MediZap
Advanced Sterilization

Common Radiation Sterilization Validation Methods

There are many proven methods to validate radiation doses for all compounded drugs and pharmaceutical drugs. Each uses product bioburden enumeration to quantify the concentration of all live microorganisms. The effective dose for radiation sterilization and dose audits can be pinpointed through bioburden enumeration.

Additionally, each method uses a bioburden organism resistance sterility test or verification dose resistance experiment to ensure accuracy. The size, scope, and expected timeline of the sterilization job determine which method will ultimately be the best.

A typical validation study can furnish results in 10 to 12 weeks because of sequential microbiological testing, though the timeline and the cost hinge on the complexity and size of the tested products. Before scheduling a sterilization validation, manufacture additional samples for the entire validation study.

Below is a summary of the most common radiation sterilization methods: ANSI, AAMI, and ISO.

ANSI/AAMI/ISO 11137-2 VDmax (most frequently used)

Used primarily for frequent or infrequent production sterilization batches, this method is particularly useful in drug products with a standard bioburden of 〈1.5 CFU in establishing a minimum sterilization dose of 15 kGy, or for products with a standard bioburden of 〈1,000 CFU in establishing a minimum of 25 kGy. The sampling numbers for the validation are the same as the AAMI TIR 33 VDmax method (below).

AAMI TIR 33 VDmax

Used primarily for either frequent or infrequent production sterilization batches, AAMI TIR 33 is critical in determining a minimum sterilization dose for compounded drugs and pharmaceutical drugs in either small or large batches. Based on the product's average bioburden, Method VDmax identifies a minimum sterilization dose of 15 to 35 kGy.

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Validation is done for drug products produced frequently using bioburden testing on a sampling of 10 drug products from up to 3 distinct lots. The verification dose resistance experiment is then performed on 10 drug products from a single lot.

A similar process occurs to validate a single lot (infrequent): 10 drug products from the singular lot are evaluated for bioburden, followed by a verification dose resistance experiment. If the first two samples are higher than the standard allows, a total of 20 drug products may be used to ensure efficacy.

ANSI/AAMI/ISO 11137-2 Method 1

Used primarily for large and frequent sterilization batches, Method 1, also known as ANSI/AAMI/ISO 11137-2, establishes the sterilization dose of drug products. The initial validation uses bioburden testing on 3 different lots, and a verification dose resistance experiment follows on a larger batch of 100 samples from one previously irradiated lot. The revalidation process includes quarterly bioburden testing of 100 samples from the same lot. This method is not utilized as often as VDmax (above).

Compliance & Sterility Assurance Tests

Sterilization Process Protocol

Upon the initial sterilization process validation for products, a written validation protocol is required per cGMP regulations. Said protocol must identify:

- The drug products
- A statement of purpose
- The contract sterilizer's name
- The testing laboratory's name
- A comprehensive list of required tests
- Criteria for determining the success of tests

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In addition, clients can request specific test procedures/results to customize the sterilization validation.

Validation For Bioburden Methods

Per ANSI/AAMI/ISO Guideline 11737-1 (Sterilization of health care products – Microbiological Methods - Part 1: Determination of the Population of Microorganisms on Products), the bioburden test method must be validated for every drug product. This is required to ensure the sterilization cycle is adequate. Further, it must be proven that the bioburden method successfully recovered microorganisms from the drug product and doesn't impede the growth of the microorganisms recovered from the device. Only then can the product's bioburden be determined, and proper sterilization frequency and dose be executed.

Before bioburden testing can be implemented, the method validation must be completed. If the drug product is updated, upgraded, or changed, the method must be reevaluated before resuming bioburden testing—schedule method validation after changes in manufacturing locations, manufacturing processes, or raw material/packaging vendors.

There are two kinds of bioburden validation methods:

1) Repetitive Recovery Using Naturally Occurring Bioburden

Using this method, a bioburden test is done on a drug product a minimum of 3 separate times. Then the results are used to determine a percent recovery.

