Filling/Closing/Stoppering/Sealing

Chapter 19 is devoted to the processes of filling and stoppering. These operations must occur under Grade A/B (ISO 5) clean room conditions. Sterile products are filled into final containers as liquids, dispersed systems, or powders. Liquid filling machines operate under peristaltic, piston, or time-pressure mechanisms. Dose control is imperative, with factors such as filling speed, product viscosity, and product potential to foam thereby affecting dose accuracy. Filling rates, depending on type of product, filling volume, and container type and size, can be as high at 600 units filled per minute. Filling accuracy should be within the range of $\pm$ 0.25%. Filling machine vendors include Bosch/TL, Chase-Logeman, Cozzoli, Mateer-Burt, Inova, National Instrument, and Perry.

The main issue with dispersed system filling is maintaining dose homogeneity—a huge challenge. Actually, at the point of filling the product into the container, the potential for clogging of the filling needle or nozzle is a concern. Dose homogeneity is a function of the ability of recirculation system supporting the filling system to prevent suspension particle or emulsion globule interaction and growth.

Powder filling also must control dose uniformity and accuracy that is a function both of the engineering of the powder filling machine and the particle size characteristics dictated by methods used to produce the solid product. Control of relative humidity during filling and minimizing foreign particle contamination also are challenges with powder filling. Primary vendors of powder filling machines are Perry and Chase-Logeman.

With respect to closing/stoppering of product-filled containers, ampoules, of course, do not require rubber closures and are sealed with a flame. Vials are closed with rubber stoppers (or, for vials containing solution to be freeze-dried, the stopper is partially inserted into the vial opening), and syringes and cartridges are closed with rubber plungers at the distal end (with rubber septa sealing the proximal end except for staked-needle syringes). Rubber stoppers and plungers need to be lubricated either with applied silicone oil or emulsion or with special coatings (see chap. 7) that permit and facilitate rubber units to move easily from the closure feeder (hopper) along stainless steel tracks or rails to the openings of the primary containers (Fig. 12-6). For vial openings, the closure must fit snugly, not "pop out." Often, filling efficiencies are dependent more on the stoppering process than on the actual filling process as there are tendencies for rubber closures to slip or pop off the openings of vials. For syringes and cartridges, the placement of the rubber plunger is dictated by the desired position of the plunger within the barrel of the syringe or cartridge to deliver the claimed volume of product.

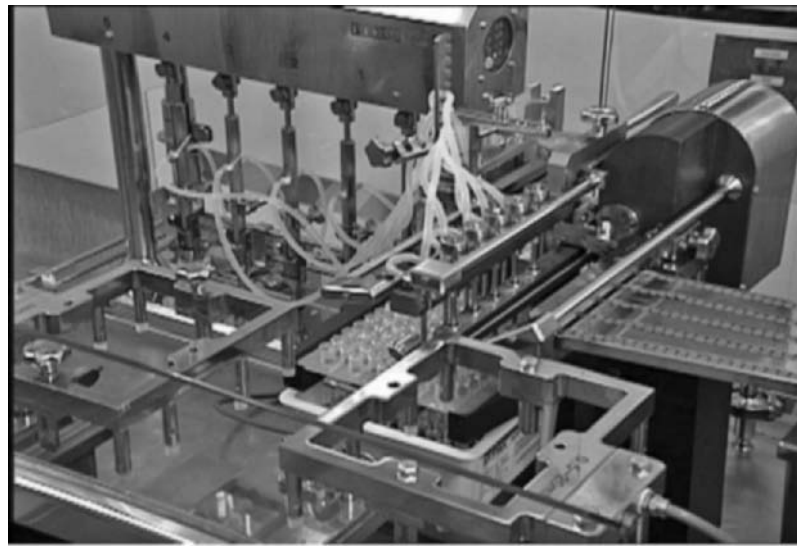

Figure 12-6 Examples showing rubber closures moving along stainless steel railings from the feeder to the container opening. *Source*: Courtesy of Baxter Healthcare Corporation.