Numerous sources are available that describe considerations for transfer of a lyophilization cycle developed at laboratory scale to a pilot- or commercial-scale aseptic processing environment [51, 69–71]. A brief summary is provided here, but the reader is directed to the references for greater depth. Lyophilization is a controlled heat and mass transfer process, primarily leveraging chamber pressure and shelf temperature to drive the sublimation process and bound water desorption. Equipment and environmental differences between the laboratory and production suite result in significant differences in product microstructure, equipment capability, effective heat transfer rates, and ultimately, drying results when the same drying cycle parameters are used. Choices made in the design and installation of the production freeze-dryer can significantly affect the driving forces for sublimation, leading to potential differences in the speed and consistency of the drying process within and between runs. A successful scale-up program will evaluate the ability to maintain control of heat and mass transfer throughout the process and across the intended range of batch sizes for each freeze-dryer.

Environmental and Equipment Considerations

One of the first differences to manifest in scale-up is a result of the increasing environmental controls that are required in the production environment. Process operations from vial filling to loading of the lyophilizer are completed in a class 100 environment for parenteral products. As a result of this very clean environment, few particles are present to serve as ice nucleation sites. A greater degree of product supercooling prior to freezing occurs in the production suite than in the laboratory [72]. This can lead to extended primary drying times of up to 10% and a 1 °C increase in primary drying temperature. A useful generalization is that primary drying times increase by ~2% for each 1 °C decrease in the ice nucleation temperature. Thus, cycle modifications are often desirable even before consideration of equipment differences between laboratory and production scale lyophilizers simply due to cascading consequences from the cleaner production environment.

Ice nucleation is a stochastic process, and a contributor to the vial-to-vial variability observed in both laboratory and production processes. One approach that is used to overcome the vial-to-vial variability in ice nucleation and the high drying resistances associated with more significant supercooling is frozen product annealing above the glass transition temperature.

An important step in scale-up or transfer of a lyophilization process to a new freeze-dryer is characterization of the heat transfer rate by position within the freeze-dryer. This should be established for both the laboratory unit used in development as well as the destination production unit, as no two units (even those of identical model) are truly identical. Understanding the differences in positional heat transfer rates, caused by a variety of equipment design and use parameters, is important from several perspectives. First, from a product quality standpoint, this will result in vials having different drying rates. Care must be taken to ensure that primary drying