The closing of primary containers will affect the final integrity of the container/closure interface. Container/closure integrity testing and validation is covered in chapter 30.

For syringes and cartridges, no further sealing is done, although units are either placed in secondary packaging for unit dosing or part of a tray system, for example, Hypak™ (Becton-Dickinson). For vials and bottles, aluminum seals are crimped around the rubber closure and top of the container. Seal force integrity can be measured by a torque-testing device.

Terminal Sterilization

The desired scenario for filled containers after closing and sealing is to transfer them to a steam sterilizer or other sterilization system (e.g., radiation) and have the entire batch terminally sterilized. Terminal sterilization offers the greatest assurance of product sterility. Unfortunately, a large majority (perhaps >80%) of all small-volume injectable products contain active pharmaceutical ingredients that are heat- or radiation-labile and cannot be terminally sterilized.

It should always be the goal to develop sterile products that can be terminally sterilized. Discussion of possibilities for sterilization cycle modifications that will allow heat-sensitive products to be terminally sterilized are discussed in chapter 17.

Freeze-Drying

Freeze-drying or lyophilization is a major sterile process operation with approximately 40% of all biopharmaceutical products requiring freeze-drying for product stability. Products to be freeze-dried are processed as solutions up to the stoppering step. Following partial stoppering, vials are accumulated in a tray either for manual or automated transfer to a shelf of a freeze-dryer. Following the lyophilization process, the freeze-dryer shelves are hydraulically lowered to fully insert stoppers into the vials. Vials are manually or automatically removed from the dryer, loaded onto a capping line for sealing and inspection. Freeze-dry processing is discussed in chapter 20.

Finishing and Inspection

Finishing includes all the operations following the closure of the primary package that are as follows:

- Sealing or capping (chap. 19)
- Attachment of a plunger rod for syringes
- Labeling (chap. 22)
- Secondary packaging (chap. 22)
- Storage and distribution (chap. 24)

Inspection of finished units of sterile products requires every single unit to be evaluated for visible foreign particulate matter and any other defect. This subject is covered in detail in chapters 22 and 29.

Quality Control Testing

An appropriate number of finished product samples are removed using a statistically valid sampling plan for final product testing before the batch of product can be released for clinical or commercial use. Testing includes a variety of chemical and physical tests and assays, whatever is required to assure product safety, purity, strength, and quality.

Three special quality control tests are unique for sterile products—test for sterility, freedom from pyrogens or endotoxins, and freedom from visible particulate matter, and excessive subvisible particulate matter. These tests are discussed in detail in chapters 27, 28, and 29, respectively.

The pharmaceutical scientist must be aware of the various issues involved in the manufacturing arena that can impact the stability and quality of the pharmaceutical product, especially protein or peptide formulation. Among the more relevant areas of concern include shear rate and stress during compounding, filtration, and filling adsorption onto process tubing and filter surfaces, and the effects of time and temperature during each step of the manufacturing process. Formulation scientists and process engineers should work together to design and implement experiments to determine processing effects on protein stability and establish an appropriate