BIOTECH

Technical Regulatory Topic

USTR 3664

Gamma Irradiation: Sterilization Validation Approach for Pall Biopharmaceutical Filters with Sterile Claim

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Contents

1 Pall's Approach to Sterility for Biopharmaceutical Filters

Pall's sterile filters are sterilized by gamma irradiation, and VD_{max} and Method 1 studies used 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 provide guidelines on how to establish a product family based on bioburden levels, methods of construction, and components. Various product family approaches have been adopted to support the range of irradiated Pall products.

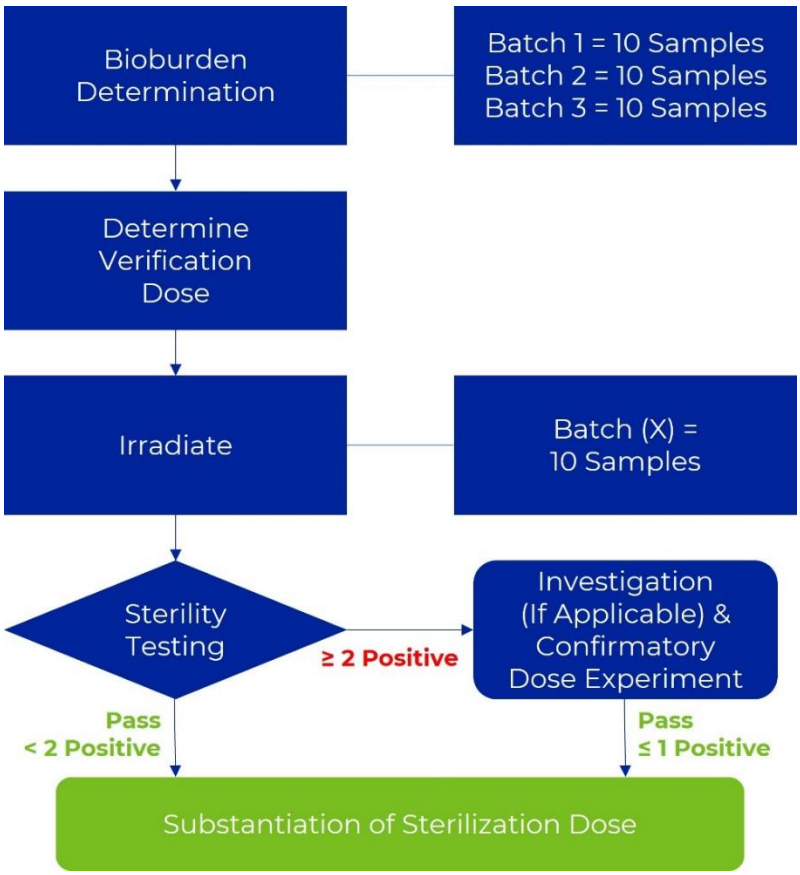
2 VD_{max} Method

2.1 Validation

VD_{max} studies are performed using a representative part number from the product family as per ISO 11137-2 and/or ISO/TS 13004. Three different batches (n=10 samples per batch) 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^{-1}. Additional samples are then irradiated at the verification dose and subsequently sterility tested as summarised in Figure 1.

