a part of the beam control system, then operating procedures should ensure that the beam is operating in a state of control.

6.6.3.2 Process interruption

The effect of process interruption on the magnitude and distribution in dose should be taken into account.

For products capable of supporting microbial growth, the process specification should include the maximum interval of time that may elapse between completion of manufacture and completion of the sterilization process, and the conditions of storage and transportation to be applied during the time interval, including irradiation.

For products not capable of supporting microbial growth, the effect of radiation dose on microorganisms is cumulative; thus, the interruption of the process in the irradiator does not generally necessitate action.

6.6.3.3 Location of dosimeters

Dosimeters should be placed in the locations previously selected based upon dose mapping studies. These locations should be documented.

6.6.3.4 Frequency of dosimeters

Dosimeters should be placed at the beginning, middle, and end of each processing run that utilizes the same parameters.

6.6.3.5 Analysis

ANSI/AAMI/ISO 11137 provides requirements for the analysis of dosimeters relative to process specifications defined during the product qualification studies.

6.7 Unloading of product

As product is unloaded from the irradiator, the following should occur:

a) count verification;

b) palletization per established specifications, if required;

c) retrieval of samples;

d) retrieval of dosimeters, verification of correct placement, and storage of dosimeters in an environmentally controlled area until processing;

e) identification of damaged product; and

f) identification of product status and storage in an appropriate designated area.

6.8 Release of product

Upon completion of the radiation process, the processing history records should be submitted for review and approval by qualified personnel.

Processing history records typically include:

a) receiving records;

b) product count verification;

c) loading and unloading records;

d) processing records;

e) conveyor operation and/or pathways;

f) source position;

g) for electron beam, the beam characteristics and conveyor speed;

h) processing deviations and associated investigations and corrective action;

i) dosimetry analysis data records; and

j) certification of dose delivery.

At a minimum, the history records should consist of those identified in ANSI/AAMI/ISO 11137, the facility quality system, and written specifications, where applicable.

6.9 Shipment of product

Prior to shipment of an irradiation load, the following should occur:

a) Product counts at receipt, load, unload, and prior to final shipment should be compared and discrepancies documented.

b) Product should be inspected for damage and identified where needed.

c) Product should be released by appropriate personnel.

7 Mathematical modeling

7.1 General

Mathematical models can closely simulate the transport of photons or electrons through the irradiator, taking into account the attenuation and scattering by materials between the source and product. Mathematical modeling of dose distribution for gamma irradiators requires accurate knowledge of the source activity distribution and the composition and position of the source, source rack, product carriers, irradiator support structures, and product. For electron beam irradiators, the beam energy, current and pulse distribution (for pulsed accelerators), product, product carriers, and adjacent scattering materials should be accurately known. Errors in any input parameter for the calculation can result in errors in the calculated dose rates, so calculated dose distributions should be verified by dose mapping studies.

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7.2 Types of models

7.2.1 Introduction

There are a number of methods for mathematical modeling of radiation transport. However, most modeling is performed using either the Point Kernel method or the Monte Carlo method. The Point Kernel method is used for calculating the dose distribution in gamma irradiators. It is not used for electron beam irradiators. The Monte Carlo method can be used for both gamma and electron beam irradiators.

7.2.2 Point Kernel method

In the Point Kernel method, the gamma source, usually consisting of a number of source capsules distributed over a rectangular plaque or a cylinder, is approximated by a number of point sources. The intervening material between each point source and each point where the dose is to be calculated is determined from the coordinates of the source, irradiator, and product volumes. The effect of this intervening material on the dose rate is estimated by assuming that the photons reaching the dose point are reduced by the inverse square relationship with distance and by exponential reduction based on the mass of material. Contributions from degraded, scattered photons are approximated by use of a factor called the build-up factor. Build-up factors have been calculated for different materials and energies for different source to product geometries. However, the published values apply only for simple homogeneous geometries (e.g., a point source in an infinite medium). In actual gamma irradiators, the source to product geometries are not that simple, and effects of boundaries and mixtures of materials limits the accuracy in the application of build-up factors.

