12 Overview of sterile product manufacturing

All pharmaceutical manufacturing operations are complicated, requiring utmost organization and control to ensure that every dosage form produced meets all quality attributes and specifications. Sterile pharmaceutical manufacturing has the added complication of assuring that all dosage forms produced are free from microbial contamination, endotoxin contamination, and visible particulate matter. Not only do all sterile manufacturing operations require mechanical excellence, but also require absolute cleanliness, sanitization, and sterilization of all product-contact components. Unit processes involved in the manufacturing of sterile dosage forms include compounding and mixing, filtration, filling, terminal sterilization (when possible), lyophilization (freeze-drying), closing and sealing, sorting and inspection, labeling, and final packaging for distribution (Table 12-1). Each of these unit processes will be the subject of subsequent chapters with this chapter presenting a general overview.

MANUFACTURING PROCEDURES

The processes required for preparing sterile products constitute a series of events initiated with the procurement of approved raw materials (drugs, excipients, vehicles, etc.) and primary packaging components (containers, closures, etc.), and ending with the sterile product sealed in its dispensing package (Fig. 12-1 for solution and lyophilized products). Each step in the process must be controlled very carefully so that the product will have its required quality. To ensure the latter, each process should be validated to be sure that it is accomplishing what it is intended to do. For example, any sterilization process must be validated by producing data showing that it effectively kills resistant forms of microorganisms (or removes them with filtration processes); or, a cleaning process for rubber closures should provide evidence that it is cleaning closures to the required level of cleanliness; or a filling process that repeatedly delivers the correct fill volume per container. The validation of processes requires extensive and intensive effort to be successful and is an integral part of current good manufacturing practices (cGMP) requirements.

TYPES OF PROCESSES

The preparation of sterile products may be categorized as small-scale dispensing, usually one unit at a time, or large-scale manufacturing, in which hundreds of thousands of units may constitute one lot of product. Small-scale processing involves early phase clinical batches, although there are some commercial products whose batch sizes are in the hundreds rather than tens of thousands. Small-scale processing also occurs in some hospital pharmacies who need to follow the requirements of the United States Pharmacopeia (USP) general chapters <797> and <1206>. Often small-scale processes use presterilized components and equipment to simplify all steps and increase the assurance of sterility.

Large-scale processing will be the focus of this chapter and other chapters related to manufacturing. Such processing begins with nonsterile components in large (thousands of square feet) facilities with state-of-the-art equipment, instrumentation, lines, and all other required technology to produce sterile products at massive numbers of unit. Underlying all sterile product production, regardless of batch size, is strict adherence to cGMP principles. The following are examples of cGMP compliance and include (Code of Federal Regulation reference(s) in parenthesis):

- Ensuring that the personnel responsible for assigned duties are capable and qualified to perform them. GMP emphasizes the need for personnel to have a combination of education, experience, and training to do their jobs (CFR 211.25).
- Ensuring that ingredients used in compounding the product have the required identity, quality, and purity (CFR 211.80, 211.84, 211.86).