Figure 1

VD_{max} substantiation procedure – validation



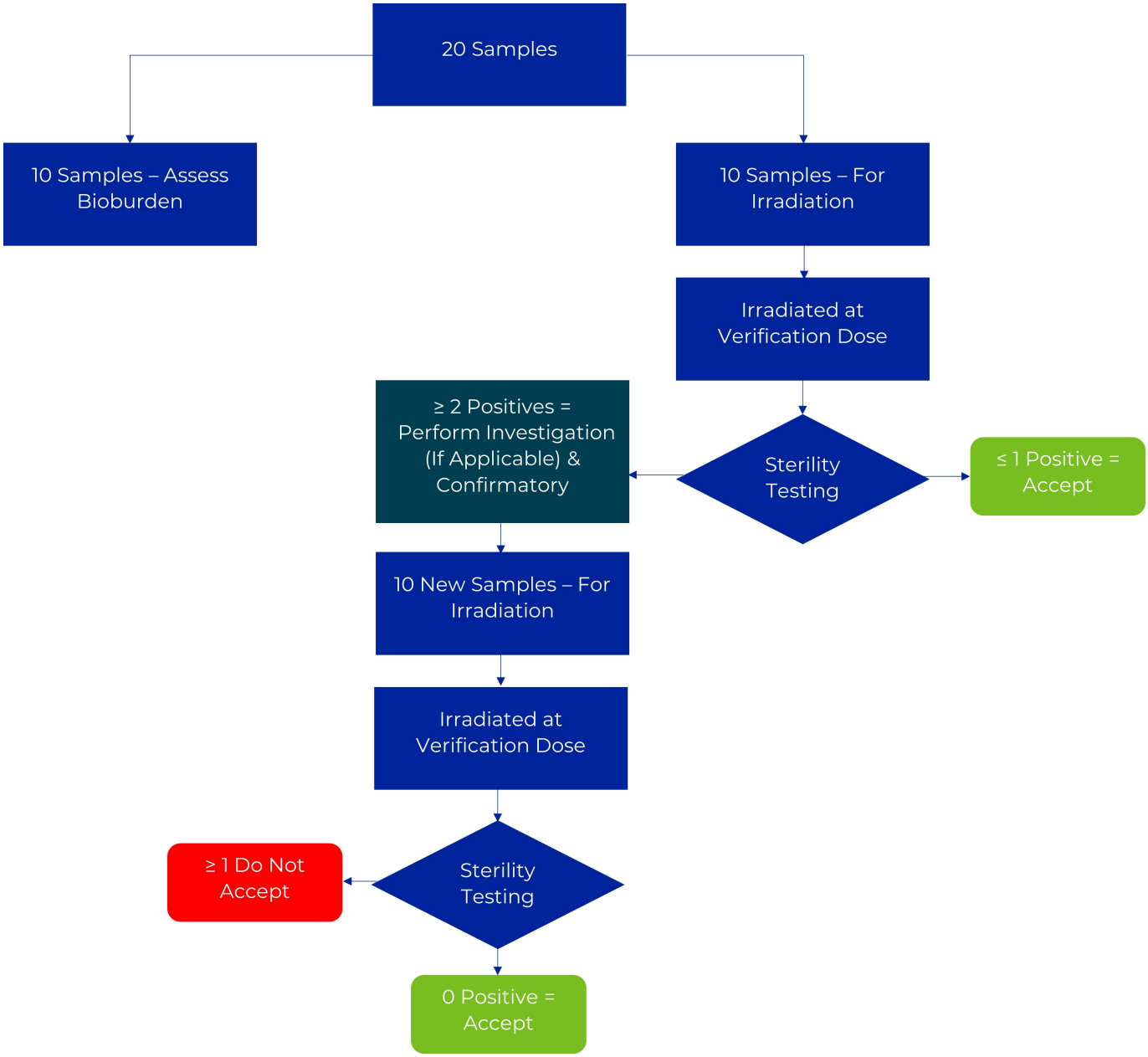
Sterilization validation, as described in Figure 1 is independently performed for each Pall filter manufacturing site.

2.2 Verification

Sterilization dose audits following the VD_{max} method outlined in Figure 2 are furthermore repeated on a quarterly basis to demonstrate continued effectiveness of the radiation sterilization process.

Figure 2

VD_{max} dose audit procedure – verification



Gamma irradiation 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

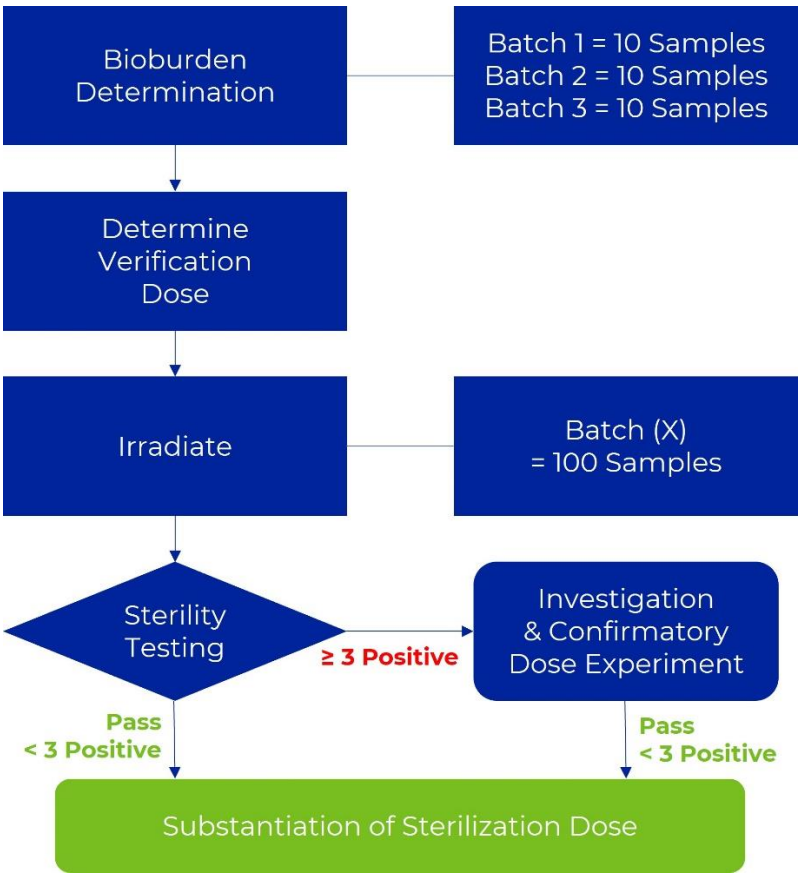
3 Method 1

3.1 Validation

Method 1 studies are also performed using a representative part number from the product family as per ISO 11137-2. Three different batches (n=10 samples per batch) 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^{-2}. Additional samples are then irradiated at the verification dose and subsequently sterility tested as summarised in Figure 3

