Release from an Electron Beam Irradiation Process Based on Irradiator Parameters (RBIP): Introductory Guidance

Scope

This document describes a method of process control and release from an irradiation process using electron beams, based on calculated dose values. The method is known as “Release Based on Irradiator Parameters” (RBIP) and employs a combination of dose calculated using monitored irradiator variables and physical dose measurements. An expansion of the method to cover x-ray and gamma irradiation will be published in subsequent documents.

Introduction

Release of product from an irradiation sterilization process is based on obtaining evidence that the product has received a radiation dose within the range given in the process specification. Detailed requirements for establishing and monitoring the process are given in standard ISO 11137 Part 1 and guidance is provided in ISO 11137 Parts 3 and 4. Terminology used in this document is consistent with that used in these standards and RBIP is an extension of methods described in Parts 1 and 4. Accordingly, the description of RBIP in this document assumes a knowledge of the 11137 series of standards. RBIP is consistent with the requirements in ISO 11137-1.

The RBIP method is a form of Parametric Release, but the term has been deliberately avoided in this document as it is not used consistently across the range of sterilization methods employed by the medical device and pharmaceutical industries. For example, using the definition in ISO 11139, both RBIP and release based on physical dose measurements are forms of parametric release[1].

Current methods of release from a radiation sterilization process are based around physical dose measurements used either individually or as part of a statistical process control regime. In order to give confidence that the process is running correctly between physical dose measurements, some irradiator variables are required to be measured and checked to be within pre-determined values (ISO 11137-1, section 10). RBIP differs from current methods in that release is made primarily on the basis of dose values at the routine monitoring location that have been calculated from monitored irradiator variables. Physical dose measurements are used at specified intervals to validate the dose calculations and to provide the required measurement traceability to national standards.

[1] In ISO 11139, *parametric release* is defined as “declaration that product is sterile based on records demonstrating that the sterilization process variables were delivered within specified tolerances”.
A *process variable* is defined as “chemical or physical attribute within a (…) sterilization process, changes in which can alter its effectiveness”.
A *process parameter* is defined as a “specified value for a process variable”, and goes on to say: “The specification for a process includes the process parameters and their tolerances”.

Using the RBIP process potentially allows for the following:

- Enhanced knowledge of $\sigma_{process}$ (see ISO/TS 11137-4)
- Individual container monitoring
- Proactive use of statistical process control (SPC) principles which would reduce the risk of undetected nonconformities
- Faster product release by eliminating delays from physical dosimeter measurement
- Reduced product rejections or reprocessing
- Reduced manual handling of physical dosimeters

1. The RBIP Concept

In the realm of radiation sterilization, ensuring process efficacy and thus product sterility is paramount. Regarding this, the international standard ISO 11137-1 states that product release shall be carried out without microbial testing of the irradiated product, basing the release instead on irradiator parameters and physical dose measurements.

RBIP – *R*elease *B*ased on *I*rradiator *P*arameters – is a comprehensive approach that uses operational qualification and performance qualification outputs, physical dose measurements, and analysis of irradiator variables to establish protocols for product release. Here, we explore the concept of RBIP: its implementation for E-beam irradiation, the link between physical dose measurement and irradiator variables, and the application of these measurements in process validation and product release.

RBIP comprises the assessment of the effectiveness of the product irradiation process, by the monitoring and analysis of irradiator variables. It involves a continuous evaluation of the process variables with a periodic verification of their relationship to traceable physical dose measurements. The frequency of these periodic measurements can be specified based on OQ results, and may be adjusted from time to time, as necessary, through a rationale which ensures that the process remains under control.

In the context of E-beam irradiation, for which this approach is initially developed, RBIP involves understanding the fundamental relationship between the key irradiator variables and the absorbed dose at the routine monitoring position, as given in Eq. 1:

$$D = K\frac{I}{V \times W_{\mathrm{b}}} \qquad (1)$$

where:

D = Absorbed dose (Gy),

I = Beam current (A),

V = Conveyor speed (m s^{-1}),

W_{b} = Beam width (m), and

K = Slope of the straight-line relationship in Eq 1, (Gy m^2)/(A s). (Units such as kGy and mA will often be used.)

Note: Eq. 1 is valid for one specified beam energy.

K represents a calibration factor for the irradiation facility, for dose measured at the routine monitoring position, D_{mon}

The value of *K* is determined during OQ and should be based on measurements covering the full range of beam current, conveyor speed and beam width that will be used during routine processing. Depending on the characteristics of the scanned beam profile, it may be necessary to prepare separate lines (i.e. values of *K*) for each beam width used, rather than one single line as shown in Fig. 1.

