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Standard Guide for Using Statistical Process Control Principles for Routine Dosimetry in Radiation Processing[1]

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INTRODUCTION

Statistical process control (SPC) is one part of the rationale used to establish rules for conformance assessment of the radiation process and processed products. The underlying rationale for product conformance assessment as it relates to the radiation process has three components: a qualified state that is demonstrated to be capable/reliable in terms of achieving the processed product specification limits; SPC applied to routine process monitoring data demonstrating no change to the qualified state, that is, a state of statistical control, and the application of a simple acceptance rule; is the process result within the process specification limits. This document provides information on the application of SPC to radiation processing with examples which include capability/reliability assessments.

1. Scope

1.1 This document provides guidance for the statistical analysis of the irradiation process from dosimetric data.

1.2 This document is one of a set of guides and practices that provide recommendations for properly implementing dosimetry in radiation processing. It is intended to be read in conjunction with ISO/ASTM 52628 and ISO/ASTM 52303.

1.3 This document employs a set of standard statistical methods and is intended to be read in conjunction with Practice E2586, Practice E2281, Practice E2587, and ASTM Manual MNL7[2].

1.4 This guide is applicable to high-energy electron beam, X-ray and gamma-ray irradiation processes.

1.5 This document assumes user knowledge of statistics, radiation processing, and radiation dosimetry. (See Annex A6)

1.6 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.7 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[3]

E122 Practice for Calculating Sample Size to Estimate, With Specified Precision, the Average for a Characteristic of a Lot or Process

E456 Terminology Relating to Quality and Statistics

E2281 Practice for Process Capability and Performance Measurement

E2586 Practice for Calculating and Using Basic Statistics

E2587 Practice for Use of Control Charts in Statistical Process Control

E3083 Terminology Relating to Radiation Processing: Dosimetry and Applications

2.2 *ISO/ASTM Standards:*[3]

51261 Practice for Calibration of Routine Dosimetry Systems for Radiation Processing

51608 Practice for Dosimetry in an X-ray (Bremsstrahlung) Facility for Radiation Processing at Energies between 50 keV and 7.5 MeV

51649 Practice for Dosimetry in an Electron Beam Facility for Radiation Processing at Energies Between 300 keV and 25 MeV

[1] This guide is under the jurisdiction of ASTM Committee E61 on Radiation Processing and is the direct responsibility of Subcommittee E61.03 on Dosimetry Application.

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[2] S. Luko, ed., *Presentation of Data and Control Chart Analysis*, 9th ed., West Conshohocken, PA, ASTM International, 2018, https://doi.org/10.1520/MNL7-9TH-EB.

[3] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

51702 Practice for Dosimetry in a Gamma Facility for Radiation Processing
51707 Guide for Estimation of Measurement Uncertainty in Dosimetry for Radiation Processing
52303 Guide for Absorbed-Dose Mapping in Radiation Processing Facilities
52628 Practice for Dosimetry in Radiation Processing
52701 Guide for Performance Characterization of Dosimeters and Dosimetry Systems for Use in Radiation Processing

2.3 *ISO Documents:*[4]
ISO 11137-1 Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices
ISO 11137-2 Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose
ISO 11137-3 Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects of development, validation and routine control
ISO 3534-1 Statistics — Vocabulary and symbols — Part 1: General statistical terms and terms used in probability
ISO 3534-2 Statistic-Vocabulary and symbols-Part 2: Applied statistics
ISO 11462-1 Guidelines for implementation of statistical process control (SPC) – Part 1: Elements of SPC
ISO 16269-6 Statistical interpretation of data – Part 6: Determination of statistical tolerance intervals

2.4 *ICRU Report*[5]
ICRU Report 85a Fundamental Quantities and Units for Ionizing Radiation

3. Terminology

3.1 *Definitions:*

3.1.1 *absorbed-dose mapping*—measurement of absorbed dose within an irradiated product to produce a one, two or three dimensional distribution of absorbed dose, thus rendering a map of absorbed-dose values.

3.1.1.1 *Discussion*—For a process load, such a dose map is obtained using dosimeters placed at specified locations within the process load.

3.1.2 *assignable cause*—factor that contributes to the variation in a process or process output that is feasible to detect and identify.

3.1.2.1 *Discussion*—Many factors will contribute to process output variation, but it may not be feasible (economically or otherwise) to identify some of them.

3.1.3 *common cause*—source of inherent random variation in a process (output) which is predictable within statistical limits (also called random cause and chance cause).

3.1.3.1 *Discussion*—Variation in the process output is inherent in all processes. The inherent variation of the process output results from multiple sources both dependent and independent contributing to the overall process output variation. These inherent sources which are always present to a greater or lesser extent are referred to as common causes. When only common cause sources of variation are present in the process output, the process is considered to be stable and in a state of statistical control. Other sources of the process output variation occurring intermittently result from sources that are not always present and not inherent to the process and are not predictable within statistical limits are referred to as special causes. (See 3.1.32.)

3.1.4 *confidence interval*—an interval estimate $[L,U]$ with the statistics L and U as limits for the parameter θ and with confidence level $1-\alpha$, where the probability $Pr(L \leq \theta \leq U) \geq 1-\alpha$.

3.1.4.1 *Discussion*—The confidence level, $1-\alpha$, reflects the proportion of cases that the confidence interval $[L,U]$ would contain or cover the true parameter value of θ in a series of repeated random samples under identical conditions. Once L and U are given values, the resulting confidence interval either does or does not contain it. In this sense "confidence" applies not to the particular interval but only to the long run proportion of cases when repeating the procedure many times

3.1.5 *control chart*—chart on which are plotted a statistical measure of subgroup versus time of sampling along with limits based on the statistical distribution of that measure so as to indicate how much common, or chance cause variation is inherent in the process or product.

3.1.6 *control limits*—limits on a control chart that are used as criteria for signaling the need for action or judging whether a set of data does or does not indicate a state of statistical control based on a prescribed degree of risk.

3.1.6.1 *Discussion*—For example, typical three-sigma limits carry a risk of 0.135 % of being out of control (on one side of the center line) when the process is actually in control and the statistic has a normal distribution.

