PROCESS VALIDATION METHODOLOGY FOR E-BEAM STERILIZATION OF HEALTHCARE PRODUCTS

1. INTRODUCTION

The objective of this document is to describe the procedure observed by Ionmed to perform the validation process for the sterilization of healthcare products. The validation, according to the international standard, consists of the following stages: process definition and performance qualification.

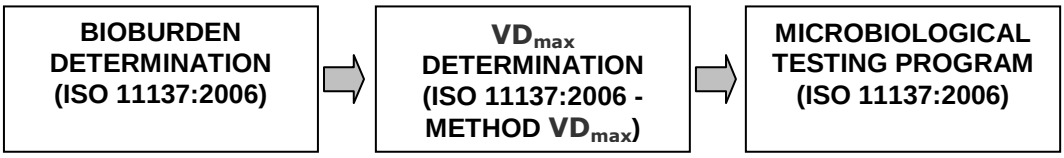
2. STERILIZATION PROCESS VALIDATION

2.1 PROCESS DEFINITION

2.1.1 Sterilization dose determination

Ionmed advises to use one of the two following procedures to determine the sterilization dose:

a) Use Method VD_{max} for substantiation of 25kGy as the sterilization dose. Select a sterilization dose of 25kGy and demonstrate, through a series of defined and appropriate microbiological tests, that the said dose assures the sterility of the product. As described in the ISO 11137:2006, VD_{max} Method can be applied to demonstrate the suitability of the dose of 25kGy.



The following briefly describes the VD_{max} Method used to determine the sterilization dose, which is included in the ISO 11137:2006:

Starting assumptions:

- the resistance of the micro-organisms to radiation can be shown through a D10 function. D10 = the dose necessary to reduce 90% of the micro-organism population.
- The distribution of the D10 values for the microbial load of the product is independent of the quantity of the micro-organisms.
- The product is considered sterile when it has received receive a sterilization dose high enough to ensure the theoretical probability of an organism surviving the dosage is no greater than one in one million units tested (SAL 10^{-6}). (SAL = Sterility Assurance Level)

Method summary:

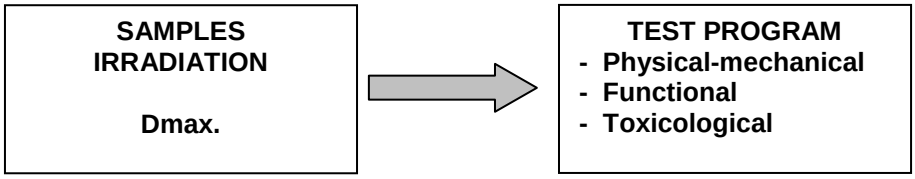
The method is based on the experimental demonstration of the resistance of the microbial load present in the product is less than a determined distribution of standard resistance. This distribution of standard resistance is what is used for the theoretical calculations in the Method.

- Determine the average bioburden in the product.
- Select from the table in ISO 1137-2:2006 the corresponding VD_{max} dose (verification dose) using the previously determined level of the bioburden of the product.
- Irradiate 10 samples of the product at VD_{max}^{25}
- Individually test for sterility the irradiated samples.
- Apply the acceptance criteria of no more than one positive test. If the number of positive tests are two then a dose confirmatory verification experiment should be carried out. And if the number of positive tests are greater than two an alternative method for substantiation of 25kGy as the sterilization dose shall be used.

b) Use Method 1 as described in the ISO 11137:2006 to determine the sterilization dose taking into consideration the pre-sterilization bioburden of the material. Demonstrate, through a series of defined and appropriate microbiological tests, that the said dose assures the sterility of the product.

2.1.2 Determination of maximum acceptable dose

It must be determined what is the maximum dose that both the product and its packaging can withstand during the irradiation process. To demonstrate the compatibility of the product it is necessary to design a test program appropriate for the product under study. The program in question must include properties such as: physical-mechanical, functional and toxicological.



The product samples that are to be submitted to the test program, must have received at least a minimum dose equal or superior to the maximum dose received during the sterilization process.

As with the minimum dose, the maximum dose received by the product presents some uncertainties. The uncertainty should be taken into account when irradiating the samples. For example, if the maximum dose obtained in the dose map is 50kGy, the samples for the compatibility tests have to receive as a at least a dose of 50x(1,10)=55kGy.

2.2 PERFORMANCE QUALIFICATION (Dose mapping exercise)

The principal object of the performance qualification is to establish the parameters of the irradiation process for a determined product. These parameters need to assure that the total volume of the product receives a dosage superior to the specified minimum dose for the said product. It is important to attest that, owing to the manner that the electrons interact with material, it is not possible to deliver the same dose to the total volume of the product. Therefore, to assure that the minimum sterilization

dose is achieved by all of the product, some areas of the product will receive a higher dose.

The performance qualification process is based on the dose mapping of a product. The objective of a dose mapping study is to identify the minimum and maximum dose zones within the product load and packaging configuration. Furthermore, dose mapping establishes the reproducibility of the sterilization process.

The following are steps to realize a dose map:

a) Register the characteristics of the product:
   - Type and units of the product per package.
   - Position of the units of the product within the package.
   - Weight, dimensions and mean surface density.

b) Select and identify the dosimetric system to be used.

c) Place the dosimeters in the product.

d) Irradiate the product, register the process parameters and the orientation used for the irradiation of the product.
   - L_b (beam width)=cts.=103cm.
   - FD (dose factor)= FD_v (mA/m/min).

     Note: the FD parameter is defined as the quotient between the intensity of the beam (mA) and the speed (m/min) that the product passes under the beam.
   - Treatment with or without turning.

e) Analyse the dosimeters and determine the minimum and maximum doses obtained and their positions.

f) Repeat the dose map to confirm the data obtained and to determine the uncertainty for the minimum and the maximum dose.

g) Adjust the process parameters to obtain the minimum dose specified taking into account the uncertainties applicable to the process.

The supplied dose to the product is subject to statistical fluctuations, so that when the process parameters are adjusted these fluctuations should be taken into account. Contributions to the uncertainty of the supplied dose to the product are the following:

- Calibration of the dosimeters: A.
- Variations of the process parameters: B.
- Uncertainties of the minimum and maximum dose: C.

The quadrature combination of the above uncertainties results in the total uncertainty of the supplied dose:

$$I = \sqrt{A^2 + B^2 + C^2} \approx 10\% \ (k=2)$$

That is to say, if the minimum dose that we want to assure is 25kGy, we have to adjust the process parameters to obtain a dose of: 25kGy x (1,10) = 27,5kGy.

In practice, the only irradiation parameter variable is the FD. The adjustment of the irradiation parameters are made by using the following data: the minimum dose obtained en the dose map $(D_{min})v$, the FD_v used for the dose map, the minimum dose specified and the total uncertainty of the supplied dose.

$$D_{min} = 25kGy \Rightarrow FD(mA/m/min) = FD_v \times \frac{25 \times (1{,}10)}{(D_{min})v}$$

Once the FD to obtain the minimum specified dose is known, we can calculate, using the same method, the maximum dose that the product will receive during its treatment:

$$D_{max} = (D_{max})v \times \frac{FD}{FDV}$$

The maximum dose data obtained, is used in the Process Definition: maximum dose determination for the product.