sure is not a significant variable. Thus, the design space is controlled by the shelf temperature and any constraint on product temperature imposed by any potential product stability issues (upper temperature limit). It is important to note that while the degradation rate will increase with an increase in product temperature, the residence time at a given temperature required to reduce the water content to the desired level will decrease as temperature increases. These effects tend to cancel and the net degradation required to obtain a target water content is relatively insensitive to the exact temperature used. Of course, the time required to reach the target water content decreases sharply as drying temperature increases, so it is common practice to carry out secondary drying at temperatures well above ambient, even as high as 50 °C or greater. In this regard, it should be noted that protein denaturation is never a problem in secondary drying as a relatively dry protein does not denature until temperatures well over 100 °C are reached.

Structural collapse is possible in secondary drying but is rarely a practical problem as the protocol will nearly always call for a hold at the shelf temperature used for primary drying for at least a few hours after all vials are devoid of ice. That is, the ramp begins only after the vapor composition in the drying chamber has decreased below 50 % water vapor, as measured by one of the PAT techniques. Alternately, one delays the ramp several hours past the time when, for whatever reason, the end of primary drying is expected. Moreover, for amorphous systems, a relatively slow shelf temperature ramp (≈ 0.1–0.2 °C/min) is employed, at least up to ambient temperature.

Finally, it must be emphasized that the rate of secondary drying is also sensitive to SSA of the solid, which is controlled in part by the ice nucleation temperature and the primary drying temperature relative to $T_g'$. That is, drying above $T_g'$ will cause some micro-collapse which will reduce SSA. Therefore, both the freezing and primary drying process will also impact the rate of secondary drying. It would be prudent to optimize the secondary drying stage only after the freezing and primary drying steps have been developed optimally with a well-defined primary drying phase. RM content is the quality attribute that is used to define secondary drying performance.

## *Lyophilization Cycle Scale-Up*

A lyophilization process is first developed to run with defined parameters of shelf temperature and chamber pressure at a laboratory scale freeze-dryer, which is then transferred to a pilot or production scale-dryer. Differences in heat and mass transfer characteristics between a laboratory- and manufacturing-scale freeze-dryer can lead to significant differences in the product temperature profile. One must remember that the objective is to reproduce the *product* temperature history in going from laboratory to manufacturing, not simply reproduce the shelf temperature–time profile.

Utilization of the experimentally determined vial heat transfer coefficient, for the dryer of interest, in calculations that attempt to model drying behavior in man-