

was observed when drying at the higher product temperature, consistent with the OCT-FDM collapse temperature determination data.

The publications by Mujat et al. and Greco et al. reported on the use of OCT-FDM to measure  $T_c$  and  $T_{cu}$  of three formulations freeze-dried in vials. This novel use of OCT provided a new technique for measuring  $T_c$  that was predictive of freeze-drying in vials, a container of practical significance. Use of OCT-FDM will be a significant advantage when processing formulations that can be freeze-dried above the LT-FDM-determined  $T_c$  without loss of product quality. There have been numerous reports of successful freeze-drying above the LT-FDM determined collapse temperatures with no evidence of macroscopic collapse of freeze-dried cake [5, 37–44], but these investigations were performed on a trial and error basis with no representative data of  $T_c$  measurements in a vial to validate the decision to dry at higher temperatures.  $T_c$  measured by OCT-FDM provides quantitative justification for freeze-drying above the  $T_c$  as measured by LT-FDM, which is in line with QbD principles.

Future application of OCT-FDM for the determination of  $T_c$  may provide more accurate determinations for drying within vials and support the development of lyophilization processes that reduce the primary drying time and increase process efficiency. The data reported in the Greco et al. [11] and other researchers suggest that the differences between the LT-FDM and OCT-FDM collapse measurements may be large for high-concentration protein formulations. Additional studies are ongoing with the goal of acquiring additional data to compare the two measurement techniques and to investigate the product formulations that display large differences when dried as thin films and bulk samples in vials. OCT-FDM may also be applicable for monitoring the growth of ice during the freeze-phase of lyophilization. Further studies are required to investigate this potential application.

## Tunable Diode Laser Absorption Spectroscopy

The application of optically based process analytical technology sensors has the potential to provide real-time, online process information using nonintrusive measurement techniques. As described above, TDLAS is one such technique that can be applied to monitoring lyophilization to provide direct measurements of the water vapor temperature (K), concentration (molecules/cm<sup>3</sup>), and flow velocity (meters/second) within the duct connecting the lyophilizer product chamber and condenser. These measurements can be combined with knowledge of the cross-sectional area of the duct to calculate the instantaneous mass flow rate,  $dm/dt$  (g/s). The mass flow rate can be integrated as a function of time to provide a continuous determination of total water removed. The mass flow rate may also be combined with freeze-drying heat and mass transfer models and additional process measurements (e.g., product chamber shelf temperature) and process-specific parameters (e.g., vial cross-sectional area and heat transfer coefficients) to determine the batch average product temperature. Continuous monitoring of product temperature, especially during pri-