7.2.3 Monte Carlo method

In the Monte Carlo method, the transport of each photon or electron from the source through the product and irradiator materials is simulated by the use of random numbers to determine the energy deposition and change of path following different interactions. The probability for each interaction is obtained from published tables. Theoretically, the Monte Carlo method can accurately simulate the actual transport of the photons and electrons. However, since each photon or electron follows a unique path, determined by the probabilities for each individual interaction, the dose contribution from a large number of photons or electrons can only be determined from a large number of photon or electron histories. The uncertainty associated with the random statistical fluctuations is estimated and the calculations are continued until an acceptable statistical uncertainty in the calculated dose is reached. However, even with modern fast computers, exact calculations require excessive computer time, so approximations are usually used. These approximations include biasing the calculations to provide additional histories for rare events.

7.3 Use of models

7.3.1 Design of irradiators

Mathematical modeling is used extensively in the design of irradiators. Calculations are performed to optimize the irradiation geometry to achieve the desired throughputs and dose homogeneity. Data from mathematical modeling is then used to determine the radiation performance of the irradiator when filled with homogeneous product. Calculations provide information on the expected dose per kilocurie of activity or kilowatt of beam power, variation of dose with product density, dose uniformity ratios, and locations of the minimum and maximum doses. Some mathematical models also can provide information on the doses received during the transition between different density products, transit doses during movement of the source or shutdown of the electron beam, and effects of voids or product heterogeneity. Some mathematical models also can provide information on the energy spectrum at the different irradiation positions in a gamma irradiator.

7.3.2 Operation of gamma irradiators

For gamma irradiators, information on the expected dose distribution provided by mathematical modeling can be used to ensure that a sufficient number of dosimeters are distributed in the expected zones for minimum and maximum doses in the irradiator dose mapping studies. Dosimeters also should be placed in the minimum and maximum dose zones predicted by the mathematical modeling, as well as other locations to confirm that the irradiator performs as expected. Since the mathematical modeling usually assumes that all source, irradiator, and product parameters are exactly those in the input, the effects of any deviation from these parameters only can be determined from dosimetry.

After the dose mapping studies have confirmed the reliability of the results from the mathematical modeling data, mathematical modeling provides an effective tool for interpolating between the measured results to determine the dose distribution for other intermediate product densities, and determining general trends such as the effects of product density changes or dose variations caused by non-homogeneous products. The use of a combination of mathematical modeling and dose mapping can significantly reduce the amount of dose mapping required, as illustrated in the following example:

a) Use mathematical modeling to calculate the dose distributions in homogeneous products for several product densities.

b) Normalize calculated results to obtain agreement with the dose map data, and determine normalization factors applicable for the range of product densities measured.

c) Calculate the dose distribution for intermediate product densities and apply the required normalization factors.

d) Calculate the dose distributions for the first and last product containers when product of different densities are irradiated sequentially.

e) Compare calculated data with dose map data for several different product densities irradiated sequentially to confirm the reliability of results from mathematical modeling.

The resultant data also can be used to confirm that dose specifications can be met when specific products are processed together, and to determine the optimum timer settings to be used during transition between products of different densities.

7.3.3 Operation of electron beam irradiators

For electron beam irradiators, information on the expected dose distribution provided by mathematical modeling can be used to ensure that a sufficient number of dosimeters are distributed in the expected zones for minimum and maximum doses in the irradiator dose mapping studies. Mathematical modeling also can be used to determine the dose in areas where there may be steep dose gradients (e.g., near edges of product) to ensure that dosimeters provide adequate resolution. Results of mathematical modeling may indicate the need to map areas with strips or sheets of dosimetric film and scan the films to determine doses near product edges.

8 Routine evaluation of process quality

8.1 General

Routine processing data may be assessed to establish confidence in the maintenance of validation. For example, data may be accumulated from individual processing records to compare actual delivered doses with the expected or specified doses to evaluate the ability of the process to consistently deliver a specified dose.