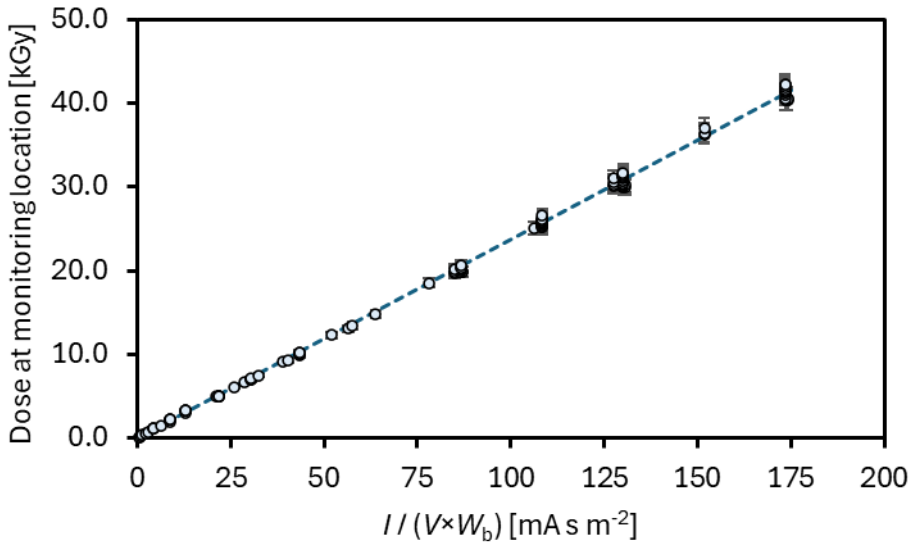

Figure 1: Example of relationship between routine dose at the monitoring location and key irradiator variables

2. The Approach

Physical dose measurement serves as the cornerstone of the validation and periodic verification of the RBIP approach. It involves the direct measurement of $D_{mon}^{physical}$, the absorbed dose at the routine monitoring location. The dosimetry system(s) used for these dose measurements must be calibrated with traceability to a national standard, including its uncertainty, constructed through use of an uncertainty budget.

Current state-of-the-art technology allows for real-time monitoring of the irradiator variables such as beam energy, beam current, beam width, and conveyor speed using calibrated instruments. Real-time analysis of these variables is then essential, to ensure that the process output can be demonstrated to be in control. Additionally, further advances in technology might allow for real-time monitoring and control of variables including the placement of product onto the conveyor.

The concept of the *virtual dose,* $D_{mon}^{virtual}$, refers to the calculated value of the dose at the routine monitoring location based on the irradiator variables and the *K* value. Monitoring the virtual dose involves continuously updated calculations based on real-time data from the irradiation facility. This information can be used to ensure that the value of the virtual dose $D_{mon}^{virtual}$ remains in control, and therefore that the irradiation process remains in control.

The following prerequisites should be documented for irradiation facilities applying the RBIP approach:

- OQ executed in accordance with 11137-1
- PQ executed in accordance with 11137-1
- Defined routine dose monitoring position
- Calibration factor is determined: $K = (D_{mon}^{physical} \times V \times W_b) / I$, from equation 1
- Measurement traceability for $D_{mon}^{physical}$
- Relationship $D_{mon}^{virtual} = K \times I / (V \times W_b)$, as equation 1
- Uncertainty budgets for $D_{mon}^{physical}$ and for $D_{mon}^{virtual}$
- Measurement reproducibility for irradiator variables, primarily
    - for monitored beam current I
    - for monitored conveyor speed V
    - for monitored beam width W_b
    - for monitored electron energy E

The virtual dose will have inherent uncertainties arising from the measurement of these irradiator variables, as well as from the uncertainties in the dosimetry for the OQ and PQ measurements. These uncertainties need to be considered just as they would be in purely physical dosimetry-based process monitoring, via the uncertainty budget.

3. Periodic Verification

In order to maintain the accuracy and reliability of the virtual dose calculations, physical dose measurements need to be made at a specified frequency. A risk-based rationale for the selected frequency of the physical dose measurements must be established and documented in accordance with ISO 11137-1. to ensure that the irradiator variables provide reliable virtual dose values throughout the time interval between successive sets of physical measurements. Any discrepancies identified through these verification exercises should then be handled subsequently via non-conformance processes.

The selected frequency of such verifications should itself be reviewed periodically.

The frequency of the periodic verification via physical dose measurement will depend on the in-line instrumentation capabilities of the irradiation facility and will need to be determined through a risk analysis exercise.