3.1.7 *dose map, dose mapping*—See *absorbed-dose mapping*.

3.1.8 *dose uniformity ratio*—ratio of the maximum to the minimum absorbed dose within the irradiated product.

3.1.8.1 *Discussion*—The concept is also referred to as the max/min dose ratio. Product generally refers to the *process load*.

3.1.9 *irradiation container*—holder in which process load is transported through the irradiator.

3.1.9.1 *Discussion*—An *irradiation container* is often referred to simply as "container" and can be a carrier, cart, tray, product carton, pallet, product package or other holder.

3.1.10 *long term standard deviation, σ_{LT},*—sample standard deviation of all individual (observed) values taken over a long period of time.

3.1.11 *lower control limit, LCL*—minimum value of the control chart statistic that indicates statistical control.

3.1.12 *lower specification limit, LSL*—specification limit that defines the lower limiting value.

[4] Available from International Organization for Standardization (ISO), ISO Central Secretariat, Chemin de Blandonnet 8, CP 401, 1214 Vernier, Geneva, Switzerland, https://www.iso.org.

[5] Available from International Commission on Radiation Units and Measurements (ICRU), 7910 Woodmont Ave., Suite 400, Bethesda, MD 20841-3095, http://www.icru.org.

3.1.12.1 *Discussion*—In terminal sterilization radiation processing, the *LSL* is the sterilization dose per ISO 11137- 2.

3.1.13 *population*—the totality of items or units of material under consideration.

3.1.14 *population parameter*—summary measure of the values of some characteristic of a population.

3.1.15 *process capability*—statistical estimate of the outcome (output) of a characteristic from a process that has been demonstrated to be in a state of statistical control and which describes that process's ability to realize a characteristic that will fulfil the requirements for that characteristic.

3.1.16 *process capability index*—an index describing process capability in relation to a specified tolerance.

3.1.17 *process load*—volume of material with a specified product loading configuration irradiated as a single entity.

3.1.18 *process output*—a measurable and monitored characteristic which is output from the process.

3.1.18.1 *Discussion*—In radiation processing, the measured characteristic is typically the absorbed dose. However, it could also be characteristics such as dwell time, conveyor speed, beam energy, beam width, or beam current.

3.1.19 *process parameters (irradiator parameters)*—specified values for the process variables.

3.1.19.1 *Discussion*—The specification for a sterilization process parameter that may include its allowable tolerances.

3.1.19.2 *Discussion*—Examples of process parameters are cycle time and process pathway for gamma and conveyor speed, beam current and scan width in electron beam.

3.1.20 *process performance*—statistical measure of the outcome of a characteristic from a process that may not have been demonstrated to be in a state of statistical control.

3.1.21 *process performance index*—index describing process performance in relation to a specified tolerance.

3.1.22 *process quality requirement*—a confidence level corresponding to a specified maximum acceptable risk.

3.1.23 *process target dose*—the expected dose or dose range at the dose monitoring location(s) of a routine processing lot for a given set of process parameters.

3.1.23.1 *Discussion*—The relationship correlating an expected dose (or dose range) and a set of process parameters at a desired level of confidence can be developed generally from irradiator OQ and specifically from PQ.

3.1.24 *processing category*—group of different products that can be processed together.

3.1.24.1 *Discussion*—Processing categories can be based on, for instance, composition, density or dose requirements.

3.1.25 *process specification*—revision controlled document that includes product specific details, specifies the product dose requirements and provides necessary process instructions to be used for routine processing of product.

3.1.25.1 *Discussion*—See ISO 11137 Part 1, Sections 9.4.3 and 9.4.4 for guidance in establishing process specifications for sterilization applications.

3.1.26 *rational subgroup*—subgroup chosen to minimize the variability within subgroups and maximize the variability between subgroups.

3.1.27 *routine monitoring position*—position where absorbed dose is monitored during routine processing to ensure that the product is receiving the absorbed dose specified for the process.

3.1.27.1 *Discussion*—This position may be a location of minimum or maximum dose in the process load or it may be an alternate convenient location in, on or near the process load where the relationship of the dose at this position to the minimum and maximum dose has been established.

3.1.28 *routine processing lot—in radiation processing*, a user defined group of product irradiated together or sequentially on or in an uninterrupted set of irradiation containers, characterized by one set of routine dosimetry results and one set of processing conditions.

3.1.28.1 *Discussion*—This is often termed a "batch", or a "run", or a "lot", where such terms are usually defined locally.

3.1.29 *sample*—a group of observations or test results, taken from a larger collection of observations or test results, which serves to provide information that may be used as a basis for making a decision concerning the larger collection.

3.1.29.1 *Discussion*—Subset of a population made up of one or more sampling units.

3.1.30 *sample statistic*—summary measure of the observed values of a sample.

3.1.31 *short term standard deviation,* σ_{ST}—the inherent variation present when a process is operating in a state of statistical control, expressed in terms of standard deviation.

3.1.32 *special cause*—source of intermittent variation in a process output.

3.1.32.1 *Discussion*—Sometimes "special cause" is taken to be synonymous with "assignable cause." However, a distinction should be recognized. A special cause is assignable only when it is specifically identified. Also a common cause may be assignable.

3.1.32.2 *Discussion*—A special cause arises because of specific circumstances which are not always present. As such, in a process subject to special causes, the magnitude of the process output variation from time to time is unpredictable, that is, not predictable within statistical limits

3.1.32.3 *Discussion*—In radiation processing an example of a special cause may be a source interrupt during processing.

3.1.33 *specification limit*—limiting value stated for a characteristic.

3.1.33.1 *Discussion*—In radiation processing an example of a specification limit is the dose specification limit, the Upper Specification maximum product dose limit (*USL* – see 3.1.42) and the Lower Specification minimum product dose limit (*LSL* – see 3.1.12). Other examples of specification limits are the limits associated with a process parameter (see 3.1.19)

3.1.34 *stable process*—prorocess in a state of statistical control; process condition when all special causes of variation have been removed.

3.1.34.1 *Discussion*—Observed variation can then be attributed to random (common) causes. Such a process will generally behave as though the results are simple random samples from the same population.

