

Upon review of PAT technologies available to date, we found that not a single PAT tool currently exists to cover these broad requirements, possibly due to the harsh conditions of the freeze-drying process (deep vacuum, low temperature during freezing, high temperature during sterilization, and sterility requirement at GMP environment). Most PAT tools only meet one or two criteria listed above, and we currently have to rely on the combination of several PAT tools in order to achieve this ideal state. In addition, while more options are available as PAT tools for application in a small-scale lyophilizer, there are fewer PAT tools which can be used in GMP commercial manufacturing scale lyophilizer. Therefore, further development of these existing and new PAT tools to cover these gaps is strongly needed.

Product temperature monitoring with thermocouples will still be used to develop a safe lyophilization cycle. Traditionally, thermocouples or RTDs have been used to monitor product temperature in real time during technology transfer and scale-up. Over the years, thermocouples have even been used to control freeze-drying cycles during commercial manufacturing. However, thermocouples are less than ideal due to their effect on the nucleation process and potential sterility challenges when used in a GMP environment. Other approaches such as TEMPRIS or the new impedance spectroscopy system may be a more advanced means to measure product temperature, but they are not yet ready to replace thermocouples due to their limitations. The invasive TEMPRIS yielded data not representative to the other vials in the chamber, and the impedance system is limited at this point to the freezing step. MTM can measure average product temperature for the whole batch and it is very useful for development; however, MTM is limited to laboratory and pilot freeze dryer and is not scalable to a large-scale manufacturing dryer.

From a primary drying endpoint perspective, the Pirani gauge remains the best option for reasons outlined earlier in the chapter. Lyotrack can be a good option when used with a stable system which is not susceptible to oxidation degradation. A Pirani gauge is less expensive than Lyotrack, while it can provide very similar gas composition profiles. In addition, the Pirani gauge may also be used as a PAT control tool if a feedback loop was programmed to continuously measure the ΔP between the Pirani and the CM and allow the automatic progression to next step when $\Delta P=0$ is reached at the endpoint of the primary drying.

Several new PAT tools such as TDLAS, NIR, and Raman have been developed in the past decades, and they have provided insights about the water removal and process transition. Among them, TDLAS is the most promising PAT tool as it can meet several criteria for lyophilization. First, it can measure sublimation rate during the primary drying and secondary drying process, and has the potential to monitor the residual moisture in the cake during secondary drying. Second, it can be used to determine the endpoint of both primary drying and secondary drying based on the change in sublimation rate. Third, based on the steady-state heat and mass transfer model, the signal measured can be used to obtain the average product temperature during primary drying, which will give the behavior for the whole batch. In addition, it can provide information about the vial heat transfer coefficient and dry layer mass transfer resistance. Research is currently ongoing to assess TDLAS for