Key factors influencing the frequency of the periodic verifications include:

3.1. Process Stability

- Consistency of Equipment Performance: If the irradiator operates consistently as demonstrated by measurement of $D_{mon}^{physical}$ without significant variation over time, the frequency of verification may be reduced, subject to documented risk-based assessments indicating that any changes will be quickly identified. Monitored $D_{mon}^{physical}$ exhibiting only statistically expected variations, will then indicate that the virtual dose calculations based on irradiator variables and the *K* value remain reliable.
- Deviations in Verifications: If measurements reveal discrepancies between physical and virtual doses outside the range expected from their respective uncertainties, then the facility's non-conformance processes must be initiated.

3.2. Equipment Maintenance and Calibration

- Component Wear or Degradation: Over time, parts of the irradiator equipment (e.g., radiation sources, conveyor systems) may degrade, affecting performance. Verification by measurement of $D_{mon}^{physical}$ can detect if the virtual dose model no longer accurately reflects physical doses due to equipment aging.
- Routine Maintenance: Following any regular calibration or maintenance of the irradiation equipment, a verification should be conducted to ensure that the virtual dose calculation remains aligned with physical dosimetry.

3.3. Health Care Product Manufacturer's requirements

- Manufacturers might require more frequent verifications. Ultimately the frequency of dosimetric verifications, should be agreed between the operator of the irradiator and the manufacturer.

3.4. Regulatory Requirements

- Standards and Guidelines: ISO 11137-1 allows the RBIP approach, provided that there are periodic dosimetric verifications, at a frequency for which there is a documented rationale.
- Validation / Verification Requirements: The initial validation of a sterilization process might demand more frequent verifications, which can then be reduced in frequency as confidence is gained in the process.

4. Summary

RBIP provides a structured framework for the release of irradiated products based on irradiator parameters and monitored variables. By implementing traceable physical dose measurements and virtual dose calculations, RBIP ensures the safety and efficacy of radiation sterilization processes, without jeopardizing product quality.

Figure 2 illustrates the differences in the approaches of the use of physical dose measurements in the release of product from the irradiation process, and the use of the calculated virtual dose, with periodic verifications.

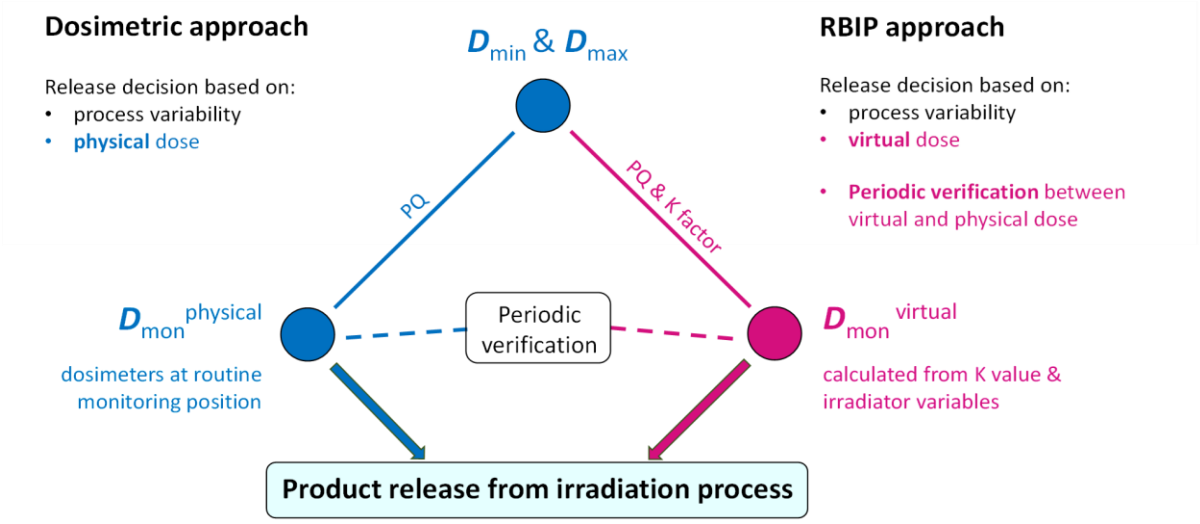

Figure 2: Illustration of the relationship between the virtual dose (pink) used in the RBIP approach to product release from the irradiation process, and the physical dose (blue) measurements, as used at PQ, in routine product irradiation release processes, and in the required periodic verifications.

5. Bibliography

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”. International Organization for Standardization, Geneva, Switzerland

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ISO 11139: “Sterilization of health care products – Vocabulary of terms used in sterilization and related equipment and process standards”. International Organization for Standardization, Geneva, Switzerland

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