Chapter 17

Sterility Assurance of Compounded Sterile Preparations

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Introduction

Sterile products are those that do not contain viable microorganisms. Sterility is an absolute concept. A compounded sterile preparation (CSP) will either be sterile, or it will be contaminated with microorganisms.

Verification of CSPs Prepared from Sterile Ingredients

In healthcare institutions, the majority of CSPs are prepared by manipulating already sterile ingredients within a closed transfer system consisting of vials, bags, syringes, needles, and the like. In these compounding scenarios, sterility assurance relies on compounding in the appropriate environment and using the appropriate aseptic techniques to maintain sterility of the components and final preparation.

In traditional patient-specific manual compounding processes using sterile starting components, contamination rates may be approximated by media fill testing and have been reported to vary between approximately 5% and 0.005%.[1,2] It is widely accepted and must be assumed that at least 1 in 1,000 CSPs prepared from sterile components will be nonsterile with the most common cause being touch contamination of critical sites during the compounding process. Contamination rates are affected by the compounding environment and processes but, most importantly, by operator technique and adherence to contamination prevention procedures.[3,4]

Verification of CSPs Prepared from Nonsterile Ingredients or Nonsterile Devices

The section entitled "Verification of Compounding Accuracy and Sterility" in USP Chapter <797> Pharmaceutical Compounding—Sterile Preparations focuses on the assurance of

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sterility when preparing CSPs from nonsterile ingredients and nonsterile devices.[5] Such high-risk compounding requires a greater degree of expertise and ability to achieve and maintain the sterility of the finished CSP. Compounding personnel undertaking nonsterile to sterile compounding must be well versed on the topics of sterility and bacterial endotoxin testing, which must be performed in accordance with USP Chapters <71> and <85> respectively.[6,7]

Sterilization Methods

Sterilization is a process intended to kill or remove all types of microorganisms. There are two principal sterilization methods:

1. Physical (filtration, saturated steam or dry heat)
2. Chemical (ethylene oxide gas or chemical liquids)

Factors determining the method to be used include the following:

- Types of microorganisms involved
- Nature of the article to be sterilized
- Time available for sterilization

Filtration is the most common sterilization method used by pharmacists and technicians during extemporaneous compounding of high-risk level CSPs. Regardless of the method, the sterilization cycle must be evaluated to ensure that it was adequate.[5]

Sterility Assurance Level

Microbiologically, it is impossible to prove that all microorganisms are destroyed by a sterilization process because the likelihood of survival of an individual organism is never zero. The sterility assurance level (SAL) of a sterilization process describes the probability of a single microorganism occurring on an item after a valid sterilization process.[8] In other words, the SAL is the probability that a single item remains nonsterile following a sterilization process (the probability of a nonsterile unit). SAL also describes the killing efficacy of a sterilization process with each log reduction in SAL (10^{-1}) representing a 90% reduction in the microbial population.[9]

Terminally sterilized commercial sterile pharmaceuticals typically have an SAL of 10^{-6} or a probability that one in one million sterilized items will be nonsterile. Pharmacy-prepared CSPs compounded using aseptic methods with no final filtration or terminal sterilization can only claim an SAL of 10^{-3} or a probability that 1 in 1,000 units will be nonsterile. There are only two possible outcomes of a sterilization process, either the CSP is sterile or it is not sterile. The sum of the probabilities for both outcomes must equal 100%.[10]

Sterilization by Filtration

Filtration is used to remove viable and nonviable particles from a liquid. It is not considered a "terminal sterilization" procedure because it does not sterilize the final product. A liquid that has been sterilized by filtration must then be aseptically placed into a container/closure system.[11,12]

Filters work by several mechanisms including sieving, adsorption, and entrapment.[11,13] A filter considered to be "sterilizing" must have a nominal pore size of 0.2 or 0.22 µm or smaller and must have been tested and certified by the manufacturer to retain at least 10^7 microorganisms of a strain of *Brevundimonas (Pseudomonas) diminutia* on each square centimeter of upstream filter surface area under conditions similar to those in which the CSP will be sterilized under normal use.[12]

Filter Selection

Filters must be evaluated and selected based on the following criteria:

- Rating for human use
- Pore size
- Compatibility with solution to be filtered
- Characteristics of the solution to be filtered (i.e., volume, particulate load, bioburden)

Filter manufacturers publish certificates of quality for their products. These documents typically provide information on the intended use of the filter, the filter's specific bubble point, and prove the filter has been tested for sterility, membrane and housing integrity, microbiological retention, nonpyrogenicity, and extractables.