ufacturing is the preferred procedure. Likewise, this “scale-up” factor to convert laboratory-measured K_v data to production K_v data can be applied when transferring from one commercial dryer to another to simplify technology transfer. Techniques such as MTM are also useful in primary drying design along with other temperature and vapor pressure monitoring techniques detailed in the PAT chapter. These PAT tools are critical in estimating the end point of primary drying and also important in monitoring the sublimation process to better understand and control the freeze-dryer process.

Other factors can also affect the heat and mass transfer, and thus have an impact on process scalability. These factors are briefly discussed below:

Lyophilizer Design Various design elements of the lyophilizer may affect different modes of heat transfer, e.g., shelf thickness (conduction), shelf-to-shelf and shelf-to-wall inter-distance (radiation), vapor tube dimensions, chamber door, etc. When scaling up or transferring lyophilization cycles, these differences in lyo design must be considered as they may impact the overall performance and product attributes. Heat transfer due to radiation is an important heat transfer mode during lyophilization [39]. Presence of a stainless steel door reduces the atypical heat transfer as observed on a laboratory-scale freeze-dryer with a Plexiglas door. There is a significant reduction in the magnitude of heat transfer via radiation in a commercial dryer relative to the usual laboratory dryer. Highly polished stainless steel as used in commercial dryers has an emissivity of less than 0.3 while the stainless steel used in laboratory dryers typically have wall emissivities of about 0.7, and emissivity of the plastic door of about 0.95. Thus, the primary drying time in manufacturing may increase significantly when compared to a laboratory-scale dryer due simply to the differences in wall and door material, particularly for cycles that employ low chamber pressure and low shelf temperature, as is common for sucrose-based formulations.

Shelf Temperature Homogeneity Presence of hot and cold spots on the surface of shelf will lead to variation in the product temperature in the vials. Normally, shelf temperature homogeneity is determined using surface thermocouples on a clean and empty dryer during OQ. However, running an empty freeze-dryer does not give representative information since there is no load on the heating and cooling system. Compared to running the dryer clean and empty during PQ, the presence of load will escalate any temperature variability between the locations on the shelf. Studies [42] suggest that, at least for the dryers compared, these differences are small. However, the differences are likely to be highly dryer dependent, and the data available are meager.

Ramp Rates in Dryer Compared with the laboratory scale-dryer, commercial freeze-dryers have limited capability to achieve high ramp rates. For example, in systems where freezing rates in excess of 2 °C/min are desired to impede crystallization, a laboratory-scale process cannot translate equivalently in a commercial-scale dryer where maximum ramp rates of only 0.5 °C/min can be achieved.