

the stroke of the syringe so that the same volume will be delivered each time. Clean, sterile, disposable assemblies (suppliers: *Burrton, Pharmaseal*) operating on the same principle have particular usefulness in hospital pharmacy or experimental operations.

PREFILLED SYRINGE PROCESSING AND FILLING

Syringes are cleaned, sterilized (by ethylene oxide or radiation), and sealed with a puncture proof cover by the syringe manufacturer before delivering to the finished product manufacturer. Syringes are contained in a plastic tub system double wrapped that maintains sterility of the syringes [e.g., Becton Dickinson's Hypak™ syringes (Fig. 7-7)]. The transfer of these tubs containing sterile syringes from a receiving area into the aseptic filling area presents a challenge with respect to maintaining sterility. Typically, the outer bag wrap is removed within a Grade C/ISO 8 area and the inner bag wrap is sanitized (alcohol or hydrogen peroxide vapor) before moving into the aseptic area. At the time of the publication of this book, low energy e-beam radiation was becoming a new alternative as a surface decontamination process that increases the level of sterility assurance in the transfer of presterilized syringe tubs into the aseptic area. In the aseptic area, an operator removes the lid of the tub and the tub is placed on the filling line. Syringes are filled row by row with precise filling volumes (can be accurate within 0.1 mL) and then the rubber plunger is accurately inserted at the predetermined location within the syringe barrel to ensure accurate delivery volume.

An example of a common syringe filling machine (Inova) is seen in Figure 19-4. Syringe fillers are designed to first fill the product into sterile syringes, then the sterile stopper is inserted. If the stopper insertion rods or tubes are not properly aligned then the product could potentially contact the rods and tubes and glass will break. Syringe fillers typically can fill 0.5 to 20 mL syringe at rates between 60 to 600 syringes per minute.

CARTRIDGE FILLING

Example of a common cartridge filling machine is seen in Figure 19-5. This is a Bausch + Stroebel machine that fills up to 3 mL cartridges at rates of 300 per minute. With cartridges, the rubber plunger is first inserted to a predetermined place within the barrel of the siliconized cartridge. The product is filled, typically with a two, even three-shot fill so that there is no significant headspace; then the cartridge is sealed with a sterile, rubber septum within a aluminum cap. Excessive air space in a cartridge will affect dose accuracy when the contents of the cartridges are ejected through a pen delivery system.

Issues with Liquid Filling

Table 19-2 lists examples of potential problems that may occur with filling of liquid products. These potential problems illustrate the extreme importance of process research and development with the ultimate goal of process validation with respect to filling accuracy and effect of filling phenomena on product quality. While many of these studies can be conducted in a laboratory, final verification and validation must be conducted in a pilot or production filling facility at scale.

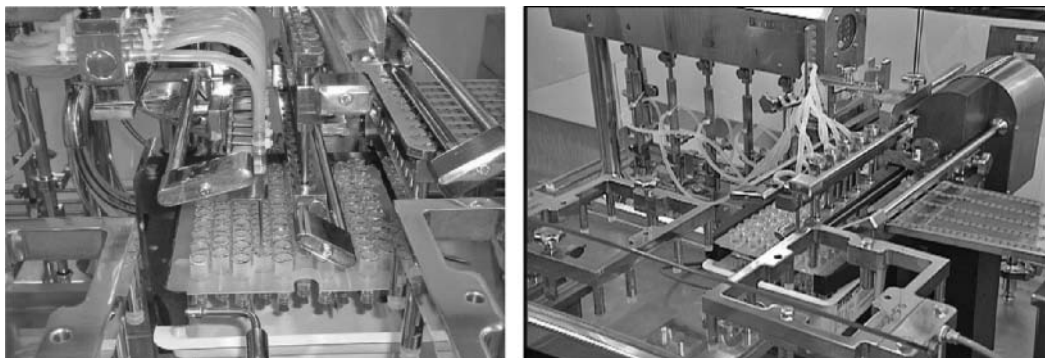


Figure 19-4 Syringe filling machine (Inova). *Source:* Courtesy of Baxter BioPharma Healthcare Corporation.