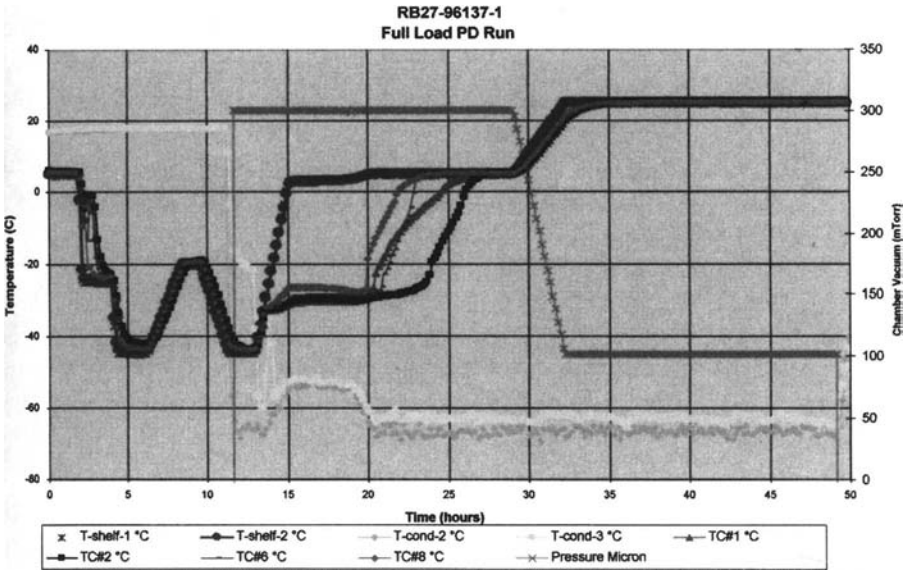

FIGURE 15 A typical freeze-drying cycle.

CONFIRM THE HYPOTHESIS

As described previously, lyophilizing a crystalline matrix type of formulation allows "micro-collapse" of the amorphous components. This allows primary drying to be performed at a relatively high product temperature without loss of the cake structure. The hypothesis we made is that the micro-collapse would not compromise product quality, particularly in stability. Here we discuss this issue and particularly a study that we performed to confirm the hypothesis.

In the case of pharmaceuticals, collapse of the cake structure during freeze-drying results in a pharmaceutically unacceptable product. There are several obvious potentially detrimental effects of collapse on the stability and desirability of a freeze-dried product. The collapse of a system during freeze-drying will reduce the surface area of the cake and so will prevent efficient secondary drying. Also, the collapse may remove the pores or channels left by the sublimated ice, and so may increase the resistance to water vapor moving out of the product, thereby inhibiting primary drying to a greater extent. Since the secondary drying is less efficient, the final product may contain higher levels of moisture than is optimal and the higher moisture content of the cake can then lead to increased levels of instability of the protein being lyophilized. The collapse of the cake may also promote protein aggregation (29). A further complication brought about by collapse is that the reconstitution step may take longer to complete since the surface area of the cake is greatly reduced. Although some investigations (10,29–36) have been published on the effects of collapse on freeze-dried materials, little has been published on the effects of collapse on the long-term storage stability of freeze-dried proteins. Therefore, it is necessary to conduct an investigation of the long-term storage stability. The previously described protein in the crystalline matrix formulation was