both single and multiple-dose vials is compromised whenever the rubber plunger is punctured with a needle, but the presence of an antimicrobial preservative agent allows the multiple-dose container to be punctured multiple times.

A multiple-dose container is designed so that more than one dose can be withdrawn at different times while maintaining a seal between uses. It should be evident that with full aseptic precautions, including sterile syringe and needle for withdrawing the dose and disinfection of the exposed surface of the closure, there is still a substantial risk of introducing contaminating microorganisms and viruses into the contents of the vial. Because of this risk, the USP requires that all multiple-dose vials must contain an antimicrobial agent or be inherently antimicrobial, as determined by the USP *Antimicrobial Preservatives Effectiveness* tests (24). There are no comparable antiviral effectiveness tests, nor are antiviral agents available for such use. In spite of the advantageous flexibility of the dosage provided by multiple-dose vials, single-dose, disposable container units provide the clear advantage of greater sterility assurance and patient safety.

Manufacturing

Tubing glass is manufactured by starting with a tube of glass of the appropriate diameter formed by either the Danner or Vello processes (22,25–26). In both processes, glass flows vertically from the bottom of the furnace. Liquid glass is drawn, horizontally, away from a mandrel in the Danner process and is drawn vertically in the Vello process. The Danner process is typically used for glass formulations containing 10% or less B_2O_3 and the Vello process is not suitable for diameters of approximately 45 to 50 mm.

In the forming part of the process (Fig. 7-5), the tubing is preheated to form the shoulder of the container and form the finish of the glass opening. The tube is then cut to form the bottom, heated to smooth the bottom, treated if desired, and cooled. The heat used during smoothing vaporizes the glass and the vapors condense on the inside, producing a rough surface (27). These rough spots are chemically different from the rest of the surface and can be more reactive and less durable. A sulfur treatment using ammonium sulfate can be used to make the sodium borate deposited at the surface of the vial more soluble. The deposits are then washed away during the cleaning process. The treatment can help to reduce pH shifts in solutions resulting from the sodium ion but has no effect on the smoothness or durability of the vial surface.

The heat used when forming the vials directly affects the level of extractables at the surface of the vials. Therefore, some manufacturers offer vials produced at lower temperatures, referred to as a cold forming process. This improves the resistance of the glass to reduce the level of extractables.

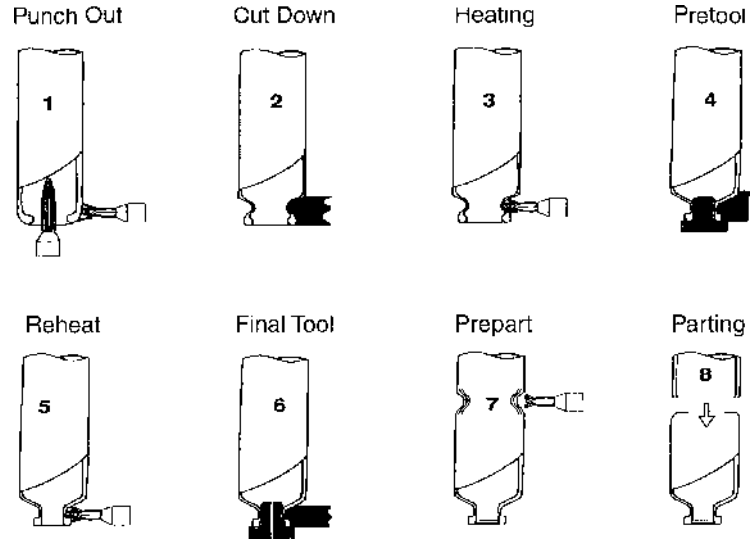

Figure 7-5 Formation of tubing glass. *Source*: Courtesy of Schott Glass.