Sterilization with radiation is a predictable and reproducible process provided that it is appropriately controlled. The expected dose from a gamma irradiator is based upon fixed isotope decay and time adjustments. The expected dose from an electron accelerator is based upon establishment of the speed/current/energy relationship. Therefore, the output of the routine irradiation processing can be compared against calculated results or a mathematical model's predicted results to determine if the process is in control.

8.2 Collection and review of data

Processing data should be accumulated, organized, and reviewed to evaluate process quality. This data may include, for example, results of dose measurements, processing parameters, and non-conformances. The method of analysis depends on the data type, the irradiator design and application, and the needs of the users. The results of this analysis can be used to identify processing runs that have approached the processing specification limit and possible process trends, allowing for corrective actions to be taken.

One useful analysis technique is a control chart. An example of a control chart is shown in Figure 2.

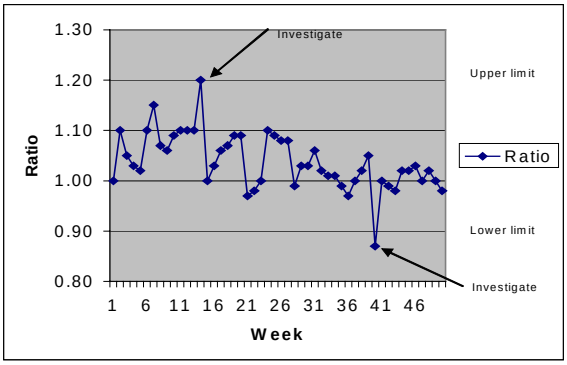

Figure 2—Ratio of measured dose vs. expected dose

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The chart represents the ratio of the routine measurement dose versus an estimated (calculated) dose. The estimated dose was determined by adjusting the dose received at the original validation by a factor related to isotope decay and the cycle time used in the routine production cycle time.

Control charts are graphical representations of the output of a process. For example, a plot of delivered process doses or data from the initial validation as compared to the records of routine processing provide the needed data sets to establish process control charting. The comparison of actual results versus expected results or specifications provides an objective evaluation of control of the process.

9 Maintenance of process effectiveness

9.1 General

Validation maintenance is accomplished through a calibration program and a requalification program.

9.2 Calibration

Critical process instrumentation should be calibrated at regular intervals. The calibration frequency should be based on the stability, purpose, and usage of the equipment, and is typically prescribed by the equipment manufacturer. Some examples of critical process instrumentation follow.

For gamma irradiators:

a) dosimetry system;

b) weighing and measuring equipment; and

c) cycle timers.

For electron beam irradiators:

a) dosimetry system;

b) weighing and measuring equipment;

c) beam energy and current instrumentation;

d) scan width and frequency instrumentation; and

e) instrumentation for monitoring conveyor speed.

9.3 Irradiator requalification

9.3.1 Introduction

Any equipment design change that affects dose distribution may require a repeat of part or all of the installation qualification. It is important to note the difference between calibration and qualification. Requalification is a test of the physical performance of a system, and is an event-driven process. The requalification process may include one or more of the following: equipment documentation, equipment testing, equipment calibration, and irradiator dose mapping. The extent of requalification required depends on the nature of the design change. Tables 1 and 2 are examples of items that may need to be performed during requalification of an irradiator. Actual requirements may vary dependent on differences in the equipment employed.

9.3.2 Requalification documentation requirements

The following quality records, where applicable, should be maintained regarding requalification:

a) description of the modification that was made to the irradiator;

b) drawings, specifications, etc., of any design change that was made;

c) engineering Change Record for those changes regarding the irradiator design;

d) records of source location and activity;

e) dose map dosimetry reports; and

f) reports of mathematical modeling.