3.1.34.2 *Discussion*—This state does not imply that the random variation is large or small, but rather that the variation is predictable within statistical limits.

3.1.34.3 *Discussion*—In radiation processes, the operation of the irradiator due to cost considerations or efficiency considerations may define the standard process to include special causes, thus defining some special causes as anticipated common causes, for example, partially filled irradiation containers. In doing so, the process output characterization sampling must include sampling of these special causes to ensure the statistical model of the process output accurately captures these sources of variation.

3.1.35 *standard deviation—of a population*, σ, the square root of the average or expected value of the squared deviation of a variable from its mean; - of a sample, *s*, the square root of the sum of the squared deviations of the observed values in the sample divided by the sample size minus 1.

3.1.36 *standard error*—standard deviation of the population of values of a sample statistic in repeated sampling or an estimate of it.

3.1.36.1 *Discussion*—If the standard error of a statistic is estimated, it will itself be a statistic with some variance that is dependent on the sample size (for further description of the concept of standard error, see E2586, subsection 6.19).

3.1.37 *Statistical Process Control (SPC)*—set of techniques for improving the quality of process output by reducing variability through the use of one or more control charts and a corrective action strategy used to bring the process back into a state of control.

3.1.38 *stratified sampling*—sampling in which the population to be sampled is first divided into mutually exclusive subsets or strata, and independent samples are taken within each stratum.

3.1.38.1 *Discussion*—Strata partitions are collectively exhaustive (no population element is excluded).

3.1.38.2 *Discussion*—A stratified sampling method is conducted as a proportionate allocation or an optimum allocation. Stratified sampling ensures that at least one observation is selected from each strata.

3.1.38.3 *Discussion*—Proportionate allocation ensures the sample size from each stratum is proportionate to the population size of the stratum. Proportionate allocation ensures the estimate of the overall population mean is equal to the unweighted sample average.

3.1.38.4 *Discussion*—Optimal allocation ensures larger samples are taken in the strata with the greatest variability relative to the population.

3.1.38.5 *Discussion*—Stratified sampling will nearly always provide a greater precision/reliability than random sampling for estimating population parameters. The greater the difference between strata, the greater the gain in precision/reliability compared to random sampling.

3.1.38.6 *Discussion*—Strata partitions are defined based on the population characteristic under study and the experimental design of the study.

3.1.38.7 *Discussion*—In dose mapping, strata are denoted by dose magnitudes; maximum dose strata, equivalent maximum dose strata, minimum dose strata, equivalent minimum dose strata, and intermediate dose strata so that no population element is excluded.

3.1.38.8 *Discussion*—In radiation processing, strata can be defined by characteristics that represent known common cause sources of variation acting on the routine process and expressed in the process output summary statistics. An example of this are partially filled irradiation containers or variation of loading configuration geometries and leading/trailing edge effects.

3.1.39 *subgroup average,* $\bar{x}_i$—average for the *i*th subgroup in an *X*-bar chart.

3.1.40 *subgroup standard deviation,* s_i,—sample standard deviation of the observations for the *i*th subgroup in an s-chart.

3.1.41 *upper control limit, UCL*— maximum value of the control chart statistic that indicates statistical control.

3.1.42 *upper specification limit, USL*—specification limit that defines the upper limiting value.

3.1.42.1 *Discussion*—In terminal sterilization radiation processing, the *USL* is the maximum acceptable dose per ISO 11137-3.

3.2 Definitions of other terms used in this standard that pertain to quality and statistics may be found in Terminology E456. Definitions of other terms used in this standard that pertain to radiation measurement and dosimetry may be found in Terminology E3083. Definitions in Terminology E3083 are compatible with ICRU 85a; that document, therefore, may be used as an alternative reference.

4. Significance and Use

4.1 Control charts are the primary process monitoring tool in SPC for radiation processing. The general objectives of implementing a SPC program with control charts are to:

4.1.1 Increase knowledge of the process,

4.1.2 Control the process to provide a targeted or required process output,

4.1.3 Reduce variation of the process output or in other ways improve the performance of a process, and

4.1.4 Identify single process run results that are outside of established control limits but may be within the *USL* and *LSL* limits.

4.2 These objectives when achieved:

4.2.1 Reduce costs through reduction of losses due to scrap, rework, and investigation time,

4.2.2 Improve consistency of the process output,

4.2.3 Facilitate preventive process adjustments, and

4.2.4 Provide evidence of accurate process targeting and process performance; state of statistical control.

5. Prerequesites

5.1 The dosimetry system has been calibrated in accordance with ISO/ASTM 51261 and the user's measurement management system; see ISO/ASTM 52628. These standard practices and user requirements establish traceable dosimetry with a defined level of uncertainty appropriate for the conditions of use.

5.2 Irradiator installation qualification (IQ), irradiator operational qualification (OQ), and performance qualification dose mapping (PQ) have been completed and user documented performance acceptance criteria have been met.

5.3 Implementation of appropriate product processing procedures to provide control and management of the process inputs within their normally expected or specified limits. Such procedures are part of an SPC control plan (see ISO 11462-1).

NOTE 1—In radiation processing, process inputs embody a number of factors and characteristics each with specification limits that ensure process output (for example, dose) meets expectation. The specific factors and characteristics will vary due to differences in product definition, process definition, radiation source and irradiator control systems, qualified control parameters values from performance qualification of the product or product family and the resulting common cause sources of variation present or acting on the process.

6. Overview – Control Charts

6.1 This section provides a general description of control charts using dose measurements. Section 7 provides guidance specific to the application of control charts for radiation processes.

6.2 A control chart is the SPC analysis tool for trending and evaluating a process based on the process output (for example, dose). The control chart is composed of three parts; the center line, control limits above (UCL – upper control limit) and below (LCL – lower control limit) the center line, and the plot of the process output dosimetric data.

NOTE 2—Dose measurements can be plotted as the measured value or as a residual value representing the difference between the measured value and the standard. Dose measurements can also be plotted as normalized dose values, for example, dose rate corrected for exposure process parameters like cycle time in gamma or conveyor speed in electron beam.

