MediZap

Advanced Sterilization

Irradiation in Drug Compounding: A Deep Dive into Sterilization Standards and Bioburden Management

The utilization of ionizing radiation (E-Beam, X-Ray) is the preeminent modality for the terminal sterilization and bioburden elimination of sterile drug compounding within the last decade. This article delineates the distinctions between a validated sterility process and finished drug compound sterility claim.

FDA, ISO, USP, and cGMP regulatory standards dictate the sterilization process validation for compounded pharmaceutical products. Such sterility claims demand a Sterility Assurance Level (SAL) of 10^{-6} or better, signifying a less than one in one million chances of a non-sterile drug product. Compounders/manufacturers claiming sterility typically combine multiple operational controls to maintain a sterile barrier and drug product. Expectedly, these standard operation procedures would employ a validated sterilization process with a SAL of 10^{-6} or higher. Heat-sensitive drug products or those with viscous active pharmaceutical ingredients/excipients cannot be aseptically filtered for sterility without significant time and yield loss. These are examples of compounded drugs that necessitate sterilization by irradiation; furthermore, drug products sterilized through aseptic filtration require all components (API, excipient, primary packaging) to be combined in a sterile cleanroom environment.

By investing in terminal sterilization by irradiation, compounders/manufacturers can purchase bulk drug substances, following a risk-centric model, not requiring sterility but are labeled as low bioburden or bioburden-controlled processes. These processes hinge on minimal bioburden contributions to determine the risks to process and product quality. While the bioburden may be minuscule or absent, other controls ensure product quality, such as specific storage conditions. Notably, the absence of bioburden doesn't equate to sterility, considering the necessary SAL of 10^{-6}.

ISO 11137 〈Sterilization of Healthcare Products〉 is the standard to validate a terminal sterilization process through irradiation in the compounding/manufacturing of drug products. The most common method employed is a VDmax 25 validation technique for compounded drug product sterilization. At its core, this method allows sterility claims based on an internal verification dose of 25 kGy or more for compounded drugs with fewer than 1000 colony-forming units (CFU) per unit. Additionally, VDmax 15 is a method used if bioburden of known sterile drug products is no greater than an average of 100 CFU's per drug product. ISO 11137 requires periodic dose audits (including bioburden testing) if perimetric based release is selected.

- Practically, terminal sterilization by irradiation is affected by aspects like bioburden levels, package density, and validation target dose and limits. Bioburden testing frequency varies by time-period since initial sterilization process validation as prescribed in ISO 11137.
    - Year 1: Quarterly Dose Audit
    - Year 2, and 3: Semi-Annual Dose Audit*
    - Year 4: Annual Dose Audit*

*Bio-Burden Only Testing completed quarterly in between Dose Audits

For compounders/manufacturers consistently producing analogous compounded drug products with steady bioburden levels, the VDmax 15 – VDmax 25 method affords significant adaptability. Moreover, the VDmax approach is associated with known bioburden levels ranging from VDmax 15 with an average of 100 CFU's per device, up to VDmax 25 with an average of 1,000 CFU's per device.

In conclusion, this article serves as a guide for differentiating between the requisites for a terminal sterilization process by irradiation and understanding microbial control in compounding/manufacturing processes, thereby enabling pharmacists and quality stakeholders to make informed decisions concerning terminal sterilization modalities and bioburden management.

MediZap with our contract research laboratory manages your ISO 11137 sterilization process validation including B/F, bioburden recovery, bioburden, and sterility.