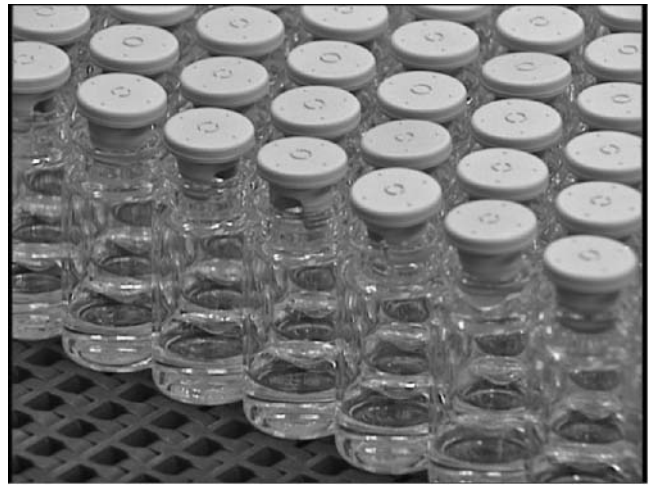

Figure 10-1 Partially slotted stoppers in solution vials prior to loading into freeze-dryer.

Tables 10-1 and 10-2 present two lists of commercial freeze-dried products. Table 10-1 presents general information about these products, whereas Table 10-2 focuses more on the specific quantitative formulations for each product. They are not exhaustive and will not be up to date at the time of this publication, but provide excellent representative information about freeze-dried formulated products being successfully used to save and affect lives.

Besides overcoming stability problems by converting a solution to a dry powder, freeze-drying also offers the advantages of processing the product in the liquid form. Sterile powders can also be produced by other processes (not covered in this book) such as spray-drying, spray-freeze drying, or sterile crystallization followed by powder filling. However, freeze-drying offers certain advantages over other powder production processes including the fact that the product can be dried without the need for elevated temperatures, product sterility is more easily achieved and maintained, the contents of the dried material remain homogeneously dispersed, and the reconstitution times generally are faster. Also, for drugs that are oxygen sensitive, freeze-drying is a better powder-producing alternative, because the environment during the freeze-drying process can be an oxygen-free condition and an inert gas can fill the headspace of the container prior and during closing of the container.

Freeze-drying also has certain limitations, perhaps the foremost being cost compared to other powder-producing processes and certainly more expensive than liquid filling and stoppering. Volatile compounds in the formulation could be removed if high vacuum levels are required and high vacuum has been known to increase the extractable levels from the rubber closure. The freezing and drying steps are known to cause stability problems with some proteins that usually can be overcome using stabilizers called cryo- or lyoprotectants. Because the product has been previously sterilized prior to loading into the freeze-drying chamber, sterility must be maintained during the loading and unloading process and also during the freeze-drying process itself. The ability to maintain aseptic conditions during these processes as well as validating the sterilization of the freeze-dryer chamber and all connections and gases leading into the chamber must be demonstrated.

ATTRIBUTES AND REQUIREMENTS OF A FREEZE-DRIED PRODUCT

The ideal freeze-dried product has a very pleasing aesthetic appearance (i.e., intact cake, uniform color, and appearance) (Fig. 10-2), sufficient strength of active ingredient, chemical and physical stability, sufficient dryness and other specifications that are maintained throughout the product shelf-life, sufficient porosity that permits rapid reconstitution times, and freedom from microorganisms (sterility), pyrogens, and particulate matter after reconstitution. Also, after the drug is in solution, it must remain within certain predetermined specifications (e.g., potency,

(Text continues on page 154.)