the whole batch. In addition, since it requires a special arrangement of the Raman probe, it will be difficult for an in-line application in an industrial lyophilizer.

Impedance Spectroscopy

During this literature review, a potential new technology to measure product temperature was identified. An impedance spectroscopy method was introduced as a minimally invasive method of measuring product temperature during the freeze-drying process [30]. This approach was shown to be useful to monitor the freezing step, but at this point in the early development of the technology, it cannot monitor the product temperature during primary drying. The experimental setup consists of placing planar electrodes on the external vial wall, and these electrodes are then coupled to a high impedance analyzer. The impedance measurement is converted to temperature using an algorithm [30]. The placement on the external vial wall does not influence the nucleation event of the freezing process. If this technology evolves to monitor the product temperature during primary drying, it will significantly improve its value to lyophilization cycle monitoring. However, similar to the thermocouple approach, this system must be applied to the vial manually, which means that it would be a challenge to apply to commercial process monitoring.

Summary

Table 1 summarizes the major advantages and disadvantages of each PAT tool discussed above. It gives an overview of each PAT tool's capabilities and its practical application and scalability to large-scale freeze dryer. The major limitations associated with each tool are also listed in the Table.

Conclusions and Future State

Based on the QbD requirements, an ideal PAT tool for freeze-drying should be able to meet the following needs: (1) monitor the product temperature during *all* steps of freeze-drying process including freezing, primary drying, and secondary drying, and the temperature measured should be representative of the whole batch; (2) determine the endpoint of major steps including primary drying and secondary drying; (3) monitor the sublimation and determine the residual moisture during primary drying and secondary drying; (4) provide real-time product quality information such as the protein structure and excipient phase transition; and (5) integrate to different types of lyophilizer from laboratory scale to GMP manufacturing scale.