Table 1—Gamma irradiator requalification requirements

Irradiator change	Equipment documentation	Operational testing	Equipment calibration	Irradiator dose mapping	Minimum required dose mapping
Addition, removal, reconfiguration of isotope	✔			✔	Homogeneous dose maps
Carrier/irradiation container redesign	✔	✔		✔	Installation qualification—irradiator dose maps
Removal or relocation of over head conveyor inside irradiation cell	✔	✔		✔	Installation qualification—irradiator dose maps
Removal or relocation of stop units in the critical product path	✔	✔		✔	Installation qualification—irradiator dose maps
Removal or relocation of stop units outside of the critical product path	✔	✔			
Replacement of source cables	✔	✔			
Redesign of the source drive system	✔			✔	Transit dose maps
Redesign that affects the source-to-product distance	✔	✔		✔	Installation qualification—irradiator dose maps
Redesign of the source rack system	✔	✔		✔	Installation qualification—irradiator dose maps
Changes to type of irradiator cycle timer	✔	✔	✔		
Changes to type of irradiator radiation safety monitoring devices	✔	✔	✔		
Changes to type of irradiator pool water monitoring devices	✔	✔	✔ (if applicable)		

NOTE 1—Addition of source without reconfiguration of the source geometry may only require that part of the homogeneous dose mapping study be performed to confirm the results of mathematical modeling or modification objectives. Whereas, addition of source with change of source geometry may require that all homogeneous dose maps be repeated in addition to some of the ancillary studies such as center loading or partial load.

NOTE 2—Pending results of operational testing (e.g., verification of source position), homogeneous dose mapping may be required following replacement of source cables.

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Table 2—Electron beam irradiator requalification requirements

Irradiator change	Equipment documentation	Operational testing	Equipment calibration	Irradiator dose mapping	Type of dose mapping
Accelerator mechanical alignment	✔			✔	Y- and Z-direction dose mapping
Steering or focusing magnet systems	✔			✔	Y- and Z-direction dose mapping
Bending magnet systems	✔		✔	✔	Z-direction dose mapping
Beam current monitoring system	✔		✔	✔	X-direction dose mapping
Scanning magnet system	✔		✔	✔	Y-direction dose mapping
Conveyor speed monitoring and/or control circuitry	✔		✔	✔	X-direction dose monitoring Process interruption testing
Conveyor system motors, belts, and gearing	✔	✔			

NOTE 3—(per 4.3.1.1):

X-direction: the direction of conveyor travel

Y-direction: the direction the beam is being scanned

Z-direction: the direction of beam travel

NOTE 4—These tables are examples. Actual requirements may vary as a result of differences in the equipment employed.

9.4 Preventive maintenance and irradiator change control

9.4.1 Preventive maintenance

The maintenance program should be established and include specific guidelines for the inspection and servicing of the following areas.

For gamma irradiators:

a) conveyor system (e.g., conveyor drive unit, drive chain, conveyor track, rotators);

b) radiation source systems (e.g., source hoist, track, sheave, and cables);

c) air compressors and pneumatic systems;

d) transfer lifts and lowerators;

e) ventilation systems;

f) water treatment system (e.g., chillers, plumbing system, purification system); and

g) irradiation containers (e.g., carrier, totes).

For electron beam irradiators:

a) electron beam accelerator (e.g., scan horn alignment, scan width, beam energy, beam magnet system, power supply);

b) conveyor system (e.g., start/stop test, guide rails, conveyor track);

c) irradiator support equipment (e.g., electrical wiring); and

d) irradiation containers (e.g., carriers, totes).

Preventive maintenance should be performed to a predetermined schedule based upon the equipment manufacturer's requirements and performance characteristics of the equipment. Preventive maintenance should be performed and recorded in accordance with documented procedures. In addition to preventive maintenance, any unscheduled maintenance performed for repair purposes should be documented.

9.4.2 Irradiator change control

Changes to the irradiator system design should be recorded and tested in accordance with documented procedures. The change record should define:

a) the change made to the system;

b) the reason for the change;

c) operating procedures affected by the change;

d) drawings or schematics affected by the change;

e) installation, operational, and performance qualification testing requirements; and

f) review and approval by appropriate personnel.