NOTE 3—SPC can also be applied to non-dosimetric process monitoring output data that is functionally related to a process output dose. Examples of non-dosimetric process monitoring output are irradiation process control parameters, such as beam current, conveyor speed, scan rate, pulse rate, etc.

6.2.1 The center line is the value of the standard given. (See 6.3 and Note 4 for description of "standard given").

6.2.2 The control limits are the $\pm 3\sigma$ statistical limits which estimate the extent of random variation about the standard given (center line) due to common cause sources acting on the process.

6.2.3 In some cases, alert/warning limits are also used which are similar to $\pm 3\sigma$ control limits but at lower coverage levels (higher levels of significance, α), for example, $\pm 2\sigma$. (See Section 8 and Annex A2).

6.3 There are two purposes for control chart analysis. One where the analysis is used to derive a statistical model of the process output dose (termed control no standard given) and the other where the analysis is used to compare the process output dose to a qualified *a priori* statistical model (termed control standard given).

NOTE 4—In radiation processing, the 'standard' in the context of 'control standard given' is the aimed-at value or process target (dose) based on characterized relationships established in prerequisite studies, see 5.2, 7.2.1.1, and 7.2.1.2 where the latter two are the basis of the *a priori* statistical model. The standard value may be an experience value based on representative *a priori* data, or an economic value established on consideration of needs of service and cost of production, or a desired or 'aimed-at' value. Examples deriving the standard value of a process level and examples of process targeting are given in A3.3 and A3.4.

6.4 Sampling is the collection of data from a number of observations that is purportedly representative of a larger grouping or population.

6.4.1 Sampling is performed to collect data from which the process level and process variation expectations are derived. This sampling is the data collected and used in the evaluation phase of SPC control chart implementation. (See 6.6.1 and 7.3) The population parameter μ is estimated with the sample mean $\bar{x}$ and the population standard deviation σ is estimated with the sample standard deviation s.

6.4.2 The quality of the sample representation of the population is dependent on the sampling procedure and sample size. An appropriate sampling procedure for radiation processing addresses process stratification by sampling from all strata with a sufficient frequency. (See 3.1.38.)

6.5 The output of a radiation process is evaluated for two characteristics: a process level (subgroup average dose see 7.4.1 and Note 10) and process variation (variation of the individual dose measurements used to calculate the subgroup average dose). SPC chart trending consists of a two chart pair, either an *X*-bar/s-chart pair or an *X*-bar/*R*-chart pair.

6.5.1 The *X*-bar/*s*-chart pair evaluates the process output level (subgroup average dose) with the *x*-bar chart and the process variation with the *s*-chart (variation of the individual dose measurements used to calculate the subgroup average dose).

6.5.2 The *X*-bar/*R*-chart pair evaluates the process output level (subgroup average dose) with the *x*-bar chart and the process variation with the *R*-chart (range of the individual dose measurements used to calculate the subgroup average dose).

6.6 Control chart implementation as part of a SPC plan consists of three phases; process evaluation, process monitoring, and process improvement.

6.6.1 Process evaluation is the derivation of the *a priori* statistical model of process output.

6.6.1.1 The process evaluation phase consists of the collection of process output sample data either from performance qualification dose mapping data or historic processing output data (see Annex A3 and Annex A4) used to determine:

6.6.1.2 Current state of the process performance (statistical model characterizing the process output).

6.6.1.3 Appropriate control limits for the process level chart ($\bar{x}$-chart) and the process variability chart (either *R*-chart or *s*-chart).

6.6.2 Process monitoring is control chart trending of the process output.

6.6.2.1 The process monitoring phase consists of continuous monitoring and control chart trending of a process for any signal that a change in the state of control may have occurred.

6.6.3 Process improvement is the restoration of the process to the qualified state.

6.6.3.1 The process improvement phase consists of investigation and when appropriate, correction of a special cause signal observed in process output.

NOTE 5—After the initial process evaluation phase, the process monitoring phase starts. When process monitoring identifies the occurrence of a likely special cause event, the process improvement phase starts. The conclusion of the process improvement phase occurs when either a special cause signal becomes an assignable cause and the assignable cause is mitigated returning the process to a state of control or the special cause signal is determined to be a Type I error, for example, risk of signal associated with the user selected α. The process monitoring phase resumes at the conclusion of the process improvement phase.

7. Radiation Process Specific Considerations

7.1 *General:*

7.1.1 SPC in radiation processing is a means of demonstrating the process target dose is achieved within statistical control limits, that is, the process output (product dose or other monitored measurement that is directly correlated to product dose) is representative of a sample drawn from the *a priori* statistical model (standard given, see 6.3 and Note 4).

7.1.2 Process targeting is based on the relationship between the irradiator control parameter values and the realized dose of the process output. This relationship is independent of Upper Specification Limits (*USL*) and Lower Specification Limit (*LSL*) of product(s) processed.

NOTE 6—A process that is in a state of control can fail to meet product *LSL* or *USL* requirements if the process is not targeted appropriately. This type of failure is a failure to appropriately target the process or accurately assess the process capability or reliability to meet product *LSL* and *USL*. (See A3.2 and A3.3).

7.1.3 A process capability or reliability assessment correlates the process targeting used, the *a priori* statistical model of processed product dose, and the *LSL* and *USL* product requirements. An acceptable process capability or reliability assessment result provides evidence that product processed will meet product *LSL* and *USL* specifications for the process in a state of control at the level of confidence used in the capability or reliability assessment.

7.2 *Control*—Standard Given:

7.2.1 In radiation processing, SPC charts are analyzed in the context of control standard given; which determines whether observed process output level and variation (see 6.5 through 6.5.2) differ from a standard value by an amount greater than should be attributed to random chance. The *a priori* statistical model of a radiation process output is based on sampling from:

7.2.1.1 Performance qualification dose mapping, or

7.2.1.2 Historic process output.

7.3 *Sampling the Irradiation Process*—Evaluation Phase

7.3.1 Samples should be taken from the actual process intended to be routinely used (conditions of use).

7.3.1.1 Historically, Performance Qualification dose mapping has used a single sample (N=1) with three replicates (n=3). This may be sufficient to determine some product dose accrual characteristics; however, it may not be sufficient to achieve the user's requirements for estimating process output population parameters (μ and σ) from sample parameters ($\bar{x}$ and s). For guidance on sample size (n) see Annex A8.

