Comparing Terminal Sterilization and Aseptic Processing of Pharmaceutical Products

The purpose of sterilization is to provide to the patient an efficient drug product that can be used with the highest safety level. Terminal sterilization and aseptic processing are two approaches to obtain a sterile drug product; however, they are two fundamentally different methods. For personnel within the pharmaceutical and medical device industries, this Industry Insight compares terminal sterilization and aseptic processing.

While terminal sterilization and aseptic processing are two different methods to obtain a sterile drug product, regulatory bodies in the United States (US) and European Union (EU) agree that terminal sterilization is preferred and should be considered first to minimize the risk of contamination and its consequences.

> "Wherever possible, a process in which the product is sterilized in its final container (terminal sterilization) is chosen."
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> **—European Pharmacopoeia**

Terminal Sterilization

Terminal sterilization is achieved by exposure to a physical (e.g., temperature, radiation) or chemical sterilizing agent (e.g., Vaporized Hydrogen Peroxide (VHP), Vaporized Peracetic Acid (VPA), Ethylene Oxide (EO)) for a predetermined extent of treatment. The product is sterilized in its final packaging (or final assembled form), which highly reduces subsequent sterility risk. The process is validated to provide a Sterility Assurance Level (SAL) lower than 10^{-6}, which means a probability of less than one unsterile product on a one million population. Terminal sterilization provides a SAL that is possible to calculate, validate and control, and thus incorporates a safety margin.

Aseptic Processing

Aseptic processing is a process performed maintaining the sterility of a material that is assembled from components, each of which has been previously sterilized. This is achieved by using adequate conditions and facilities designed to prevent microbial contamination. Aseptic processing relies on several independent factors for prevention of recontamination of previously sterilized components. Therefore, a SAL is not applicable as accidental contamination caused by inadequate technique cannot be reliably eliminated. Aseptic processing presents a higher risk of microbial contamination of the product than terminal sterilization. Any manual or mechanical manipulation of the sterilized drug, containers, or closures prior to or during aseptic filling and assembly poses the risk of microbial contamination.

Decision Making

The selection of the sterilization method follows a clearly defined decision tree that starts with terminal sterilization. There are various terminal sterilization technologies. Heat sterilization is the preferred technology. In case of temperature-sensitive products, the application of an alternative technology, ionizing radiation (Gamma or E-beam) is an alternative, followed by gas sterilization (e.g., Peracetic Acid (PA), Nitrogen Dioxide (NO2), EO). Aseptic processing is the last possibility as stated in all major standards (European Medicines Agency (EMA), US Food and Drug Administration (FDA)).

The justification for the chosen sterilization or aseptic process should include an extensive and science-based benefit risk evaluation and it should be demonstrated that suitable development efforts have been made to enable terminal sterilization (i.e., adapt formulation, container and more).

Summary

Terminal sterilization is preferred to sterilization by aseptic processing for pharmaceutical products because it provides a SAL that is possible to calculate, validate and control, and thus incorporates a safety margin. For aseptic processes, a SAL is not applicable as accidental contamination caused by inadequate technique cannot be reliably eliminated.

The manufacturer of sterile medicinal product must deploy all possible efforts during product development to use a terminal sterilization technology as it provides the highest assurance of sterility and as a result the highest patient safety level.

Reference

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