Sterigenics®
A Sotera Health company

A STERIGENICS WHITE PAPER

3 Methods to Establish the Sterilization Dose of a Medical Device

AUTHOR
Dr. Bart Croonenborghs, Technical Director Irradiation, Sterigenics

Abstract

In the medical device industry, sterilization processing is performed to obtain a Sterility Assurance Level (SAL) as required by regulatory authorities to designate the treated product as "sterile." There are several approaches—the sterilization dose setting methods 1 and 2, and the substantiation method VD_{max}^{SD}—that may be used to establish the minimum dose that results in the required degree of sterility assurance. By reading this White Paper, Quality Assurance, Sterility Assurance and other interested professionals will learn about the different aspects of each method that have to be considered in order to make the best decision for a specific product.

Introduction

Sterilization processing for healthcare product is performed to obtain a Sterility Assurance Level (SAL) as required by regulatory authorities to designate the treated product as "sterile." Such requirements may vary from country to country or region to region; for instance, the governing standards are EN 556 for the European Union and ANSI AAMI ST67 for the USA.

There are several methods that may be used to establish the sterilization dose needed to achieve the required degree of sterility assurance. Specifically for medical devices, the ISO 11137-1:2015 standard specifies in section 8.2 that there are two acceptable approaches:

- *Setting* the sterilization dose specifically for the product, based on knowledge of the number and/or resistance to radiation of the bioburden
- *Substantiation* of a pre-selected dose of 25 kGy or 15 kGy[1]

Sterilization Dose Setting Using Method 1

Establishing the sterilization dose using Method 1 sets a product-specific value for the sterilization dose. This is based on experimental determination of the average product bioburden and by performing a verification dose experiment to characterize the product bioburden's resistance to ionizing radiation.

For the verification dose experiment, product samples are irradiated at the tabulated value of the dose (called the verification dose) that inactivates to an SAL of 10^{-2} a population of microorganisms to the product's average bioburden and exhibiting a resistance to ionizing radiation as specified in the Standard Distribution of Resistances (SDR). After irradiation at the verification dose, the product items are individually subjected to a validated test of sterility.

Upon acceptable outcome of the verification dose experiment, tabulated dose values obtained in a similar way based on the SDR and the average product's bioburden are then considered valid for achieving at least a specified degree of sterility assurance for the batches sampled in the study. Continued effectiveness of the established sterilization dose needs to be demonstrated in accordance with section 12 in ISO 11137-1:2015.

General procedural elements of sterilization dose setting for this method are summarized in Figure 1 on page 3.

Note that Method 1 can be used to set the sterilization dose for a single or multiple manufacturing batches, and that for average product bioburden ranging from lower than 0.1 Colony Forming Units (CFU) up to 1000000 CFU. SAL 10^{-6} doses for these extremes of average bioburden would be 11.0 kGy and 36.3 kGy, respectively.

Method 1 sterilization dose validation may fail when bioburden numbers cannot be determined accurately, or when the product's bioburden exceeds the radiation resistance distribution set forth in the SDR.

A comparison with the other methods for establishing the sterilization dose as presented in ISO 11137-2:2015, including minimum quantities of product needed, is provided in the Conclusion of this White Paper.

[1]In practice other doses can be substantiated as well, see page 4 of this document.

