Chapter 19

Microbiological Issues in Compounding Sterile Preparations

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Introduction

From a microbiological perspective, pharmaceutical products, including compounded preparations, fall into two categories: nonsterile and sterile. For either category, manufacturers must eliminate or minimize potential health risks to patients related to microorganisms and the toxins they produce, while maintaining the other aspects of product quality.[1] Many contributing factors may affect the quality of a medicine or its ingredients, but aseptic techniques, microbial bioburden control, and proper sterilization methods are critical considerations for the manufacturer. Sterile products, which include compounded sterile preparations (CSPs), cannot allow for any microbial presence, given that they are administered into the bloodstream or other body spaces susceptible to microbial proliferation and endotoxins. Microbial contamination in sterile drugs can result in disease and—in some cases—even death.

Aseptic Techniques

Proper aseptic technique prevents contamination of products from microorganisms inherent in the compounding environment. For example, airborne microorganisms (including fungi) picked up from the compounder's body, the pharmacy/laboratory bench-top, or other surfaces, as well as microbes found on unsterilized glassware and equipment may potentially contaminate products. Using proper aseptic technique can greatly minimize or even eliminate the risk of contamination.

Microbial Risk Considerations

It is not possible to ensure that each container of aseptically compounded preparations is sterile. Because CSPs must be filled and sealed using manual operations, it should be

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assumed that each preparation contains low-level contamination. Therefore, to ensure safety, storage conditions that prevent microbial proliferation are critical. Where possible, CSPs should be refrigerated at 2–8 °C until use. All materials of natural origin, simple buffered salt solutions, and aqueous products at neutral pH (6–8) should be considered to have significant microbial proliferation risk and should be stored either at 2–8 °C, –20 °C, or used within 24 hours after compounding.[2,3] Exceptions would include formulations that are shown to be inherently antimicrobial or those that contain an effective preservative system.

Antimicrobial Preservatives

In the case of sterile, aqueous-based articles packaged in multidose containers, suitable antimicrobial preservatives are added to inhibit the growth of microorganisms (bacteria, yeast) that may be inadvertently introduced during or after the compounding process (from repeatedly withdrawing individual doses).[4]

One or more antimicrobial preservative(s) are expected in all sterile multidose units. Antimicrobial preservatives should not be used as a substitute for good compounding practices solely to reduce the viable microbial population of a nonsterile/contaminated sterile product, or to control the presterilization bioburden of a multidose formulation during preparation. All useful antimicrobial agents are toxic substances. For maximum protection of patients, the concentration of the preservative shown to be effective in the final packaged product should be below a level that may be toxic to human beings based on the recommended dosage of the medicinal product.

The concentration of an added antimicrobial preservative can be kept to a minimum if the active ingredients of the formulation possess an intrinsic antimicrobial activity. Antimicrobial effectiveness, whether inherent in the product or produced because of the addition of an antimicrobial preservative, must be demonstrated for all aqueous-based injections packaged in multidose containers and for other products containing antimicrobial preservatives.[4] For the purpose of the test, *aqueous* is defined as a water activity of more than 0.6.[5] The potential for microbial proliferation in the preparation is one of the factors that must be considered when assigning a beyond-use date (BUD), which is the date or time after which a compounded preparation shall not be used. It is determined from the date when the preparation is compounded. The BUD for multidose containers after initially entering or opening (e.g., needle puncturing) is 28 days based on an antimicrobial effectiveness test (AET) unless otherwise specified by the manufacturer.[6]

Antimicrobial Effectiveness Test

USP Chapter <51> Antimicrobial Effectiveness Testing is intended to evaluate the performance of antimicrobial preservatives added to inhibit the growth of microorganisms, which might be introduced during or subsequent to the manufacturing (compounding) process.[4] The AET is a suspension test for microbial kill. A controlled inoculum of the challenge organism(s) is placed in suspension with the sample to be tested, and then the number of survivors is determined by plating at different time points—7, 14, and 28 days—after neutralization of residual preservatives.

Growth Promotion of Media

All compendial microbiology tests are growth-based tests. Culture media are the basis for compendial microbiological tests.[7] Therefore, quality control tests should be performed on all prepared media. Tests routinely performed should include pH, growth promotion, inhibition, and indicative properties (as appropriate), and periodic stability checks to confirm the expiration dating.

Method Suitability

A prerequisite to all growth-based microbiology tests is the ability to recover viable microorganisms in the presence of potentially antimicrobial products or raw materials. Carryover of residual antimicrobial from the test article could inhibit growth in the recovery medium, leading to poor microbial recovery.[8] This potential residual activity must be neutralized, and it is necessary to demonstrate the adequacy of neutralization for