involved in the manufacture of a freeze-dried product in a dual chamber package.

Freezing

The objective of freezing is to solidify most or all of the water in the system by formation of ice and to convert solutes into crystalline or glassy solids. Proper freezing will solidify the product in all containers to a temperature below the critical temperature required for the product (e.g., glass transition temperature, eutectic temperature, or collapse temperature). As a sample is cooled, the system may remain liquid well below the equilibrium freezing point due to supercooling. The degree of supercooling may significantly affect the time to sublime ice since higher supercooling results in smaller ice crystals and a higher product surface area. As the surface area increases, the cake resistance to sublimating vapors increases and results in slower primary drying. Less supercooling (hence larger ice crystals) is desired to minimize primary drying time. Dual chamber package systems (particularly syringes/cartridges) typically have the drug product in the front chamber, which is not in direct contact with the lyophilizer shelf. This leads to significant challenges to development of the freezing phase as well as other aspects of lyophilization cycle development. Figure 10 illustrates these differences and highlights some of the considerations for dual chamber package systems of this type.

The heterogeneity between samples during freezing will generally be magnified in dual chamber packages. Differences in freezing rate will occur for both containers in different locations within a lyophilizer and across a single lyophilizer shelf. These differences will be more pronounced with increasing distance between the drug product compartment and the lyophilizer shelf and also with increasing product fill volume. Uniformity of freezing across a batch can be improved by selection of a loading system that provides appropriate spacing between syringes and enables greater heat transfer contact area between the syringe barrel and the conductive surface of the holder. A similar concern is typically noted as the manufacturing scale changes. Generally a smaller scale (e.g., laboratory) lyophilizer will be poorly insulated compared with a commercial unit. The susceptibility of the product to radiative heat from the

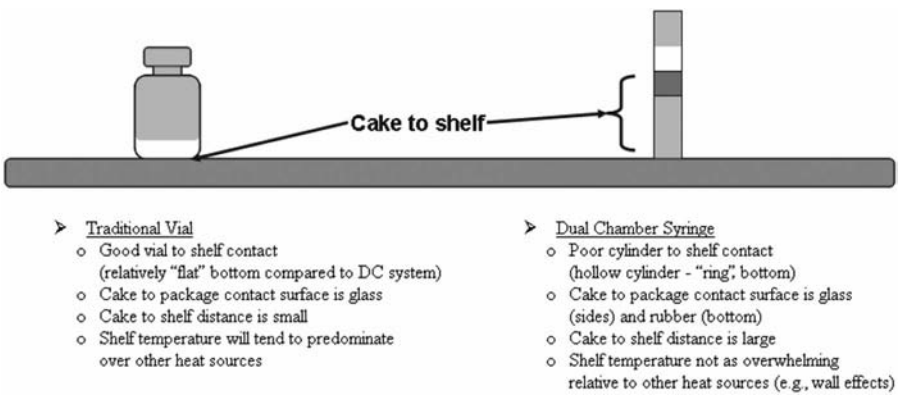

FIGURE 10 Traditional vial versus dual chamber syringe comparison.