BIOTECH

Technical Regulatory Topic

USTR 3660

Gamma Irradiation: Sterilization Validation Approach for Allegro™ Single-Use Systems with Sterile Claim

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Contents

1 Pall's Approach to Sterility for Allegro Systems

Pall's Allegro single-use systems (SUS) are sterilized by gamma irradiation following the ISO standard 11137-2 '*Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose'* and/or ISO/TS 13004 *'Sterilization of health care products – Radiation – Substantiation of selected sterilization dose: Method VDmaxSD'* to support the sterile claim as given for these products. A sterile claim can be made when a Sterility Assurance Level (SAL) of 10^{-6} has been proven.

The standards allow for a 'product family' approach to be used for establishing and maintaining the sterilization dose. The standards also give guidelines on how to establish a product family. Three options are given to establish a product family: a master product, an equivalent product, or a simulated product.

The simulated product is described in the above standards as '*a combination of components (…) that would not typically be combined for use*', and this approach has been selected for Allegro SUS and is referred to as the master set. This master set features a design with an unusual number of connections and level of handling when compared to surface area, comprising of a wide range of different materials from different suppliers. This generates a worst case, or representative, design for all product types. It is produced under identical production conditions as all Allegro SUS. As such, the Allegro master set is used to show that the components, handling, and cleanroom environment result in a final product that is within specification for the relevant requirements for sterile systems.

Because Allegro systems vary from very small tube sets to very large biocontainers with complex assemblies, it is not possible for the laboratory to perform a sterilization validation on a full-scale set to account for all variations. To allow for this possibility, the standards have adopted, where required, to use a Sample Item Portion (SIP) approach. Factors like length, mass, volume, or surface area can be used to determine the SIP factor for individual final products, and from that an estimated bioburden.

Allegro systems use an SIP approach based on the number of connections or surface area, whichever is the greatest contributor to bioburden levels. Each new system is compared against the Allegro master set to estimate bioburden level using the SIP factor and to determine coverage by the master set of all components used.

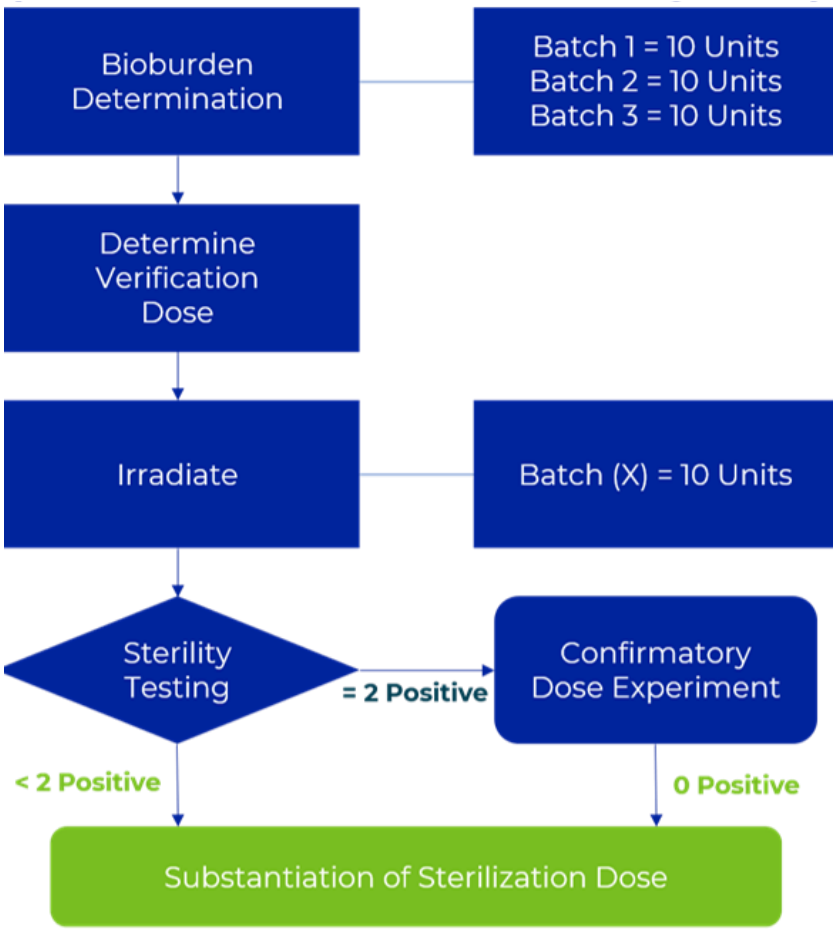
The minimum irradiation dose to obtain a sterility assurance level of 10^{-6}, the prerequisite for a sterile claim, depends on the average bioburden on the product to be sterilized. To accommodate for the variety in bioburden levels of Pall's Allegro systems, Verification Dose maximum (VD_{max}) sterilization validation approaches are used.