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Annex A

Measurement uncertainty in routine monitoring of dose

Uncertainty in the dose measurement process causes variability in replicate measurements of dose that are made at the same dose location within a product run. This variability in the measured values of dose is traceable to the dosimetry system itself and variability in processing conditions during the run. To have a high level of confidence that all measurements of minimum and maximum dose fall within an acceptable range, the uncertainty in dose measurements should be taken into account in setting parameters for routine processing of product. In those cases where dose is measured at a reference location and an adjustment factor is used to calculate minimum or maximum dose, as described in 5.2.3 and 5.3.3, an additional component of uncertainty should be taken into account in setting processing parameters. Statistical analysis of data obtained from multiple dose maps that were run during performance qualification studies can be used to estimate the uncertainty in the dose measurements. This information can be used for setting the parameters for routine processing of product. The following sections of this annex provide examples of how to estimate dose measurement uncertainty from analysis of multiple dose maps and how to use that information for setting processing parameters.

A.1 Key statistical parameters

Several statistical parameters enter into this analysis. Two key parameters are the mean or average dose from replicate measurements and the standard deviation, which is a measure of the dispersion or scatter of dose values about the mean value. Standard deviation often is expressed in terms of the variance, which is the square of the standard deviation.

If $D_{i,z}$ is the dose measured by the i^{th} dosimeter in zone z and there are n_z independent measurements made of zone z, then the mean absorbed dose expected in each zone z is estimated by:

$$(D_{avg})_z = \Sigma_i \, D_{i,z}/n_z \qquad \text{(Equation A.1)}$$

Within each zone, the variance of the dose measurements about the mean is estimated as:

$$\text{Var}(D) = \Sigma_I \, [D_{i,z} - (D_{avg})_z]^2/(n_z - 1) \qquad \text{(Equation A.2)}$$

NOTE—The number of comparisons made between replicate measurements of dose, which is referred to as the degrees of freedom, is another important parameter in statistical analysis of data. The number of degrees of freedom is equal to n – 1 for a single quantity estimated by the arithmetic mean of n independent measurements of dose. For practical reasons, dose measurements are typically characterized by a small number of degrees of freedom. For example, in those cases where three product dose maps are used to determine average doses, the number of degrees of freedom is 3 – 1, or 2. For purely statistical reasons of limited sampling, analyses involving a small number of degrees of freedom can lead to significant uncertainty in the experimental standard deviation. If the variability of dose about the mean for each dose zone in the dose maps can be assumed to be similar, pooling of the data may be possible. Pooling increases the degrees of freedom and improves the quality of the estimate.

It is implied in use of Equations A.1 and A.2 that the dose map data is properly conditioned for statistical analysis. In some cases, large variability in replicate measurements of dose in a specific zone may not be due to statistical variations. For example, if large dose gradients exist within a given dose-mapped volume, a slight change in dosimeter location could lead to a significant change in measured dose. In this case, averaging of the data and use of the standard deviation to estimate variability in dose values about the mean may not be appropriate. Other approaches such as selection of the lowest or highest dose value rather than use of a mean value may be preferred, or additional dose map data may need to be generated to better assess statistical variability of the data. The overall uncertainty in the dosimetry system and dose map data taken from irradiator qualification dose map studies provides guidelines for assessing variability in replicate measurements taken from product dose maps. Dose map data containing possible aberrant values also can be tested for outliers using standard methods.

A.2 Methods for routine measurement of dose

Three methods are commonly used to monitor dose during a production run.

1. Production dose monitoring procedure 1—This method involves measurement of minimum and maximum dose at several locations in the run.

2. Production dose monitoring procedure 2—This method uses reference point dosimetry wherein dose is measured at a reference location and minimum and maximum doses are determined through use of adjustment factors (see 5.2.4 and 5.3.4).

3. Production dose monitoring procedure 3—In this method, minimum dose is measured at several locations in the product run and maximum dose is calculated based on a ratio to the minimum dose. In effect, the minimum dose functions as a reference dose and maximum dose is determined using an adjustment factor.

The following sections provide examples of the analysis of product dose map data to (1) determine uncertainty in dose values for each of the three procedures for dose monitoring, and (2) use that information to set process parameters during production processing of product.

A.3 Production dose monitoring procedure 1—Measurement of minimum and maximum dose in routine processing of product

The following example shows how statistical analysis of product dose map data is used for setting process parameters when minimum and maximum doses are measured at various locations within the production run. The dose map data listed in Table A.1 were taken from three replicate dose maps that were run during the performance qualification studies.