This method is recommended for drug products with moderate to high bioburden potential.

2) Product Inoculation Recovery Using Simulated Bioburden

Using this method, a measured number of spores is added to an already-sterile drug product to simulate a specific bioburden level. Then the drug is tested using the same method proposed for regular analysis. The measured number of spores is compared to the recovered spores, and percent recovery is determined.

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This method is recommended for drug products that have low bioburden levels.

Enumeration Of Bioburden

The bioburden, or microorganisms, is much of what keeps a drug product from being sterile. Bioburden test data helps determine individual standards for a successful sterilization process for each drug product. Regular interval testing will verify that the bioburden level is consistent over time and that the established sterilization protocol continues to be effective. Consistency and the avoidance of bioburden spikes (twice as high or more than the control group average) within a lot are essential parts of the sterility assurance level.

To evaluate bioburden levels, typically, ten random samples from three different newly manufactured lots should be tested. The samples are recorded by manufacture date to find any bioburden inconsistencies. For culturing and microbial enumeration, membrane filtration is the favored method for products with filterable extraction fluid.

Once the initial data has been established, bioburden tests should be conducted at regular intervals, usually quarterly. In addition to monitoring microorganism levels, bioburden test data can help identify the causes of a bioburden spike and dose audit inadequacies. Testing can also be utilized as a tool for material qualifications. Bioburden testing can also be used as a material qualifications tool. For more information, consult ANSI/AAMI/ISO 11737-3:2004 (Sterilization of medical devices, microbiological methods, Part 3: Guidance on evaluation and interpretation of bioburden data).

Types Of Bioburden Analyses

- Bioburden Test Method Validation
  - Recovery study: repetitive treatment (3-5 extractions per sample)
  - Recovery study: simulated (spore inoculation)
- Bioburden Total Aerobic Bacteria and Fungi, Filtration Method
- Total Anaerobic Bacteria
- Total Aerobic Spores

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- Process Fluids (filtration method)

The Importance of Microbial Identification

By conducting microbial identification testing of bioburden, the source and/or method of contamination can be determined and addressed. Identifying the species can provide additional clues as to how a drug was contaminated, and operating procedures can be updated.

Test for Bacteriostasis & Fungistasis

The bacteriostasis & fungistasis test, required by regulatory bodies, is designed to validate the product's sterility throughout the sterilization process. It is necessary because some products contain substances that slow the growth of microorganisms, which can lead to false-negative sterility tests.

The testing process starts with a simulated sterility test. Next, low levels of certain bacteria and fungi are added. The organisms will grow if the drug does not have a bacteriostatic or fungistatic effect. In this case, the sterility protocol must be modified, and the bacteriostasis & fungistasis test must be redone.

This kind of testing should be done on all new drug products, as well as when relevant changes to the manufacturing process or materials. Between three and six sterile samples will be required to perform the test.

Bacteriostasis & Fungistasis Test, Direct Transfer Method

3 organisms in SCDM (for radiation dose audits)
6 organisms: 3 in FTM and 3 in SCDM (USP; EO sterilized products)

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ANSI/AAMI/ISO Dose Audit
This kind of dose audit tests samples of a product that have been irradiated at a prescribed kGy level (determined by the ANSI/AAMI/ISO dose validation study). New products that have been evaluated by ANSI/AAMI/ISO 11137-2 VDmax, ANSI/AAMI/ISO 1137-2 Method 1, or AAMI TIR 33 VDmax are required to be tested every quarter, or with each lot produced if lots are made less often than every quarter. The exception: the frequency of the dose audit may be pushed to semiannually or even annually if it is shown that the long-term product bioburden is stable on three criteria: microorganism levels, types, and resistance. All samples are tested using Soybean Casein Digest Medium and incubated for 14 days at 30º±2ºC.

STERILITY TESTING

Direct Transfer

- Products are rinsed with, or sub-merged when possible, in a soybean casein digest medium.
- A minimum of 10 product samples are typically necessary.
- In most cases, products are incubated for 14 days.