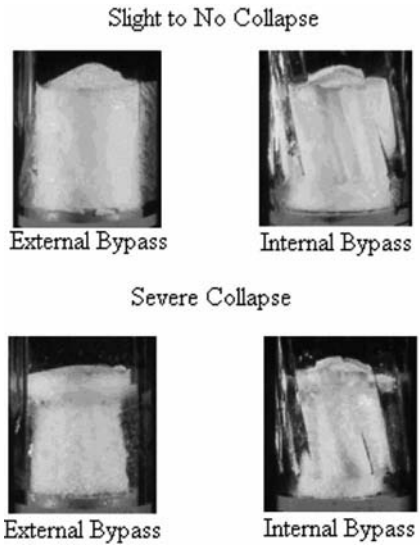

FIGURE 16 Examples of varying degrees of collapse by inspection.

products. Often, problems with the physical appearance of the lyophilized cake due to partial collapse can be indicative of variations in moisture level in the cake. As discussed previously, moisture content can vary dramatically between syringe samples in the same batch due to factors such as product temperature variations across the load leading to heterogeneity in freezing and drying plus moisture uptake from the environment postlyophilization for externally stoppered products. Variations in cake appearance may or may not be linked to critical quality problems. Inspection of syringe samples can be further complicated in some cases by the presence of the internal bypass (for transfer of diluent from the rear to the front chamber), which can in some cases obscure the lyophilized cake. During process development, it is valuable to isolate and evaluate samples showing different degrees of collapse by physical inspection. Inspection criteria can be more easily established after developing a correlation between appearance, moisture content, and quality attributes (including stability).

The example shown in Figure 16 shows freeze-dried cakes from a representative DCC product, which was freeze-dried in both an internal and external bypass DCC package system. The presence of the internal diluent bypass partially obstructs the cakes and made inspection more difficult for this package system. Product quality was assessed for samples representing each "degree of collapse" by inspection. It was found for this example that only the "severely collapsed" samples were unacceptable from a product quality perspective. However, this correlation would need to be evaluated on a case-by-case basis to establish appropriate inspection criteria for other dual chamber freeze-dried products.

TERMINAL STERILIZATION FEASIBILITY

Traditionally, freeze-dried products are processed using established sterilizing filtration and aseptic filling methods. Recently, however, European regulatory guidance requires the evaluation of terminal sterilization for