Table A.1—Dose map data—Procedure 1

Doses	Dose maps		
	Dose map 1	**Dose map 2**	**Dose map 3**
D_{min}	26.1 kGy	25.8 kGy	25.2 kGy
D_{max}	40.0 kGy	41.0 kGy	40.6 kGy

For purposes of this example and the subsequent examples given in this annex, specifications for the acceptable minimum and maximum doses were assumed to be 25 kGy and 45 kGy, respectively.

A.3.1 Calculation of average dose, variance, and standard deviation

Using the minimum and maximum dose values in Table A.1 and Equations A.1 and A.2, determine the average dose, variance, and standard deviation of D_{min} and D_{max}.

Average dose calculation:

$$(D_{min})_{avg} = (26.1 + 25.8 + 25.2)/3 = 25.7 \text{ kGy}$$

$$(D_{max})_{avg} = (40.0 + 41.0 + 40.6)/3 = 40.5 \text{ kGy}$$

Variance calculation:

$$\text{Var}(D_{min}) = [(26.1 - 25.7)^2 + (25.8 - 25.7)^2 + (25.2 - 25.7)^2]/(3 - 1) = 0.21 \text{ (kGy)}^2$$

$$\text{Var}(D_{max}) = [(40.0 - 40.5)^2 + (41.0 - 40.5)^2 + (40.6 - 40.5)^2]/(3 - 1) = 0.25 \text{ (kGy)}^2$$

Standard deviation calculation: (Square Root of Equation A.2)

$$S(D_{min}) = \sqrt{\text{Var}(D_{min})} = 0.46 \text{ kGy}$$

$$S(D_{max}) = \sqrt{\text{Var}(D_{max})} = 0.50 \text{ kGy}$$

The quantities Var(D) and S(D) in the preceding calculations are the variances and standard deviations in the respective doses.

A.3.2 Estimate of uncertainty in dose measurements

The standard deviation, which is a measure of the dispersion or scatter of dose values about the average dose, can be used to estimate the uncertainty in the measurement of dose. To provide a high level of confidence that the measurement of dose will fall within the interval given by the estimate of uncertainty, the standard deviation is normally multiplied by a coverage factor. This additional measure of uncertainty that provides such a confidence level is termed expanded uncertainty. A coverage factor of 2 corresponds approximately to a confidence level of 95 %, and a coverage factor of 3 corresponds approximately to a confidence level of 99 %. A coverage factor of 2 provides a high level of confidence that measured doses will fall within the acceptable range, and is frequently used to set process parameters. In some cases where a higher level of confidence is desired and process conditions permit it, a coverage factor of 3, which corresponds to a confidence level of 99 %, may be used.

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The standard deviation usually is expressed in terms of a percentage by dividing its value by the average value of dose. Based on the cited example, the expanded uncertainty in minimum dose at a 95 % confidence level is:

$$2S(D_{min})/(D_{min})_{avg} \times 100 = [2 \times 0.46 \text{ kGy}/25.7 \text{ kGy}] \times 100 = 3.58 \%$$

Following the same procedure that was used to calculate the expanded uncertainty in minimum dose, the expanded uncertainty in maximum dose is:

$$2S(D_{max})/(D_{max})_{avg} \times 100 = [2 \times 0.50 \text{ kGy}/40.5 \text{ kGy}] \times 100 = 2.47 \%$$

A.3.3 Setting process parameters

A.3.3.1 Minimum dose

To have a high level of confidence that no measurement of minimum dose falls below the acceptable value of 25 kGy, processing parameters should be set to deliver a minimum dose of 25.9 kGy, which is 3.58 % greater than 25 kGy. For gamma irradiators, this would involve adjusting the cycle time; in the case of electron beam irradiators, it could involve adjusting conveyor speed or beam current. For example, in the case of gamma irradiators, the cycle time equation developed from results of the operational qualification studies could be used to calculate a cycle time for delivering a minimum dose of 25.9 kGy. Alternatively, the cycle time setting used in the dose map study to deliver an average minimum dose of 25.7 kGy could be increased by the ratio 25.9 kGy/25.7 kGy = 1.008. A similar approach involving adjustment of conveyor speed or beam current could be used for electron beam irradiators to give a high level of confidence that measurements of minimum dose exceed the acceptable value of 25 kGy.