NOTE 7—A larger number of samples (N) will improve the estimates of the 'between/reproducibility' sample of process variation. A larger number of sample replicates (n) will improve the estimates of the 'within/repeatability' sample of process variation.

NOTE 8—Conditions of use in 7.3.1 refer to the common cause sources of variation in the routine process. If, for example, partially filled irradiation containers are intended to be used, stratified sampling will include partially filled irradiation containers in the process from which samples of the process are taken.

7.3.2 *Dose Map Data Source:*

7.3.2.1 Performance qualification dose mapping is conducted to determine the dose distribution throughout the process load (see ISO/ASTM 52303). The dose map data then represents the low doses, high doses, and intermediate doses for the range of dose delivered to the processed product. The range of doses can be grouped, for example, high doses and low doses, or in the extreme, to a number of groups equal to the number of dose map locations.

NOTE 9—Dose map grid locations and grouping of dose map grid locations are defined by the user based on the user's design of experiment and intended analysis of the variable(s) of interest. (See ISO/ASTM 52303.)

7.3.2.2 Different groups of dose map dose values have different process level values and may have different process variation values which are often a consideration when defining a group of dose map dose values. One example of grouping is equivalency in the case of a minimum detectable difference, MDD. (See ISO/ASTM 52303 for information on minimum detectable difference.)

7.3.2.3 One limitation of sampling the process output from performance qualification dose map data is the number of sample replicates (n). (See 6.4.2 and Note 7.) The process level associated with the minimum dose and maximum dose from N=1 and n=3 in radiation processing is usually a good estimate of the level. However, the process variation estimate with N=1 and n=3 may be inaccurate **(1)**.[6]

7.3.2.4 The potential inaccuracy of the estimate of the repeatability of/within a sample (N=1) of process variation can be mitigated by using a c4 correction factor (see Annex A5), using a t-distribution factor, or in some cases a pooled standard deviation of a partition, for example, where the partition represents the low dose and equivalent low doses based on a minimum detectable difference partition.

7.3.2.5 Another limitation of sampling the process output from performance qualification dose map data from a single sample (N=1) is that no information is collected for the 'between/reproducibility' of a sample (between samples N_1, N_2, N_3, …) of process variation. (See Note 7).

7.3.3 *Historic Process Output Source:*

7.3.3.1 Process output data in terms of product minimum and maximum dose can be used to prepare accurate unbiased

[6] The boldface numbers in parentheses refer to a list of references at the end of this standard.

estimates of the process level 'standard given' and the process variation 'standard given.' (See 6.3 and Note 4.)

7.3.3.2 The assumption of a state of control is based on the process level and process variation standards, their corresponding control limits, and process output values occurring within the control limits.

7.3.3.3 For this to be the case, all rational subgroups (see 7.4.1 and Note 10) should achieve the process target within the statistical limits defined by the control limits.

7.3.3.4 A one-way analysis of variance (ANOVA) can be used to prepare estimates of the process level and process variation standard and demonstrate the samples (*N*1, *N*2, *N*3, …) were sampled during a state of control. (See Annex A4).

7.4 *Plotting Control Chart Data*—Monitoring Phase

7.4.1 Radiation processing consists of sequences of individual processing runs. The individual processing run represents a rational subgroup, *N*. The runs (rational subgroups) are monitored in accordance with a routine process monitoring dosimetry practice that specifies a monitoring location(s) and monitoring frequency resulting in '*n*' replicate measurements for each subgroup.

NOTE 10—The nomenclature for the rational subgroup and replicate measurements corresponds to sampling nomenclature, that is, *N* samples (processing runs) of *n* replicate measurements or observations (monitored irradiation containers). The sample size adjustment applied to statistical computations is the number of measurements/observations, *n*. (See Annex A5.)

7.4.2 When the monitoring frequency represents a near constant sampling rate of the subgroup, control chart control limits will have a constant value. When the monitoring frequency does not represent a near constant sampling rate of the subgroup, control chart limits must be updated for each subgroup. (See examples 4 and 6 in Chapter 3 of MNL7[2] for sample size adjustments for control limits).

NOTE 11—Generally, in radiation processing when routine monitoring frequency does not represent a near constant sampling rate, this typically occurs in an off-product reference point routine monitoring practice process, that is, an off-product reference location that precedes the run and an off-product reference location that follows the run where run size is variable subgroup to subgroup.

7.4.3 Data used in the SPC chart trending of the process level may need to be normalized for processing control parameters such as:

7.4.3.1 Cycle timer setting and activity for gamma (see Annex A4).

7.4.3.2 Conveyance speed, beam current, and scan for electron beam.

NOTE 12—The fundamental dose delivery control parameters are the radiation field intensity and duration of exposure. Typically, a single primary control parameter is used to control duration of exposure regulating dose delivery magnitude, for example, cycle timer setting in gamma and conveyor speed in electron beam and X-ray. However, secondary parameters representative of the radiation source must also be considered in some instances, for example, a source activity value in gamma, and two values in electron beam and X-ray; beam current and scan (analogous to source activity) and pulse rate in pulsed systems.

8. Interpretation of Control Chart

8.1 *General:*

8.1.1 In radiation processing, the process level and process variation control chart pair are used to:

8.1.1.1 Provide documented evidence of the state of statistical control of the process; process output observations falling within predicted statistical limits (control limits).

8.1.1.2 Signal the user to likely special cause events; process output observations falling outside of predicted statistical limits (control limits, alert/warning limits).

NOTE 13—Signaling can also be represented by additional interpretation rules, see 8.2 and Note 14.

8.2 The interpretation of the control chart data represents evaluation of the observational data in comparison to the control chart control limits (and potentially alert/warning limits) to detect special cause events.

8.2.1 Special cause events are signaled:

8.2.2 If the subgroup observation exceeds the 3σ control limits.

8.2.3 If the subgroup observation exceeds the 2σ alert/warning limits at a frequency greater than is predicted by the confidence level of the alert/warning limits.