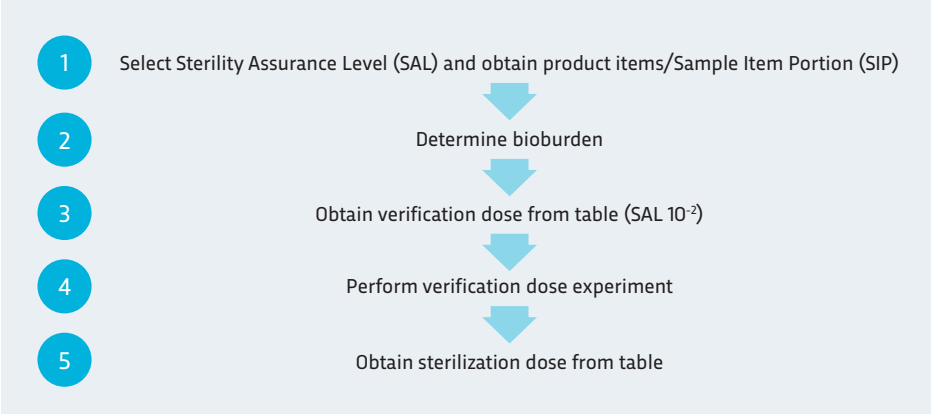

Figure 1: General procedural elements of sterilization dose setting using Method 1.

Sterilization Dose Setting Using Method 2

Method 2 sets a product-specific value for the sterilization dose based on incremental dose irradiations and a verification dose experiment to determine a product-specific extrapolation factor for achieving SAL levels of 10^{-2} and lower. Tests of sterility are conducted after each incremental dose and the results are used to determine the extrapolation factor.

Product bioburden data is only used as part of the routine monitoring of manufactured product. Method 2 sterilization dose setting will always be successful and, for the same product, renders a lower sterilization dose than Method 1. This comes at the expense of a significant increase of the number of product items and laboratory testing (see Table 1 in the Conclusion).

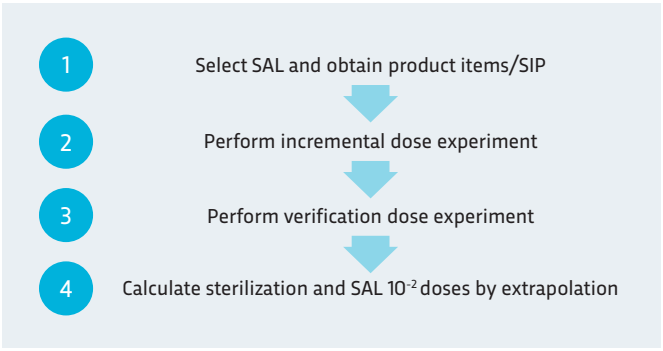

Figure 2: General procedural elements of sterilization dose setting using Method 2.

Sterilization Dose Substantiation Using Method VD_{max}^{15} or VD_{max}^{25}

There is a third method for establishing the sterilization dose. Method VD_{max}^{SD} substantiates a selected sterilization dose (SD) for obtaining an SAL of 10^{-6} or less using procedural elements similar to those for dose setting Method 1 described earlier. It builds in a conservativeness of at least the SDR and also requires a determination of average bioburden, as well as the performance of a verification dose experiment. The difference with Method 1 resides in the quantity of product items needed for the verification dose experiment. General procedural elements are described in Figure 3.

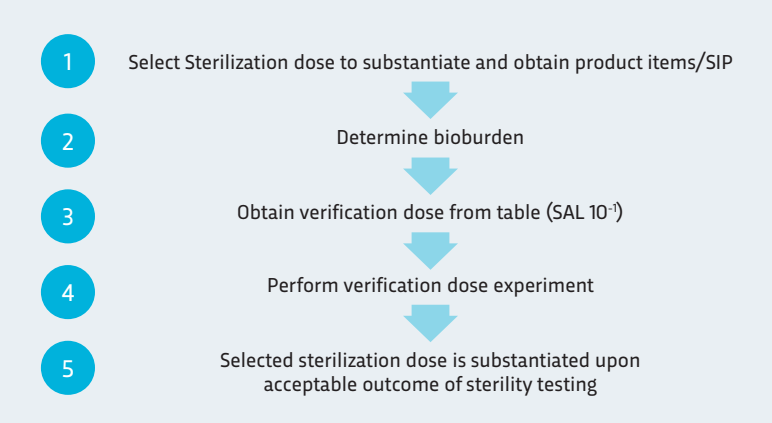

Figure 3: General procedural elements of sterilization dose substantiation using Method VD_{max}^{SD}

This method is described in ISO 11137-2:2015 for selected sterilization doses of 25 kGy and 15 kGy, and can be applied for a single or for multiple manufacturing batches. The method for 25 kGy is applicable to products having an average bioburden not exceeding 1000 CFU, whereas 15 kGy can be substantiated for product with an average bioburden of not more than 1.5 CFU.

