be brought forward into safety assessment/toxicology studies. Normally, the formulation is not optimized at this point, but contains excipients that are likely to be utilized in the clinical formulation for phase I and beyond.

As the program proceeds through the development and enters into phase I, the second stage of development is initiated where additional formulation changes may be examined, as more knowledge of the degradation mechanisms become known and the ability to characterize the vaccine increases. It is likely that the analytical methods and stability-indicating assays have been improved and can significantly improve the success of the vaccine candidate by better teasing out differences in product stability. This stage of development is focused on delivering a robust manufacturing process and an optimized formulation for clinical development. Use of QbD and PAT becomes more common in this stage of development and is used to shape the CQAs and CPPs associated with the product while de-risking the investment [17].

Although QbD is common within this stage of development, it is likely that the application of QbD is limited. Unlike TPs and small molecules, the variability and complexity associated with vaccines make it difficult to apply to all areas of product and formulation development. Two operations where QbD can be applied and often is applied in vaccine development include lyophilization and adjuvant production. Application of QbD to the vaccine drug product development should be evaluated on a case-by-case basis.

The final stage of vaccine drug product development consists of working toward technology transfer into the final commercial manufacturing facility and the potential issues with scaling the process. Here, it is essential to have a deep understanding of the regulatory environment within the expected markets, identify the potential differences between development and manufacturing facility (e.g., glycol cooling systems), equipment comparability between development and manufacturing (e.g., shelf to condenser ratio, internal vs. external condensers), and respective process compatibility and process map (e.g., tank design and formulation suite capability). This information is necessary to ensure a robust technology transfer and successful phase III campaign can occur, thus ultimately leading to licensure of the new vaccine.

Introduction to Formulation Development

During early drug product development, the formulation scientist is challenged due to the lack of representative bulk drug substance that can be utilized for formulation screening. As a result, formulation scientists must try and utilize high throughput screening technologies to examine formulations and complete the studies at accelerated conditions (i.e., 25, 37, and 45 °C) to try and identify conditions that will stabilize the product [18–24]. One caveat of utilizing accelerated conditions is that it does not always mimic the degradation mechanisms observed under marketed shelf-life storage conditions. Thus, it is important for the formulation scientist to