8.2.4 The user may choose to identify additional rules based on their process for the interpretation of control chart data. The following are examples of additional rules that some users may choose to use when appropriate for their process:

8.2.4.1 Two out of three consecutive observations outside of defined alert/warning limit on the same side of the center line.

8.2.4.2 Four out of five consecutive observations fall outside of a 1σ limit on the same side of the center line.

8.2.4.3 Nine consecutive observations on the same side of the center line.

NOTE 14—The rules in 8.2.2 and 8.2.3 are generally applicable to all processes. However, the application of additional rules such as those identified in 8.2.4.1 through 8.2.4.3 may vary from user to user. Users whose process have either a large number of common cause source(s) of variation or a few common cause sources of variation that are very large in magnitude are more likely to benefit from implementing additional rules or alert/warning limits in terms of identifying and eliminating special cause sources of process variation and reducing common cause source process variation. A thorough discussion of chart types and rules for interpretation can be found in Refs (**2 and 3**).

8.3 Special cause events, when signaled by the identified rules, are investigated to determine the root cause, and to identify corrective action and preventative action to return the process to a state of control.

8.3.1 If the assignable cause is a systematic change that cannot be corrected, that is, an engineering change to the irradiator altering the irradiator performance or an irreversible change to the product, an update to the process level and variation standard and their respective control limits is necessary. This may necessitate a repeat in whole or in part of OQ or PQ.

9. Keywords

9.1 common cause; control chart; control limit; process improvement; radiation processing; rational subgroup; special cause; state of statistical control; statistical process control

ANNEXES

(Mandatory Information)

A1. PROCESS CONTROL, PROCESS TARGET, PROCESS CAPABILITY, PERFORMANCE, AND RELIABILITY

A1.1 Scope

A1.1.1 This annex describes the concepts, relationships and application of Process Control, Process Target, Process Capability, Process Performance, and Process Reliability with respect to radiation processing.

A1.2 Process Control

A1.2.1 A process is conducted to produce a product with a desired or targeted process added value (product dose). The process added value is defined in terms of a process specification or specification range; a dose range specification in radiation processing consisting of an *USL* – upper specification limit (maximum acceptable dose per ISO 11137-3) and an *LSL* – lower specification limit (sterilization dose per ISO 11137-2). The quantity of process added value (dose) is controlled by the irradiator process control parameter(s). The process output (processed product) to be defined as successful (conforming) has a process added value (dose) that falls within the process specification range (dose range specification). A common interest for all processes is whether the process has the ability to produce an output that will conform to the product specification. This ability of the irradiation process to produce a conforming product dose can be estimated in several ways; a process capability index, a process performance index, or a process reliability estimate. (See A1.4.) These measures represent the quality of the process output or the degree of process control with respect to product dose specifications; to what degree the process can routinely produce a conforming product dose. These types of evaluations allow the user to assess a process output and the process targeting in the context of a product dose range specification.

A1.3 Process Target

A1.3.1 The irradiation process is targeted through specifying process control parameter values, that is, cycle timer setting, process pathway, conveyance velocity, beam current, scan, etc. The values of these control parameters are selected to target a specific process output dose result (quantity of process added value). This process target dose is the 'aimed-at' value. (See Note 1 and Note 6) The relationship(s) of the control parameter values and the irradiation process output dose are generically characterized in irradiator OQ studies and specifically characterized for an individual product or product family in product PQ studies. The process target dose is identified in the context of the product dose range specification.

A1.4 Process Capability, Performance, and Reliability

A1.4.1 To determine whether an identified process target provides a process added value that meets the process specification limit(s), a sample of the process output is used to prepare either a capability, performance or reliability estimate.

A1.4.2 *Process capability and performance:*

A1.4.2.1 Process capability (PC) or process performance (PP) is defined as the range of the process added value. The standard practice is to estimate the process capability or process performance as a '6-sigma' relationship.

$$PC = 6\sigma_{ST} \tag{A1.1}$$

$$PP = 6\sigma_{LT} \tag{A1.2}$$

The process capability or performance is related to the process specification as an index (Cp or Pp) calculated as the ratio of a process specification range (*USL-LSL*) to the process added value output range (6σ).

$$Cp = \frac{USL - LSL}{6\sigma_{LT}} \tag{A1.3}$$

$$Pp = \frac{USL - LSL}{6\sigma_{ST}} \tag{A1.4}$$

A1.4.2.2 Process capability (Cp) and process performance (Pp) are estimates under the assumption the process target and process output are centered within the process specification limits. Similar estimates where the assumption that the process target and process output are not centered are denoted with Cpk and Ppk. When the process target and process output are not centered within the specification limit, the capability or performance of the process with respect to the *USL* and *LSL* are not the same; see A3.2 example. To account for this, the index (Cp or Pp) is split into two separate single-sided estimates (see Eq A1.5 and Eq A1.6). These estimates consider the product dose average against a single or double sided specification limit estimating to what degree the process can routinely produce an average product dose within the product dose specification limits.

$$\hat{C}pk; \frac{USL - \bar{x}_{\max}}{3\sigma_{ST}}, \frac{\bar{x}_{\min} - LSL}{3\sigma_{ST}} \tag{A1.5}$$

$$\hat{P}pk; \frac{USL - \bar{x}_{\max}}{3\sigma_{LT}}, \frac{\bar{x}_{\min} - LSL}{3\sigma_{LT}} \tag{A1.6}$$

The capability or performance index for the average product minimum or maximum dose is estimated at a confidence level represented by the multiplier applied to the short term (σ_{ST}, see

TABLE A1.1 Reliability Determination for k_3 and Interpretation

Sample Size	k_3 Factor	Confidence Level	Reliability Level	Interpretation
n=5	2.862	90 %	≥91 %	In 90 % of subgroups, at least 91 % of observations above *LSL*
		95 %	≥84 %	In 95 % of subgroups, at least 84 % of observations above *LSL*
		99 %	≥67 %	In 99 % of subgroups, at least 67 % of observations above *LSL*

3.1.31) or long term (σ_{LT}, see 3.1.10) standard deviation of the index ratio denominator. A Cpku index for a *USL* is shown graphically in Fig. A1.1.

