capture all interactions and also environment factors such as clean room and an isolator usage at large scale. As discussed earlier, ice nucleation may lead to the major differences between the laboratory- and large-scale dryer, and play a significant role in differences in product temperature during primary drying. In order to minimize gaps between the scale-down model and large-scale process performance, extra equipment and process characterization studies in the small scale and large scale may be necessary. In the laboratory-scale studies, all product vials were washed and depyrogenated, and the solution was filtered and filled in a laminar flow hood to minimize the particle introduction. In this case, it was found that the degree of supercooling was comparable to that in the large scale (about 12 °C), and thus the potential impact of nucleation is relatively small in this case. In addition, continuous process monitoring from commercial batches can build more process knowledge at large scale. By combining the scale-down studies, large-scale studies, comparability evaluation, and stability monitoring, a robust process validation at manufacturing scale is expected. This QbD approach can be used to accelerate the scale-up process and facilitate a smooth technology transfer.

Summary

Rational development of a freeze-drying cycle requires a deep understanding of the heat and mass transfer process. The vial configuration is most commonly used in the lyophilization field, and the most important parameter associated with the vial is the K_v value as a function of pressure. This K_v value will enable measurement of R_p and with these data, will allow the impact of the freeze-dryer design on the product temperature history during primary drying to be quickly and accurately calculated. Understanding the variability in K_v from vial to vial as a function of location is very important. Edge vials, especially at the door of the freeze-dryer, will complete primary drying at a faster rate because they normally display higher product temperatures as a result of the increase in K_v due to high radiation heat transfer during primary drying. This product temperature must be carefully monitored so that it will not result in product quality issues during development and scale-up. Ice nucleation also plays an important role in freeze-drying cycle performance. Due to the random nature of ice nucleation, control of this event is very important if one is to control and standardize the freezing step and minimize vial-to-vial variability. In general, larger ice crystals result in lower cake resistance and shorter primary drying times.

Scaling-up of a freeze-drying cycle is challenging due to the many differences between the laboratory- and manufacturing-scale lyo. Various design elements of the lyophilizer may affect heat transfer, e.g., shelf thickness, shelf-to-shelf and shelf-to-wall inter-distance, vapor tube dimensions, chamber door, etc. Different tools should be used to understand the performance of each freeze-dryer. IQ/OQ can provide very useful information about the equipment capability, especially under the load conditions. Extra studies to measure the K_v value are critical to characterize each dryer, and the vial-to-vial variability needs to be addressed. Dryer loading also