amorphous NaCl and/or a (combined) amorphous mixture of NaCl and lactose. A similar pattern of behavior has also been observed in our laboratories when the concentration of sucrose included as an excipient in an influenza antigen, preparation was varied between 1% and 2% (w/v).

A further consideration here is the possibility of microcollapse, as discussed by Wang later in this volume and elsewhere (13,14). A simple example of microcollapse, and one that we have frequently observed in our laboratories, is the one that occurs in formulations containing mannitol together with amorphous components (which may be excipients and/or the active ingredient). A solution containing 2% mannitol and 1% glucose where the mannitol crystallizes during freeze-drying (either as a controlled event during a deliberate annealing step or perhaps in a less-controlled manner during sublimation) would be expected to comprise separate phases in the frozen (and drying) structure where mannitol exhibits a T_{eu} of $-1.4^{\circ}C$ but glucose undergoes viscous flow around $-41^{\circ}C$, thus microcollapsing onto the scaffold of crystalline mannitol. In this case, a conservative estimate of the critical temperature might be considered to be $-41^{\circ}C$, although we have observed that in such a mixture total loss of structure at the macroscopic level often does not occur until above $-20^{\circ}C$. This is still significantly lower than the eutectic temperature of crystalline mannitol alone; whether this is attributable to significant levels of viscous flow in the amorphous glucose phase at this temperature that was able to counter the mechanical strength afforded by crystalline mannitol or whether indeed some of the mannitol persisted in the amorphous phase because of the presence of amorphous glucose and/or the thermal history of the sample, was not clear. This example illustrates the point that combining crystalline and amorphous components does not always give a single critical temperature that can be predicted from the behavior of the individual components, and that exceeding a particular ratio could lead to step changes in critical temperature with respect to the macroscopic structure due to phase/state changes in one or more of the components, which may also be a function of thermal history. Similar observations were made by Adams and Irons for mixtures of sodium chloride and lactose (15).

Conceivably, in mixtures where the eutectic temperature (T_{eu}) of the crystalline phase is lower than the collapse temperature (T_c) of the amorphous phase, a phenomenon may occur where the crystalline solute phase melts onto the "backbone" of the rigid amorphous phase when freeze-dried above T_{eu}. We have notionally termed this phenomenon "micromelting", since it is analogous to microcollapse. An example of this that has been observed in our laboratories is that of a biological product containing a small amount of calcium chloride as part of a buffer system; in this case, while macroscopic collapse was not observed until temperatures above $-30^{\circ}C$ by FDM, the use of other methods suggested significant mobility changes around $-53^{\circ}C$, the eutectic temperature of calcium chloride. When the formulation was freeze-dried above $-53^{\circ}C$ no shrinkage was observed at the macroscopic level, although there was evidence of heterogeneity in the form of small visible "spots" on the base of the cake.

It has been noted in studies focusing on specific formulations that there are instances where it yields no measurable benefit to keep below the lower (or lowest) critical temperature, since lyophilization will, by definition, take longer at lower temperatures and may not confer any greater stability on the final