TECHNICAL TIP

OVERVIEW OF AN E-BEAM IRRADITION VALIDATION OF HEALTHCARE PRODUCTS

Introduction

Prior to beginning routine processing with electron beam (E-beam) irradiation, a product with a sterile claim needs to complete a validation process to ensure the sterility assurance level claimed is achieved. ISO 11137 provides guidance for completing such a validation through three parts that are included under the general title "Sterilization of health care products – Radiation"

- Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices
- Part 2: Establishing the sterilization dose
- Part 3: Guidance on dosimetric aspects

This TechTip will provide a step-by-step overview of an E-beam irradiation validation process that complies with the standards set forth in ISO 11137.

Maximum Acceptable Dose Determination

When designing products to be processed with E-beam, consideration should be given to the impact of the irradiation process on the product and its packaging. Exposure to radiation has an effect on polymers (e.g. cross-linking, chain scission, oxidation), which could result in discoloration, oxidation, or molecular disruption that manifests in a deleterious manner on the physical, mechanical and/or chemical properties of the product and/or its associated packaging. As a result, a product and its packaging must be assessed to assure it meets its specified functional requirements throughout its defined lifetime (i.e. accelerating and real-time aging must be considered), assuming the maximum allowable dose is delivered. These potential effects should be considered while designing the product to be sterilized[1].

To determine an appropriate maximum acceptable dose, representative samples of the product should be irradiated to no less than the intended maximum dose to determine if any unacceptable radiation-related changes are observed. For the E-beam process, the maximum dose being tested should be at least two times greater than the established minimum dose. However, it is ideal to exceed two times the established minimum dose where possible. If the minimum dose is not yet known, then please reference ISO 11137 for assistance.

The maximum acceptable dose samples should be defined and clearly labeled on paperwork supplied to the Radiation Technology Center (RTC) or radiation facility, for example "MAXIMUM 50 kGy." This maximum dose reference will be utilized by the RTC/radiation facility for application of dose to product samples. When the dose has been applied, the product samples will be sent back to the Customer or testing laboratory, as agreed with the Customer, for evaluation and testing.

Establishing the Minimum Dose - Sterilization Dose Determination

The natural product bioburden is used to determine the minimum dose required to deliver the required sterility assurance level.

Multiple methods are available for substantiating or establishing the minimum dose within ISO 11137 and ISO/TS 13004.

Samples of the product should be submitted to a microbiology laboratory to quantify the population of microorganisms in colony forming units (CFUs) through a validated *Bioburden Determination (ISO11737-1)*[2]. Based on the bioburden results and testing method recovery factor, reference tables in ISO 11137 or ISO/TS 13004 will provide the required verification dose to apply to the product to verify a specified sterility assurance level (SAL) has been achieved. The verification dose has a logarithmically greater SAL than the minimum dose. For example, a $VDmax^{25}$ verification dose is SAL of 10^{-1}, while the sterilization dose of 25 kGy substantiated by this method is SAL of 10^{-6}.

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The verification doses are generally low and are required to be delivered in a narrow dose range. The highest dose delivered to the product samples should not exceed the verification dose by more than 10%, while the arithmetic mean of the highest and lowest doses to product samples should not be less than 90% of the verification dose. If the arithmetic mean of highest and lowest doses to the product samples is less than 90% of the verification dose, the verification dose may be repeated in the event the product tests of sterility fail.

The RTC delivering the dose will apply the requested verification dose to the appropriate number of product samples and measure the dose via the use of calibrated dosimeters.

Once the verification dose has been applied, the product samples will be routed back to the microbiology laboratory to perform a test of sterility (ISO11737-2) [3] which will confirm if the sterility assurance level required was achieved (refer to ISO 11137-2 or TS/ISO13004 for details and acceptance criteria of each available method).