A.3.3.2 Maximum dose

In addition to setting process parameters to satisfy minimum dose requirements, it also is important to show that no measurement of maximum dose will exceed the acceptable value of 45 kGy to a high level of confidence. Given an expanded uncertainty of 2.47 % in the maximum dose, it can be shown that these conditions are met if measurements of maximum dose on average do not exceed 43.9 kGy. Based on a maximum to minimum dose ratio of 1.58 that is found from analysis of the dose map data in Table A.1, and a minimum dose of 25.9 kGy, maximum dose should not exceed 40.9 kGy, which is significantly less than 43.9 kGy. Therefore, no measurement of dose should exceed the maximum acceptable value of 45 kGy to a high level of confidence. If the maximum to minimum dose ratio had been much greater than 1.58, as may be the case for higher density product, doses could have exceeded 43.9 kGy. In this case, it may be necessary to take appropriate action such as center loading of product to reduce the dose ratio.

A.4 Production dose monitoring procedure 2—Measurement of reference dose and use of adjustment factors to calculate minimum and maximum dose in routine processing of product

The following example shows how statistical analysis of dose map data is used for setting process parameters when dose is measured at a reference location and adjustment factors are used to calculate doses at the minimum and maximum dose locations. Dose values used in the analysis and adjustment factors are based on the following representative data taken from three replicate dose maps generated during process qualification of the product. Values of minimum and maximum dose are the same as those in Table A.1.

Table A.2—Dose map data—Procedure 2

Doses	Dose maps		
	Dose map 1	**Dose map 2**	**Dose map 3**
D_{ref}	30.4 kGy	31.2 kGy	30.6 kGy
D_{min}	26.1 kGy	25.8 kGy	25.2 kGy
D_{max}	40.0 kGy	41.0 kGy	40.6 kGy

A.4.1 Calculation of adjustment factors

Adjustment factors for the minimum and maximum dose are calculated from equations 1–4 in 5.2.4 and 5.3.4. These expressions are given by:

$$AF_{min} = (D_{ref})/(D_{min})$$

and

$$AF_{max} = (D_{ref})/(D_{max})$$

The adjustment factors in Table A.3 were derived from these expressions and the data in Table A.2.

Table A.3—Adjustment factors for minimum and maximum dose

Dose map	AF_{min}	AF_{max}
Dose map 1	1.165	0.760
Dose map 2	1.209	0.761
Dose map 3	1.214	0.754
Mean value	1.196 ≈ 1.20	0.758 ≈ 0.76

A.4.2 Uncertainty attributable to adjustment factors

Use of a reference location for routine monitoring of dose introduces an element of uncertainty in the estimate of maximum and minimum dose. This uncertainty should be taken into account when setting process parameters for the run. The variance and standard deviation in the adjustment factors can be determined from the data in Table A.3. Based on the data in Table A.3, the variance and standard deviations in the adjustment factors are:

$$Var(AF_{min}) = [(1.165 - 1.196)^2 + (1.209 - 1.196)^2 + (1.214 - 1.196)^2]/(3 - 1) = 7.27 \times 10^{-4}$$

$$Var(AF_{max}) = [(0.760 - 0.758)^2 + (0.761 - 0.758)^2 + (0.754 - 0.758)^2]/(3 - 1) = 1.45 \times 10^{-5}$$

$$S(AF_{min}) = \sqrt{Var(AF_{min})} = 2.70 \times 10^{-2}$$

$$S(AF_{max}) = \sqrt{Var(AF_{max})} = 3.81 \times 10^{-3}$$

The standard deviations, $S(AF_{min})$ and $S(AF_{max})$, can be used to correct the adjustment factors. The value of AF_{min} should be corrected to give the smallest possible value for the minimum dose, and the value of AF_{max} should be corrected to give the largest possible value for the maximum dose. Using a coverage factor of 2, which is approximately equal to a confidence level of 95 %, the corrected adjustment factors are:

$$(AF_{min})_{corr} = 1.20 + 2S(AF_{min}) = 1.20 + 0.05 = 1.25$$

and

$$(AF_{max})_{corr} = 0.76 - 2S(AF_{max}) = 0.76 - 0.01 = 0.75$$

These corrected values for the adjustment factors should be used to calculate minimum and maximum doses for the production run.