2 Validation

VD_{max} studies are performed using the Allegro master set as per ISO 11137-2 and/or ISO/TS 13004. Three different batches, each comprising of ten samples, are tested for bioburden and an average result is obtained. This average bioburden result is used to establish the verification dose (kGy) to yield a sterility assurance level (SAL) of 10^{-6}. Ten additional samples are then irradiated at the validation dose and tested for sterility. If no more than one positive result is obtained after the incubation period, then the validation is accepted.

Figure 1

VD_{max} substantiation procedure - validation



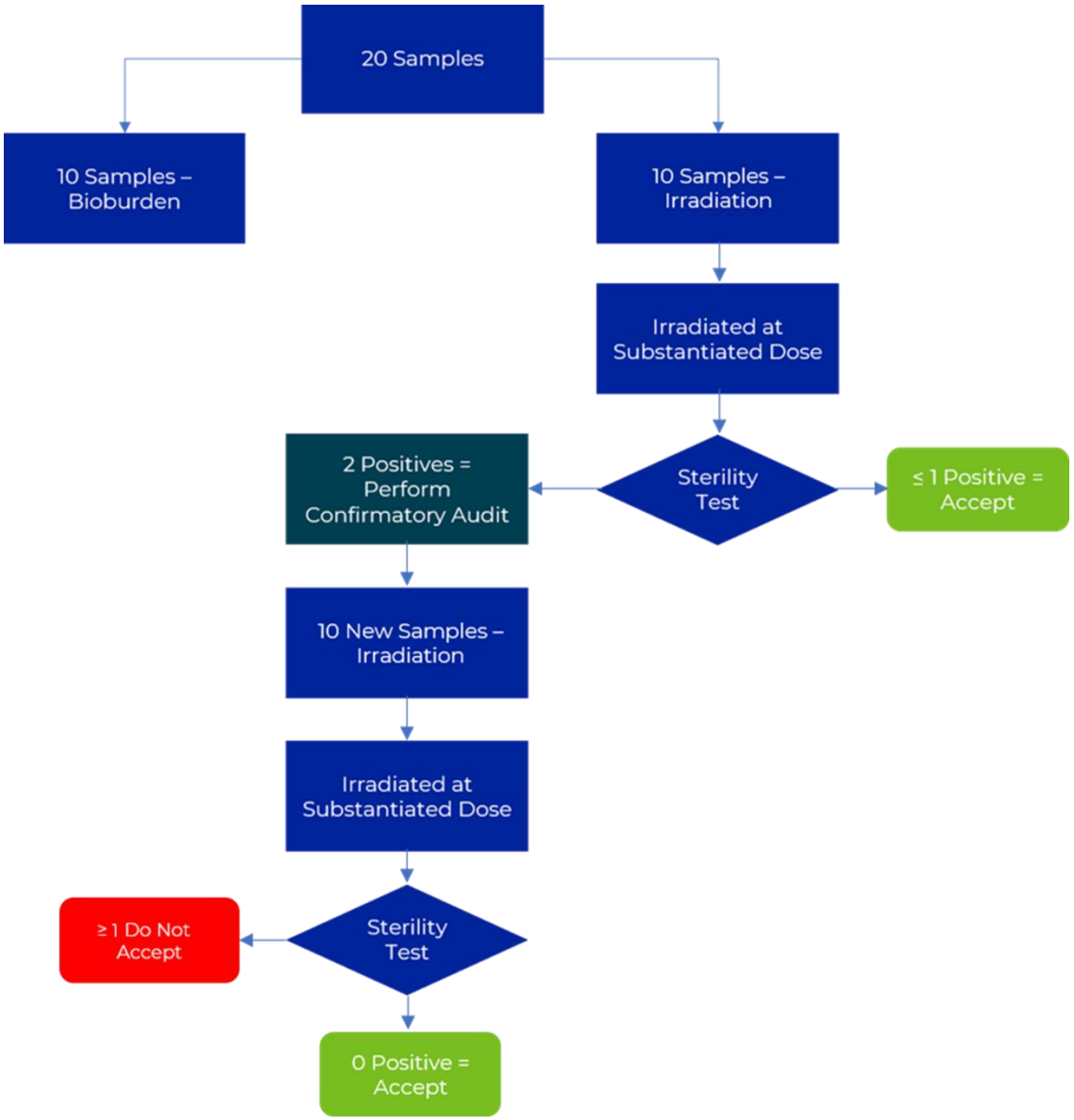
Sterilization validation, as described above, is independently performed for each Pall single-use technology (SUT) site. Each Allegro SUS manufacturing site shall perform a similar validation independently.

