- The formulation and filling processes associated with vaccines are more complex. This results in multiple batch records, increased product quality and consistency tests, and the number of critical process steps are increased [59].
- The sensitivity of a vaccine to the final manufacturing process is extreme. Thus, there can be substantial lot-to-lot variability when manufactured using the same process and that can impact product quality. In addition, raw materials utilized within the process can be complex and vary from manufacturer to manufacturer. This variability in the raw materials can impact product quality as well and should be carefully monitored [60, 61].
- Building a strong link between product quality attributes and the clinical safety and efficacy for vaccines is difficult to ascertain [59, 60]. This results in differences in how PAT is employed with vaccines and where within the process, if at all, it is utilized to its full potential [58, 62].

Applying PAT in Drug Product Operations

PAT tools that have been utilized in traditional small molecule development and approach could be employed in the vaccine space as well. These technologies, while not fully discussed here, include Raman spectroscopy with wide area illumination (WAI) [63], laser-induced breakdown spectroscopy (LIBS) [64], and nuclear magnetic resonance (NMR) [65].

For example, as described previously, in vaccine development and especially in the case of an LVV, lyophilization is a common unit operation. Here, water is removed for the product by first freezing and then sublimation of water occurs in both primary and secondary drying. Lyophilization is a long unit operation in manufacturing and delivering an efficient cycle is critical to minimize production costs and ensure product quality is achieved. Because of the criticality of this unit operation, it is a desired place for implementation of PAT. Real-time monitoring of residual water during lyophilization can be achieved by utilizing TDLAS. This technology can measure the water vapor pressure between the lyophilization cabinet and the condenser and can predict the end point of sublimation and secondary drying [66]. Understanding the end points of both primary and secondary drying, a more efficient and cost-effective unit operation can be achieved.

Similarly, as a follow-up to ensure that what has been determined through TDLAS as an efficient lyophilization cycle, near infrared technology (NIR) can be used to examine the final moisture content of all vials following lyophilization [67, 68]. Moisture is a CQA associated with vaccines and can significantly impact stability. Historically, moisture analysis was done on a subset of vials within a lyophilization cabinet run and was a destructive test. With the implementation of NIR, 100% of lyophilized vaccines can be analyzed for moisture in a nondestructive way. By now, monitoring the moisture associated with all vials, improved product quality can be achieved. Vials where moisture levels in the past may have been missed due to a small sampling analyzed, now can be fully monitored and discarded when