A.4.3 Estimate of uncertainty in dose measurements

Using the minimum and maximum doses of 25 kGy and 45 kGy and corrected values for the adjustment factors, the acceptable minimum and maximum reference doses for the run are:

$$(D_{ref})_{min} = (AF_{min})_{corr} \times D_{min} = 1.25 \times 25 \text{ kGy} = 31.25 \text{ kGy}$$

$$(D_{ref})_{max} = (AF_{max})_{corr} \times D_{max} = 0.75 \times 45 \text{ kGy} = 33.75 \text{ kGy}$$

A.4.4 Setting process parameters

To provide a high level of confidence that doses will not fall outside the acceptable minimum and maximum doses of 25 kGy and 45 kGy, process parameters should be set to deliver an average reference dose in the range of

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31.3 kGy to 33.8 kGy. Based on the settings used in the dose map run, which resulted in an average reference dose of $(D_{ref})_{avg}$ = (30.4 + 31.2 + 30.6) = 30.7 kGy, the cycle time or conveyor speed should be adjusted by the factor 31.3 kGy/30.7 kGy ≈ 1.02 for production processing of product.

A.5 Production dose monitoring procedure 3—Measurement of minimum dose and use of adjustment factor for maximum dose in routine processing of product

The following example shows how statistical analysis of product dose map data is used for setting process parameters when minimum dose is measured at several locations within the production run and maximum dose is calculated based on an adjustment factor that uses minimum dose as the reference dose. Dose values used in this analysis are based on the dose map data in Table A.1.

Average values of D_{min} and D_{max}, variances, and standard deviations are given in A.3.1.

A.5.1 Calculation of adjustment factor

In this example, the average minimum dose is used as the reference dose. Therefore, the adjustment factor for maximum dose is given by:

$$AF_{max} = 25.7 \text{ kGy}/40.5 \text{ kGy} = 0.63$$

where 25.7 kGy is the average minimum dose and 40.5 kGy is the average maximum dose.

This value should be corrected for uncertainty in the calculated adjustment factor.

The variance in the adjustment factor can be determined from the data in Table A.4.

Table A.4—Adjustment factors for maximum dose

Dose map	AF_{max}
Dose map 1	0.653
Dose map 2	0.629
Dose map 3	0.621
Mean value	0.634

The variance and standard deviation are given by:

$$Var(AF_{max}) = [(0.653 - 0.634)^2 + (0.629 - 0.634)^2 + (0.621 - 0.634)^2]/(3 - 1) = 2.78 \times 10^{-4}$$

$$S(AF_{max}) = \sqrt{Var(AF_{max})} = 1.67 \times 10^{-2}$$

The corrected value for the adjustment factor is given by:

$$(AF_{max})_{corr} = 0.63 - 2S(AF_{max})_{corr} = 0.63 - 0.03 = 0.60$$

A.5.2 Setting process parameters

As shown in A.3.2, the cycle time or conveyor speed should be adjusted by 3.58 % to deliver a minimum dose of 25.9 kGy, which gives a high level of confidence that measurements of dose will not fall below the acceptable value of 25 kGy. In this example, maximum dose is not measured, rather it is calculated using a corrected adjustment factor of 0.60. Based on a minimum dose of 25.9 kGy and use of 0.60 for the adjustment factor, it is seen that maximum dose is 25.9 kGy/0.60 = 43.2 kGy. This number is less than 43.9 kGy, thus ensuring with a high level of confidence that no value of dose will exceed the maximum acceptable value of 45 kGy.

Annex B
(informative)

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