## Sterile Cleanroom Management

Manufacturing applications in sterile environments require special consideration. It is essential to ensure that the range of cleanroom consumables, from wipers and gloves to swabs and tubing, will not impact the aseptic environment. This is even more critical for environments where the sterility of the final product depends upon sterile processing as opposed to sterilization of the final product. Because introduction of a contaminated consumable could cause failures in the manufacturing process, an understanding of effective sterilization methods is critical.

A number of methods may be used in product sterilization, including autoclaving, e-beam and gamma radiation. There are advantages and disadvantages to each, depending on the application at hand.

The autoclave method employs steam and pressure to achieve sterilization. The drawback to this approach is that the product packaging must be permeable – leading to the repackaging of many products, wasting time and money. Yet because autoclaves are reasonably priced, sterilization can be performed within the home facility, which is particularly effective when working in small batches.

E-beam, or electron beam sterilization methods offer limited utilization for low density products due to a relatively low penetrating power.

The preferred option for high density products and larger batches, gamma radiation offers a higher level of penetrating power to more effectively sterilize through standard product packaging with minimal variation in temperature. This method is particularly useful in the food, cosmetics, and medical industries.

Produced using Cobalt-60 sources, gamma rays are especially suitable for ionization, a type of radiation with enough energy to eradicate orbital electrons without introducing radioactivity. Lethal to microbial life, gamma radiation offers a reliable method of achieving sterility.

**Irradiation Alone Is Not Enough**

Irradiation is not the same thing as sterilization, and it is not recognized independently by the FDA or pharmaceutical companies as a means of sterilization. While the term “irradiation” implies that a substance has been exposed to gamma rays, it does not ensure that a sufficient dose has been used to achieve sterility. With irradiation alone, no Sterility Assurance Level (SAL) can be determined.

Sterilization process validation can be achieved with documentation to support methodologies and processes using global standards established by ANSI/AAMI/ISO. While various sterility validation guidelines are applicable, ANSI/AAMI/ISO 11137 Method 1 is the most common. Raw materials, components, packaging and environmental controls all must be considered in the validation process.

Ability of the product and packaging to withstand irradiation should be qualified prior to beginning a sterility validation process, as substances may weaken or become discolored, rendering them useless. Testing the materials against varying levels of irradiation can determine the maximum tolerated dose.

**Performing the Initial Validation: ANSI/AAMI/ISO 11137 Method 1**

Bioburden tests are used for viable organism removal, enumeration and recovery testing. A bioburden study is performed on ten samples taken from three lots of randomly-selected product immediately prior to the sterilization process. In the event of large or expensive items, a sample item portion (SIP) may be tested for bioburden and the resulting corrections applied to the entire production. Once 100 samples have been irradiated to achieve a SAL of $10^{-2}$, a sterility test is performed. The necessary dose to accomplish this is based on the bioburden of an individual product.

**Quarterly Audits**

It is recommended that audits be performed every three months to reconfirm sterilization dose. This is done with 110 randomly selected items prior to sterilization, which are tested for bioburden. 100 items are then exposed to the predetermined validation dose to verify any changes in bioburden, including resistance to radiation. Package integrity studies are ideal during quarterly audit testing.

**Irradiation Facilities**

There are many considerations in selecting an appropriate irradiation facility, such as product type, cost and location. The facility should be cGMP and ISO9000 compliant, with the capacity to perform a dose mapping to identify where the minimum and maximum levels of radiation are absorbed by the product. Using strategically placed dosimeters, a loading pattern will be developed and maintained.

**Limitations of Irradiation Indicators**

Commonly utilized for inventory control, irradiation indicators do not necessarily denote sterility. They can, however, be used to determine if a product has been exposed to a radiation cycle, as the indicator color will shift from yellow to red. However, it should be noted that a change in PH balance could also cause this effect.

Available from consumables manufacturers, a Certificate of Sterility, or CoS, provides assurance that a product has completed a validated sterilization process. This CoS will include the catalog number, lot number, irradiation run number and date, sterilization method, and maximum and minimum specified dose.

**Environmental Monitoring**

Because both processes and the environment introduce potential contamination which can impact bioburden levels, environmental monitoring is recommended. Bioburden present in the air can be sampled onto a media strip using a Rotary Centrifugal Air Sampler (RCS) and incubated to determine bioburden levels.

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