produce a material that occupies the same volume as the initial fill, with a high surface area to volume ratio. Indeed, it has been well established that appearance often goes hand in hand with activity and stability, since a product that displays a macroscopic loss of structure often contains higher levels of water than its "intact" counterpart, has a lower specific surface area that can lead to increased reconstitution time, and will mean that the various components are in more intimate contact with each other during and after freeze-drying.

Product appearance itself may be assessed in a number of ways, but usually this is restricted to the use of qualitative, relatively subjective methods such as judging color, degree of shrinkage, and level of uniformity by eye, which provides information solely on the macroscopic structure. These parameters are often used as part of an assessment to indicate the success of technology transfer or scale-up. In terms of quantifying various aspects of the microscopic structure, estimates of total surface area may be made using the Brunauer-Emmett-Teller (BET) method, which calculates surface area from experimental measurements of multilayer gas adsorption onto a material (3). Hibbert et al. (4) explain how this has been applied to freeze-dried powders, while Rey (5) further discusses the practicalities and limitations of using this method and provides data allowing calculation of the specific surface area of a real-life pharmaceutical material. Porosity can be assessed using scanning electron microscopy (SEM), although SEM relies on representative sampling of the lyophile and that the preparation of the sample for imaging does not itself cause changes in the sample. Some of the methods currently under investigation for quantifying aspects of lyophile substructure and various physical phenomena brought about by the freeze-drying process itself (some of which have even been applied in process during freezing and/or drying) include Fourier transform infrared spectroscopy (FTIR) (6), temperature scanning FTIR (7), near infrared (NIR) spectroscopy (8), dielectric relaxation spectroscopy (9), Raman spectroscopy (10,11), and temperature-controlled Raman microscopy (12).

At the most fundamental level, to achieve a lyophile with acceptable macroscopic appearance, the primary objective for crystalline materials is not to exceed their eutectic temperature and that for amorphous materials is not to exceed their glass transition temperature or collapse temperature between the initial cooling phase and the end of the sublimation process. However, often a formulation will contain a mixture of crystallizing and amorphous components, in which case, the critical temperature may not be so obvious. One approach is to assume complete phase separation will occur, assess the individual components separately, then aim to cool the starting material to below the lowest of the critical temperatures and maintain it below this temperature until the end of the sublimation process. For example, an aqueous solution containing lactose and sodium chloride may have a T_g' of -32°C (lactose) and a T_{eu} of -21°C (NaCl) in the frozen state, and therefore if complete separation occurred, the critical temperature may logically be assumed to be -32°C. However, what this approach does not take into account is the fact that the presence of lactose may inhibit crystallization of the sodium chloride and that in a real freeze-drying situation amorphous sodium chloride may be present. We have observed in our laboratory that while a solution of 1% (w/v) lactose and 1% (w/v) NaCl tends to collapse around -30°C—implying that most or all of the NaCl is crystalline—a solution containing 1% lactose and 0.3% NaCl collapses around -46°C, suggesting the presence of a phase within the frozen structure consisting of