utilize low-fill volumes. These low-fill volumes can be difficult to accurately control. Therefore, it is paramount that careful control of the fill volume for both the active containing and diluents chambers be maintained to satisfy product release specifications.

PACKAGING SELECTION PROCESS

A key component to development of a sterile freeze-dried product is the understanding that the product is a sum of the formulation, process, and package. The interrelationships of all three must be understood to develop a product of acceptable quality that will meet its specifications over its intended shelf life. It should be noted that the container closure system design can impact the lyophilization process with respect to resistance to heat transfer and processing throughput. Additionally, the container closure system can impact the product quality in the following ways: chemical compatibility, extractables/leachables, moisture ingress, sorption, particulate matter (e.g., via silicone oil, etc.), seal integrity, stability, and functionality. When working with new drug candidates it is not unusual for formulators to be presented simultaneously with problems of drug substance impurities, chemical instability, and packaging-derived instability. Carefully designed experiments should be integrated into the initial formulation design exercise to ensure that the impact of packaging components be identified. Therefore, one or more of the product components (i.e., the formulation, the package, or the process) may need to be optimized to meet the desired characteristics for a specific product within available manufacturing capability and at an acceptable cost of goods.

Elastomer Selection

An example of a compatibility issue that can be a concern includes those that impact the physical/chemical stability of the active ingredient or cause sorptive loss of a key excipient. Several of the marketed DCS/DCC/DCV lyophilized products contain a preservative in the diluent chamber. It is well-known that many of the preservatives utilized (e.g., benzyl alcohol or parabens) can be lost from solution due to sorption to rubber closures (9,10). Typically, a butyl rubber is selected as the closure material for most dual chamber packages because this rubber is generally inert, has low moisture/gas permeability, and has a low sorption potential. Despite this low sorption potential, it must be considered that the diluent-containing chamber exposes a relatively high surface area of rubber to the diluent due to the exposure of liquid to two rubber surfaces for most DCS package systems. The high surface area of exposed rubber compared to the low diluent volume present can contribute to a significant preservative loss to the butyl rubber.

Rowles et al. (9) reported on studies evaluating the sorptive loss of benzyl alcohol to rubber closures. The sorptive loss data fit a passive diffusion model whereby the amount of benzyl alcohol lost was proportional to the square root of time. According to this model, the benzyl alcohol loss to the package was relatively rapid but slows with time. Data for the sorptive loss of the preservative, benzyl alcohol, for the DCS product (CAVERJECT IMPULSE®) is summarized in Figure 5. Fitting this data to the passive diffusion model whereby the amount of benzyl alcohol lost is plotted versus the square root of time is illustrated in Figure 6. The temperature dependence of this sorptive process is