

product (31). It should be noted that CCIT cannot replace sterility testing during product release. Before making the decision to use CCIT in lieu of sterility testing, the following should be considered: (i) confirm regulatory acceptance of this option in the country of filing and (ii) confirm that the methodology chosen is appropriate for the container closure system and is adequately validated.

COST ANALYSIS

The comparison of cost between a lyophilized product in a dual chamber package and a vial is complex due to the number of factors that need to be considered. Several of these key cost considerations are summarized in Table 2. It is difficult to generalize this topic since many of the factors are dependent on specifics of the product. One of the foremost cost differentiators is related to decreased overfill in a dual chamber system. Consider the example of a 1-mL fill in vial versus dual chamber system. The USP suggests a 0.15-mL overfill for 1-mL fill vial products due to loss during withdrawal and administration (32), which equates to a 15% overfill. However, the overfill for a dual chambered system is only dictated by hold-up volumes between chambers and that caused by the delivery needle. This is typically ≤ 0.1 mL (i.e., $\leq 10\%$ overfill) for a 1-mL dual chamber system. This consideration is especially important for biologics drugs where the drug itself is expensive. Freeze-drying time and yield are specific to the formulation, primary package, and lyophilization parameters, but is generally less optimal for dual chambered systems. However, if a product in DCS has a relatively high collapse temperature and an efficient loading configuration in the lyophilizer, the overall difference in lyophilizer time and yield may not be much greater than for an identical product in vial. The number of accessories needed to reconstitute and deliver drug from a lyophilized drug in vial is much greater than for the lyophilized drug in a dual chamber system. This greater number of accessories must be taken into the overall cost of the final drug product. One exception is that drugs in DCCs must be delivered with a pen delivery system, which varies widely in cost. Finally, an overall cost differential that favors vials may not matter if a dual chamber system is required to compete in the market, which is the case for home administration of insulin and growth hormone.

SUMMARY

An increased use of lyophilization and the demand for more unit dose/unit of use packaging have created a requirement for new package forms. Lyophilizing in dual chamber packages eliminates the manual aseptic reconstitution step and greatly improves patient convenience and safety. However, lyophilizing a drug in dual chamber systems can be challenging compared with lyophilization in a standard vial due to differences in package configuration, heat flow, and lyophilizer trays. Appropriate considerations for the proper amount and fill for each chamber must be taken into account to produce a product designed to deliver the target label dose on use. Compatibility of the formulation with the package must be properly evaluated since these systems tend to be siliconized and possess large surface areas of the glass/rubber to volume, which can potentially impact product physical/chemical stability. Freeze-dry cycle development can be difficult due to poor heat transfer to the product during sublimation. Significant drying heterogeneity can occur within the dryer depending