of ice nucleation means variation in the ice nucleation temperature, which in turn means variation in drying behavior as the ice nucleation temperature plays a major role in determining the size of the ice crystals formed. The size of the ice crystals determines the size of the "pores" through which water vapor must pass during primary drying and therefore the "resistance" to mass transfer. The degree of supercooling depends on the solution composition, the shelf temperature–time profile during freezing, and the operating environment. In the laboratory, ice nucleation generally occurs at a higher temperature than in manufacturing, probably due to the higher level of ice-nucleating particulates in the laboratory [48]. This systematic difference in freezing causes the formation of cake with a higher resistance to mass transfer in manufacturing, which causes primary drying to be longer in manufacturing but at a higher product temperature. The freezing difference between small and large manufacturing freeze-dryer is considered to be a major challenge to scale-up of lyophilization cycles.

Heat and Mass Transfer Differences

Generally, there are differences in dryer design and configuration between laboratory and manufacturing scale, and such differences in the chamber, duct, condenser, or refrigeration system could lead to systematic shelf surface temperature differences between laboratory and manufacturing even when using the same set points for shelf temperature control. Gas flow variations may result in "choked flow" in one dryer but not in another, leading to the loss of chamber pressure control in the dryer with choked flow. The loss of pressure control may also result from inadequate condenser design and/or insufficient refrigeration capacity to convert the water vapor back to ice at a low temperature [40]. Therefore, different dryers do not necessarily perform the same way, and some modification in cycle design during scale-up is normally necessary to avoid problems.

Differences in Primary Drying Time

Due to the expected differences in freezing and heat transfer between laboratory and manufacturing, the cycle would be expected to take longer at commercial scale, especially during the primary drying step. As a general rule, one would expect that primary drying needs approximately 20% more time to complete in production scale [40]. However, as with any general rule, there will be significant deviations from the rule, and it will be important to predict the length of the primary drying step for both scales for each specific case, and also important to directly monitor each step using process analytical technology (PAT) tools.