It should be noted that ISO TS 13004:2013 extends Method VD_{max}^{SD} to other selected doses, ranging in increments of 2.5 kGy from 17.5 kGy up to 35 kGy. Each dose level may be substantiated for a specified upper limit of average bioburden, which is 440000 CFU for 35 kGy.

There is no reason to restrict the use of Method VD_{max}^{SD} to the selected doses for substantiation in ISO 11137-2:2015 and ISO TS 13004:2013. Provided that the correct verification dose and upper specification for average bioburden are determined and applied, the Method VD_{max}^{SD} would be valid for all doses ranging from 15 kGy up to 35 kGy.

Conclusion

Table 1 provides a schematic overview of the practicalities around the sterilization dose setting and substantiation methods as listed in ISO 11137-2:2015. In selection of an approach to establish sterilization dose, these aspects should be considered, together with other aspects, including but not limited to, the product's resistance to ionizing radiation (maximum acceptable dose level) and the capabilities of the selected irradiator for efficient and reliable product irradiation within the range set by the sterilization dose and the maximum acceptable dose.

	Method 1	Method 2	Method VD_{max}
Sterilization SAL	Any	Any	10^{-6}
Verification SAL	10^{-2} (100 samples)	10^{-2} (100 samples)	10^{-1} (10 samples)
Sterilization Dose	Product Specific	Product Specific	25kGy[1] or 15kGy[2,3]
Bioburden	10 samples of 3 batches	NA	10 samples of 3 batches
Total Products	≥ 130 (Single batch 110)	≥ 580 or 640	≥ 40 (Single batch 20)

[1] Average Bioburden ≥1000

[2] Average Bioburden ≥1.5

[3] Other doses can be chosen based on ISO/TS 13004:2013

Table 1: Direct comparison of practical aspects for sterilization dose setting and substantiation methods in ISO 11137-2:2015. For Method 2 explicit distinction is made between Methods 2A and 2B. Both require the same procedural elements, but Method 2B is for ultra-low bioburden product only and therefore requires the smaller number of product items.

References

ISO 11137-1:2015 & A2:2019 (International Standards Association) Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices

ISO 11137-2:2015 Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose

ISO/TS 13004:2013 Sterilization of health care products – Radiation – Substantiation of selected sterilization dose: Method VD_{max}^{SD}

EN 556-2:2015 Sterilization of medical devices – Requirements for medical devices to be designated "sterile"

ANSI (American National Standards Institute) AAMI (Association for the Advancement of Medical Instrumentation) ST67:2019 Sterilization of health care products—Requirements and guidance for selecting a sterility assurance level (SAL) for products labeled "sterile"

About Sotera Health

Sotera Health Company is a leading global provider of mission-critical end-to-end sterilization solutions and lab testing and advisory services for the healthcare industry. Sotera Health goes to market through three businesses - Sterigenics®, Nordion® and Nelson Labs®. Sotera Health is committed to its mission, Safeguarding Global Health®.

About Sterigenics

Sterigenics is a leading global provider of outsourced terminal sterilization services for the medical device, pharmaceutical, food safety and advanced applications markets. With our industry recognized expertise, we help to ensure the safety of millions of patients around the world every year. Across our 48 global facilities, we offer our customers a complete range of sterilization services, primarily using the three major technologies: Gamma irradiation, Ethylene Oxide processing and Electron beam irradiation. We are committed to addressing the growing need for sterilization across the world and partnering with our customers to eliminate threats to human health.

For more information: +1 (800) 472-4508 | sterigenics.com