

## *Systems Considerations*

There are several other elements of the process and equipment design that, when looked at as an end-to-end process, have the potential to significantly impact the quality and consistency of transferred process. One example is the choice of lyophilizer door design, often related to the decision to accommodate automated vial loading. Commercial lyophilizers are in use with standard, side-hinged, full doors that enable access to the entire chamber from top to bottom as well as slot-style “pizza” doors that only expose a few shelves at a time and are most amenable to automated loading. Differences in the loading and shelf indexing approach used in these systems should be considered from a standpoint of operational ease and efficiency as well as compatibility with intended product types. For example, the product warming associated with multiple openings of a standard lyophilizer door and multiple shelf indexing steps was found to result in unintended and variable product annealing for a labile live virus product transferred to the lyophilizer in prefrozen vials [74]. While not a standard industry process, this example highlights how small operational choices, such as the lyophilizer loading and indexing procedure, can influence final product quality outcomes.

The extent of process automation to pursue should balance total system cost, consistency, and flexibility. While manual and automated systems can both deliver high quality products, there are some considerations to keep in mind both for the transition from laboratory to production scale as well for routine production-scale operation where automation is concerned. First, many activities that were performed manually during laboratory development will be automated in a standard production line. One example of this is the automated partial stoppering of vials that occurs on filling lines. Drying cycles should be designed to be robust to the typical line setup variability and resulting small differences in stopper position.

Second, the implementation choices for automating a process can have unexpected consequences for supply chain management and process validation. For example, a sample that was easy to obtain for a manually loaded and unloaded process at laboratory or production scale may be very difficult to obtain for an automated process. If non-standard supplemental samples are expected to be required as part of process validation activities or potential manufacturing deviation resolution, forethought should be given to the process for obtaining such samples, including alignment with existing media challenge interventions. The cause for such sample challenges can range from lack of human operators in the processing area where nonstandard samples would need to be collected to handling and subsequent automated transfer concerns caused by disruption of tray or shelf pack integrity. One example of unintended supply chain consequences is from an automation choice in a new facility that leveraged automated transfer carts for movement of vials in and out of the lyophilizer on a shelf by shelf basis. Although this system greatly streamlined certain operational steps and improved sterility assurance, it could only accommodate transfer of full shelves, equivalent to thousands of vials. Therefore, it was highly desirable to plan batches that minimized partial shelves, as partial shelves would have to be backfilled with empty glass and represented lost lyophilization capacity. This represented a new planning constraint that needed to be managed for efficient operation. An example is shown below.