Figure 3

Method 1 substantiation procedure – validation



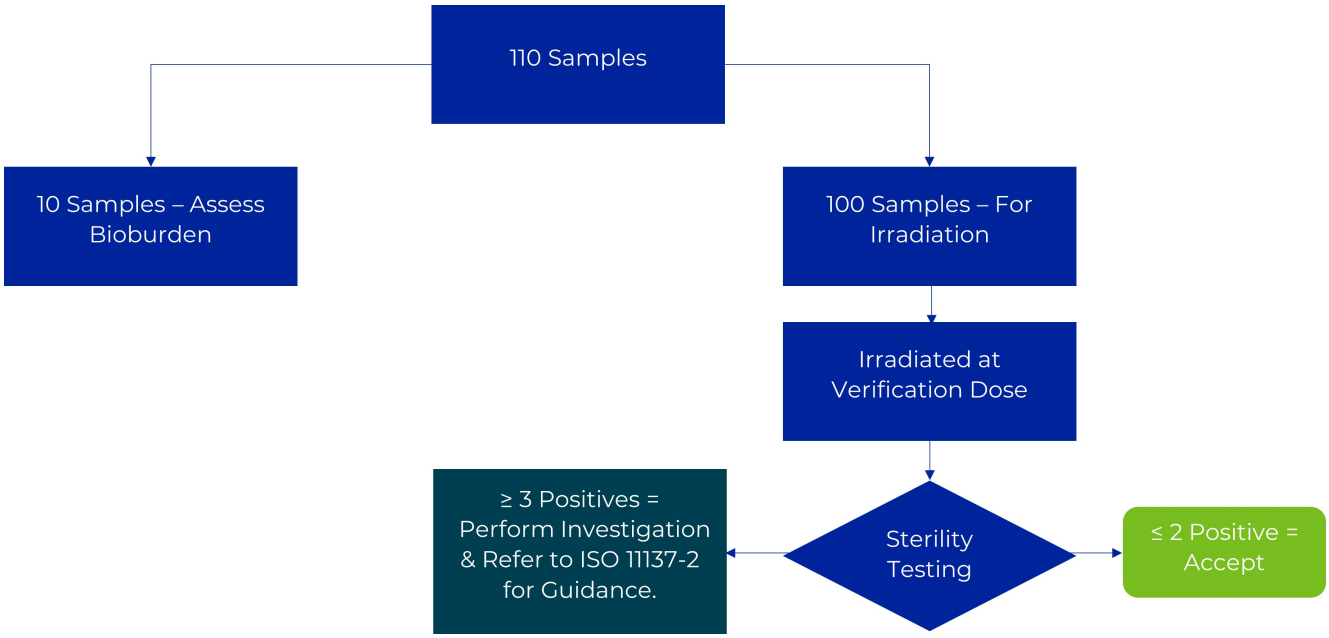
Sterilization validation, as described in Figure 3, is independently performed for each Pall filter manufacturing site.

3.2 Verification

Sterilization dose audits following Method 1 outlined in Figure 4 are furthermore repeated on a quarterly basis to demonstrate continued effectiveness of the radiation sterilization process

Figure 4

Method 1 dose audit procedure – verification



4 Dose Mapping

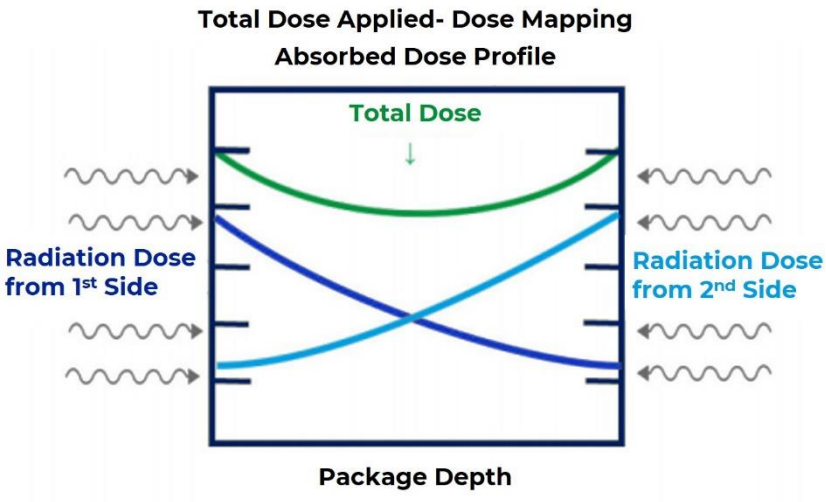
Each 'product family' is dose mapped, by placing dosimeters throughout the product load. This is to verify that the minimum specified dose is applied to the product, within the product packaging, and that the maximum specified dose is not exceeded.

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 production process will apply the dose from two sides as the product passes around the source. The total dose is the accumulated values – see Figure 5.

Figure 5

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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