A1.4.3 *Process Reliability:*

A1.4.3.1 Process reliability is another measure of the ability of the process to produce a process added value output that falls within the process specification limit(s). However, the reliability estimate is not for the average product minimum or maximum dose like the capability or performance index, but is for any individual product minimum or maximum dose observation. This is done with a single-sided tolerance interval instead of a confidence interval. A reliability estimate is composed of two qualifiers used to assess the process, a confidence level and reliability level. The reliability is the percent of the subgroup individual observations that fall within the tolerance interval. The confidence level represents the percentage of process subgroups the reliability percentage applies to. For example, 95 % reliability at a 99 % confidence means that in 99 % of all sub groups, the range of sub group values will be contained in the tolerance interval 95 % of the time. In radiation processing, any individual subgroup observation that falls outside of the process specification limits results in a non-conforming subgroup.

A1.4.3.2 The estimate of reliability consists of rearrangement of the capability index solving for the coverage factor denoted as k_3 to indicate a tolerance rather than a capability assessment.

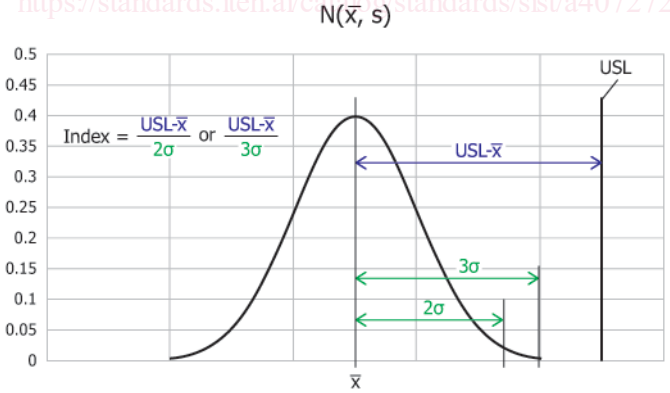

FIG. A1.1 Indices for *USL* (Cpku uses σ_{ST} and Ppku uses σ_{LT})

$$k_{3\min} = \frac{\bar{x}_{\min} - LSL}{S_{\min}} \quad \text{(A1.7)}$$

$$k_{3\max} = \frac{USL - \bar{x}_{\max}}{S_{\max}} \quad \text{(A1.8)}$$

NOTE A1.1—The k_3 one-sided tolerance limit factor denotes a specific premise of knowledge or state of characterization of the sampled population parameters. The k_3 factor is used for determining upper and lower tolerance limits when the population parameter σ is unknown; estimated from a sample standard deviation *s*. Other tolerance limit factors and their corresponding assumptions can be found in ISO 16269-6.

NOTE A1.2—The k_3 factor nomenclature is the nomenclature used in ISO 16269-6, however other documents use k_1 or simply *k* to represent the one-sided tolerance limit factor. The reader is advised to ensure when sourcing published values for a one-sided tolerance limit factor that the factor is for an unknown population variance/standard deviation, that is, it is based on a sample estimate.

The estimate of the coverage factor derived from Eq A1.7 or Eq A1.8 is then compared to a single-sided tolerance coverage factor for the specified confidence level to determine the reliability level.

As an example, a reliability estimate for minimum dose derived from 5 dose maps given a minimum dose sample standard deviation estimate of s_{min} = 0.524, and average minimum dose of $\bar{x}_{\min}$ = 26.5 kGy, and a lower specification limit (*LSL*) of 25.0 kGy gives a $k_{3\min}$ reliability coverage factor for Eq A1.7 of:

$$k_{3\min} = \frac{26{,}5 - 25.0}{0{,}524} = 2.862$$

Looking up the $k_{3\min}$ value from a one-sided tolerance limit table for a normal distribution, a coverage value of 2.862 provides the following estimates of reliability for various confidence levels (See Table A1.1):

NOTE A1.3—Reliability values in Table A1.1 are from a more extensive table of k_3 limits (**4**, **5**) than are provided in ISO 16269-6.

NOTE A1.4—The reliability interpretations in Table A1.1 can also be phrased as less than 1-reliability level of observations below the *LSL*, for example for a 90 % confidence level and 91 % reliability; In 90 % of subgroups, less than 9 %, (1-0.91) % of observations below the *LSL*.

A2. CONTROL CHART: CONTROL LIMITS / ALERT-WARNING LIMITS

A2.1 Scope

A2.1.1 There are several means of establishing special cause signaling for a control chart; control limits and alert-warning limits. Control limits are the standard industry practice for signaling a suspect special cause event. In addition to control limits, some users as a means to limit type II errors implement alert-warning limits and associated rules for signaling suspect special cause events.

A2.2 Control Limits

A2.2.1 Control limits are threshold limits above (UCL – upper control limit) and below (LCL – lower control limit) the center line of a control chart. Control limits are generally specified as a 3σ confidence interval. General interpretation of the control limits are if the process output observations fall within the control limits, the process is in a state of statistical control. This is analogous to a hypothesis test where the null hypothesis (H_0) is that the process is in a state of statistical control, that is, ±3σ control limits represent the threshold for rejecting the null hypothesis. ±3σ control limits represent an α-risk of 0.30 %, 0.15 % at +3σ and 0.15 % at -3σ. Generally, the larger the α-risk the lower β-risk. The amount of β-risk is not directly proportionate to the α-risk. Several factors including the actual magnitude of the change in the process, the sample size, and potential bias in the estimate of σ influence the amount of β-risk. (See Table A2.1.)

