However, obtaining product resistance data at several temperatures in a relevant range is straightforward, but does require at least one additional experiment. One does indeed need to measure the corresponding cake resistance at different drying temperatures when drying close to or exceeding the T_g' in order to get more accurate result using this modeling approach.

The ICH Q8, Q9, and Q10 guidelines stress a continuous process verification strategy, spanning from the process design stage at a development laboratory through commercial production. The guidance aligns well with the QbD concept, and reinforces the importance of performing more upfront development work to have a deep understanding of the relationship between process parameters and product quality. In order to establish the process robustness ranges to support the validation process and potentially expand the design space for this protein product, systematic experimental studies have been performed based on a scale-down model approach. The systematic study employed typical QbD elements including identification of potential CQA and potential CPP, risk assessment based on prior knowledge, establishment of a scale-down model, experimental studies to identify the failure point, etc. Finally, a broader design space is generated based on the process and product understanding. More details are discussed below.

Establishment of a Scale-Down Model

Since performing a useful number of studies at the manufacturing scale is not practical, development of a scale-down model is needed to support process validation and commercial manufacturing activities. In addition, its establishment will enable a better understanding if a change in material (e.g., drug substance source, container, etc.) or lyo process will have any product impact. The objective is to create a laboratory-scale system that is comparable to its large-scale counterpart. The established scale-down model can then be used to achieve reliable process understanding about the relationship between process parameters and final performance [44]. This concept has been widely used in the cell culture and purification field, and has been found to be extremely useful for process characterization and production support [43, 44].

A scale-down model needs to be first developed by taking into account of scalable factors. Similar geometries would be important in that the overall design geometries of each lyo (small vs. large) are close enough to result in insignificant performance differences. For small and large lyophilizers, it is ideal to have the same ratio of shelf area/condenser area, and it is perhaps important that the ratio of shelf area to duct area divided by duct length be the same in both dryers. In addition, one need to consider the dryer-dependent factors such as the position of hot and cold spots on the shelf, duct position/configuration, loading effect, etc. As part of this study, a qualified Virtis laboratory scale Lyophilizer was used. Water sublimation tests were performed, and the sublimation rate normalized by shelf area was found to be comparable between both scale lyophilizers at same drying condition.