number of commercial scale "engineering" or "development" batches must be produced to optimize the freeze-dry cycle in the final production unit.

Regardless of development efforts to alleviate issues of scale, one should be prepared for scale-up issues to be encountered. Lyophilization is a process inherently dependent on and influenced by the unit in which the process is run and the scale of that unit. The total shelf area, refrigeration/compressor capacity, condenser area, chamber wall thickness, ability for the wall temperature to be maintained etc. have a tremendous influence on the product temperatures encountered. As a lyophilization process is transferred to a larger scale unit (whether from a development lyophilizer to a pilot or clinical dryer or from a lab or pilot dryer to production) one should expect to see differences and plan engineering/qualification runs in advance to address these concerns. The issue that will most commonly be encountered is that product temperature as a function of shelf temperature and chamber pressure may be lower in a production unit. Therefore, as a result of the lower-than-expected product temperatures, the total time required for primary drying might be longer than expected. The implication of this is that when scaling up the freeze-dry cycle to larger freeze-dry units one must make sure that primary drying is complete before secondary drying is started or significant product melt-back/collapse may occur.

Other factors to consider when determining optimum primary drying conditions include the shelf-loading pattern. When dealing with syringe and dual chamber syringe products, the configuration of the shelf load (i.e., the positioning of the containers relative to each other in the load) can have a significant impact on the primary drying temperature and, in particular, on the susceptibility of the load to be influenced by factors such as radiative and convective heat within the chamber. Also note that for such products, extreme differences between product temperatures for containers on the "outside" and the "inside" of the shelf or tray-load can result. This can be an even greater challenge when dealing with products with relatively low T_c and, hence, low primary drying product temperatures. Conservative cycle design for such systems can often result in extremely long drying cycles. The low shelf temperatures required to maintain the outside samples below the T_c result in extremely low product temperatures for the inside containers and, thus, slow drying. Optimization of this type of configuration for a reduced total drying time can be achieved by operating in the region of "microcollapse." Microcollapse is a phenomenon where a small but acceptable degree of collapse occurs (at the microscopic level), to an extent that allows for greatly enhanced vapor flow through the cake and thus rapid drying. If a set of freeze-dry conditions can be achieved where microcollapse is achieved for the outside samples, this will also provide the maximum allowable drying conditions for the inside, rate determining, samples. It is important to ensure the reconstitution time and product stability remain acceptable. Also, this type of cycle development may be extremely sensitive to scale-up issues, and final cycle design will typically require development cycles to be performed in the production units.

INSPECTION CRITERIA

DCS/DCC products present an additional challenge in the establishment of inspection criteria for the final lyophilized cake. Residual moisture level in the lyophilized cake is considered a key stability impacting parameter for freeze-dried