that is specific for that vial and the freeze-dryer. Figure 1 shows the K_v of a 10-cc tubing vial as a function of chamber pressure and vial location in an IMA Lyomax 29 manufacturing dryer and a LyoStar II pilot freeze-dryer. The normalized weight loss map as a function of shelf location is given in Fig. 1a, and it shows that there is a clear difference in weight loss between the center and edge vial. In this case, the edge vials result in a maximum weight loss of approximately 2.4 times of that in the center vial at 100 mTorr. The maximum weight loss was recorded at the edge of the shelf on the maintenance door side of the freeze-dryer. The high K_v at this location is expected since the door has a major effect on the K_v of the edge vial due to elevated heat radiation from the door itself. Figure 1b shows that the K_v increases with increasing pressure within the pressure range studied. The data indicate that at lower pressures, the K_v of the center vial is closer to that of the edge vial and therefore the edge effect can be deemed minimal at lower chamber pressures. However, using lower pressures will result in lower product temperatures, lower sublimation rates and therefore, a longer primary drying time. When developing the primary drying segment of the cycle, it is important to balance conditions with time, while obtaining acceptable product stability should always be the major consideration. Secondly, when developing the primary drying step, it is important to consider the edge vial along with the center vial as each vial will dry at different rates due to the edge effect. In addition, the K_v of the same 10-cc tubing vial in the LyoStar II pilot unit was slightly higher than that of the center vial of the Lyomax 29 at low pressures but equalized at higher pressures. Therefore, the data suggest that if the primary drying step was to be developed in the LyoStar II unit (this is the scale where most cycles are developed), differences in K_v must be considered during scale-up.

With a model for K_v developed, primary drying design and scale-up are simplified. Once the product resistance (R_p) is obtained for samples subjected to a representative freezing process, it is possible to predict product temperature performance for conditions within the experimental chamber pressure range at various shelf temperatures, thereby developing a primary drying design space. In terms of scalability, it is recommended to measure K_v at laboratory, pilot, and commercial scale.

Variation in drying behavior and statistical uncertainty in parameter estimation should also be incorporated in building a design space [42]. Using only the mean values of K_v and R_p to build the design space may lead to errors in selection of appropriate primary drying conditions. There is variation of both drying temperature and drying time within a batch, and after all, only a few vials dry at the mean values. Moreover, there is always uncertainty in the evaluated input values of mean K_v and mean R_p. Evaluation of the impact of these "variations" on design space is nontrivial, and requires a combination of modeling calculations and use of statistics to evaluate the distribution of drying times and temperatures arising from variation in K_v, R_p, shelf temperature, fill volume, and chamber pressure. Variation in this context means both intervial variation in a batch and the impact of experimental error on the characterization of the input parameters such as K_v and R_p. Attempts to quantitatively evaluate the impact of variation on process design (and design space) have been outlined in the literature [2, 3, 31]. Alternately, one can impose arbitrary "safety margins" in an attempt to include variation; but even if chosen based on