TABLE A2.1 Hypothesis Test – Type I and Type II Errors

Decision about the state of the process	True state of the process	
	Process is in a state of control	Process is out of a state of control
Process in control	No error is made in decision	Type II error β-risk
Process out of control	Type I error α-risk	No error is made in decision

A2.2.2 If the 3σ confidence interval is biased, that is, the estimate of σ contains bias, the sensitivity of the control chart is impacted and can increase the likelihood of committing a type I or a type II error. For example, if the estimate of σ is biased high, the control chart loses sensitivity to detect a change in the process resulting in an increase in the probability of committing a type II error. If the estimate of σ is biased low, the control chart provides a larger number of false special cause signals resulting in an increase in the probability of committing a type I error. (See Note A4.3)

A2.3 Alert-Warning Limits

A2.3.1 Alert Limits are similar to control limits and are sometimes incorporated in control charts to 'alert' the user prior to an actual loss of a state of control, that is, reduce the probability of committing a type II error. Alert limits are generally specified as a ±2σ confidence interval. Specific rules for control chart interpretation employing alert limits are necessary as 2σ alert limits represent a higher α-risk. 2σ alert limits represent an α-risk of 4.6 %, 2.3 % at +2σ and 2.3 % at -2σ.

A2.4 SPC Hypothesis

A2.4.1 The SPC charts perform an on-going analysis that is analogous to a hypothesis test, that is, does the plotted subgroup data point statistically appear to be a sample drawn from the 'standard given' population (qualified process in a state of control). The threshold or critical value that is used to determine whether or not the subgroup data point statistically appears to be drawn from the qualified process in a state of control are the control limits of the respective control chart. An observation in excess of a control limit signals a potential special cause event, that is, a sample that statistically appears to be drawn from a population other than the 'standard given' population.

A3. EXAMPLE OF PQ DATA ANALYSIS FOR DEVELOPING PROCESS LEVEL AND PROCESS VARIATION CONTROL CHARTS

A3.1 Scope

A3.1.1 This annex provides a computational example of an estimate of process capability, a practical example of process target and process targeting, and the development of the standard (expectation) and control limits for a process level and process variation controls chart from Performance Qualification (PQ) data.

A3.1.2 *PQ map data*—See Table A3.1.

A3.2 Process Capability Indices

A3.2.1 A process is capable when at a specified level of confidence the average minimum dose will be observed above the *LSL* and the average maximum dose will be observed below the *USL*. A capability assessment of the performance qualification dose map data of Table A3.1 gives capability index estimates shown below. The estimate of the sample standard deviation for minimum and maximum average dose may or may not include sampling error bias. Several methods for preparing an unbiased sample standard deviation estimate are identified in 7.3.2.4. The following assumes no sampling error or bias of the sample standard deviation estimate of the population standard deviation.

$$Cpkl_{95\%\ \text{confidence}} = \frac{(\bar{x}_{\min} - LSL)}{k(s)} = \frac{(24.2 - 25.0)}{2(1.484363)} = 0.269 \quad \text{(A3.1)}$$

$$Cpku_{95\%\ \text{confidence}} = \frac{(USL - \bar{x}_{\max})}{k(s)} = \frac{(50.0 - 38.8)}{2(1.650253)} = 3.393 \quad \text{(A3.2)}$$

where:

Cpkl = capability index associated with the *LSL* (lower specification limit), and

TABLE A3.1 Performance Qualification Dose Map Data

Map 1				Map 2				Map 3			
Location	Dose	Location	Dose	Location	Dose	Location	Dose	Location	Dose	Location	Dose
1A1	39.6	24A1	34.2	1A1	37.6	24A1	34.7	1A1	32.8	24A1	37.1
1A2	35.5	24A2	35.4	1A2	35.3	24A2	37.6	1A2	32.7	24A2	33.5
1A3	30	24A3	34	1A3	29.1	24A3	32.5	1A3	27.1	24A3	29.9
1A4	35.4	24A4	29.8	1A4	36.6	24A4	30.9	1A4	33.9	24A4	31.9
1B1	39.6	24B1	35	1B1	33.8	24B1	37.6	1B1	32.2	24B1	33.6
1B2	39.3	24B2	28.7	1B2	36	24B2	30.7	1B2	34.5	24B2	28.6
1B3	30.3	24B3	31.2	1B3	29.9	24B3	31.6	1B3	28.7	24B3	29.6
1B4	33.2	24B4	30	1B4	28.9	24B4	29.7	1B4	26.5	24B4	27.7
8A1	40.4	32A1	31.6	8A1	38.8	32A1	34.4	8A1	33.1	32A1	31.4
8A2	36.2	32A2	36.5	8A2	36.4	32A2	35.8	8A2	34.5	32A2	34.7
8A3	35.3	32A3	34.2	8A3	34.9	32A3	33.5	8A3	31.2	32A3	32.7
8A4	32.5	32A4	31.5	8A4	33.1	32A4	31.4	8A4	26.3	32A4	30.9
8B1	29.2	32B1	37.5	8B1	32.3	32B1	36.9	8B1	31.5	32B1	35.6
8B2	30.7	32B2	24.6	8B2	31.9	32B2	25.5	8B2	26.3	32B2	29.6
8B3	32.8	32B3	28.5	8B3	30.9	32B3	28	8B3	29.8	32B3	27.5
8B4	28.8	32B4	29.6	8B4	29.5	32B4	32.9	8B4	29.5	32B4	31.1
16A1	27.8	38A1	31.5	16A1	37.6	38A1	30.5	16A1	34.2	38A1	28.3
16A2	39.6	38A2	30.8	16A2	37.4	38A2	32.5	16A2	36.6	38A2	28.8
16A3	35.1	38A3	37.5	16A3	35.8	38A3	37.5	16A3	33.3	38A3	24.7
16A4	27.7	38A4	25.5	16A4	30.7	38A4	26.5	16A4	25.8	38A4	24.2
16B1	33.2	38B1	31.3	16B1	31.6	38B1	37.6	16B1	28	38B1	31.3
16B2	28.4	38B2	34	16B2	27.2	38B2	33	16B2	25.5	38B2	29.3
16B3	32.5	38B3	25.5	16B3	29.9	38B3	26.1	16B3	27.9	38B3	24.6
16B4	29.2	38B4	30.3	16B4	27.4	38B4	28.6	16B4	22.6	38B4	26.3
Map 1				Map 2				Map 3			
Minimum Dose =		24.6		Minimum Dose =		25.5		Minimum Dose =		22.6	
Maximum Dose =		40.4		Maximum Dose =		38.8		Maximum Dose =		37.1	
DUR =	1.642			DUR =	1.522			DUR =	1.642		