Performance Qualification (PQ) - Dose Mapping Studies

The first two steps of the process dose range validation for E-beam consist of determining:

(a) the sterilization dose needed to support a claim of sterility (SAL), and

(b) the maximum acceptable dose identified in high dose testing – as noted above

Once these two values are determined, detailed performance qualification studies must be undertaken. Performance qualification studies must be performed at the E-beam location where routine processing will subsequently take place. Processing via E-beam is entirely dependent upon understanding dose distribution within the product configuration and consistent presentation of the product to the beam. Performance qualification in E-beam is a very detailed study that entails placement of dosimetry throughout the product configuration, both internally and externally. E-beam performance qualification considers a number of critical elements in order to achieve a successful performance qualification study, including:

- The internal product configuration
- The bulk density of the product
- The product's placement in relationship to the beam

Furthermore, performance qualification in E-beam must be performed on a sufficient number of irradiation containers or processing units to capture differences in dose distribution among these studies (a minimum of three containers or processing units).

Performance qualification will:

- Study how the product is placed in an irradiation container or on a product handling system for routine processing
- Identify the locations and magnitudes of the minimum and maximum doses within the product configuration
- Determine the mathematical relationships between the minimum and maximum doses in the product load as compared to dose(s) received at the standard monitoring or routine monitoring position(s)
- Ascertain if the product load (as dose mapped and configured during the study) will fall within the range of minimum and maximum doses (which have been established and validated for the process dose range) during routine processing

Note: The performance qualification exercise may be performed outside the specified dose range to reduce the uncertainty component of the dosimetry system.

Routine production may not begin in an E-beam facility until successful performance qualification has been completed. Should a change in location be required either by the Customer

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or the sterilization contractor, performance qualification would need to be repeated at the new facility to which the product is being transferred, however minimum or maximum dose studies do not need to be repeated. In situations where two unique beam lines are housed within one location, performance qualification on the second beam would also need to be undertaken to assure complete understanding of dose distribution.

Routine Processing

The routine processing dose range cannot be lower than the sterilization dose needed for the SAL required for the product and no higher than the maximum allowable dose confirmed for the specific product.

Once all processing validation activities have been completed, routine processing may take place based upon the product code (as received at the facility) and the irradiation process will commence. It is essential that any product and/or packaging changes (dimensions, density, design) are communicated to ensure the validation that was completed remains appropriate and maintains process effectiveness. Note: Based on the assessment of the changes (change control, risk assessment), the entire validation or part of the validation detailed in the document may need to be repeated.

Dose Audits

As the initial sterilization dose establishment was based on the natural bioburden of the product and/or packaging, ISO 11137 or ISO/TS 13004 recognizes that the microbial population (quantity and/or type) can change with seasonal or periodic manufacturing change. Thus, in addition to routine microbiology control and monitoring of the product during manufacturing, ISO 11137 requires quarterly dose audits when in continuous production. Testing at these quarterly intervals includes a bioburden determination (to monitor and trend bioburden amounts over time) and a verification dose experiment (tests of sterility at the established verification dose). This process shows the continued effectiveness of the established dose by monitoring the number of organisms present in relation to the specified bioburden limit and to monitor the radiation resistance of the bioburden on a product. Sterilization dose audits (including the verification dose experiment and bioburden testing) continue throughout the life of a product, but the frequency of the audits may be changed with appropriate data. The irradiations for these audits shall be performed by an irradiation facility with the same dose constraints as discussed in “Sterilization Dose Determination” section of this document[3].

Guidance on reducing the frequency of dose audits over time is provided in ISO 11137-1 based on audit data and the manufacturing process control of product. At a minimum, four consecutive dose audits including bioburden determination and characterization of the bioburden (not just bioburden number) must be completed before considering reduction of audit frequency. The most common approach to increasing intervals between audits is to go from quarterly to biannual and then if appropriate, to annual. When the verification dose experiment is less frequent, bioburden is still required quarterly or monthly as required in ISO 11137-1. Dose audits and bioburden provide valuable data to assure bioburden limits are met and the manufacturing process is in control. Changes to testing frequency, if desired, should be considered carefully.

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REFERENCES

1. See STERIS Applied Sterilization Technologies TechTips #02, #04, and #09 at www.steris-ast.com for more information

2. See ISO 11737-1:2018, *Sterilization of health care products - microbiological methods - Part 1: Determination of a population of microorganisms on products*, for more information

3. See ISO 11737-2:2019, *Sterilization of health care products - microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process*, for more information

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