3 Verification

Sterilization dose audits are furthermore repeated on a quarterly basis to demonstrate continued substantiation of sterilization dose.

Figure 2

VD_{max} dose audit procedure – verification (Quarterly Monitoring – 20 Systems)



Gamma dose levels to assure SAL 10^{-6} reduction, and hence sterility, according to ISO 11137-2:

Table 1

VD_{max} sterilization dose versus maximum colony forming units (CFU) count

VD_{max} sterilization dose	Maximum colony forming units (CFU) count
≥ 25.0 kGy	< 1,000
≥ 27.5 kGy	< 5,000
≥ 30.0 kGy	< 23,000

4 Dose Mapping

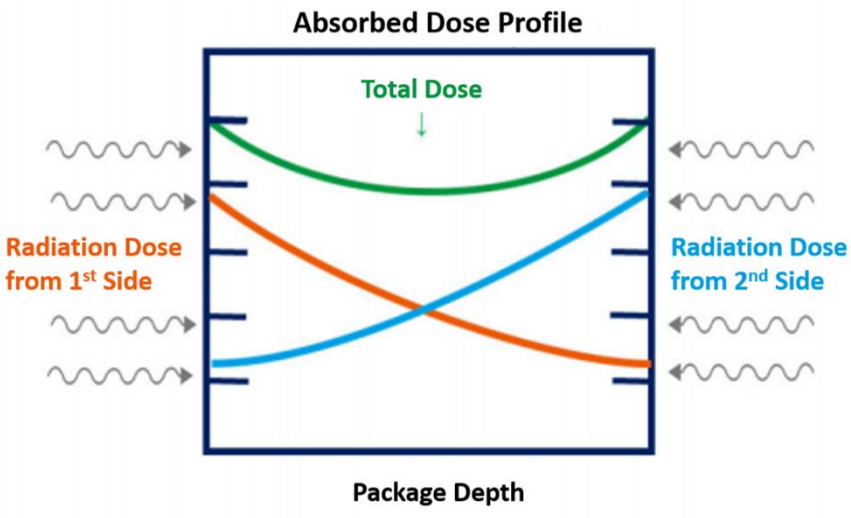
Each 'product family' is dose mapped, by placing dosimeters throughout the product load. This is to verify that the minimum specified dose is applied to the product, within the product packaging, and that the maximum specified dose is not exceeded.

Exposure to gamma irradiation generates a reaction in the dosimeter, resulting in a measurable change. The extent of this change is measured after exposure and correlated to a dose in kGy, using the applicable calibration curves.

A typical irradiation line will apply the dose from two sides as the product passes around the source. The total dose is represented by the overall accumulated values – see Figure 3.

Figure 3

Total dose applied – dose mapping



Production batches are supplied with a Certificate of Irradiation (CoI) with the specified minimum and maximum dose range and the actual dose received during processing.

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