Early Stage Formulation Development (Identification of Safety Assessment/Toxicology Formulation):

Based on initial efforts in preformulation, the formulation scientist can begin to determine whether a liquid formulation can be achieved. However, since preformulation efforts are minimal, it is necessary for the formulation scientist to assess both real time and accelerated stability within the formulation development space and assess the ability to generate a liquid product that will meet the necessary GTPP characteristics [19]. In the event that the liquid stability data will not align with the desired GTPP, the development of a lyophilized or frozen product will be initiated. Data generated during the liquid formulation screening early in formulation development can be then utilized to aid in identifying a good lyophilization formulation for the vaccine product (if required).

Liquid formulations are preferred when compared to lyophilized formulations [10]. This is driven by many factors including convenience of delivery to the patient, minimizing the operations within manufacturing, and not requiring a reconstitution time in the patient setting. Although preferred, developing a liquid formulation that will align with the desired GTPP can be challenging, especially with the desired 2–3 years shelf life expected for vaccines to enhance drug product supply.

One specific example where the likelihood for a liquid vaccine product is low is when developing an LVV. From experience, liquid degradation rates can be as high as 10% per hour even under refrigerated conditions [13]. Additionally, it has been observed that during freeze-thaw of frozen liquid material, losses of greater than 30% can be observed [13]. As a result of these issues, developing a liquid formulation is not feasible and lyophilizing the product becomes a viable, and in most cases the only option.

Similar to preformulation efforts, an in vivo animal model will be utilized to help shape the final formulation, as well as the formulation process for both DS and DP. This ensures that any changes during DS processing and DP formulation and filling do not impact the immunogenicity of the product. It should be noted, that although in vivo models will help the formulation scientist during development, there are limitations in correlating animal study results with human immunogenicity. The preclinical animal models can be utilized to infer differences, but usually can be considered disaster checks for gross changes in the process or final drug product and the impact to immunogenicity. Identifying a definitive in vitro immune marker to build a correlation of protection with human immunogenicity is usually lacking and can impact the development timelines. As a result, making changes within the formulation or formulation process after initiating clinical development is challenging and usually met with significant resistance once entering the pivotal clinical studies for efficacy (phase II). If changes are necessary following phase II, it is likely that additional clinical bridging studies will be required to demonstrate comparability, this in turn increases the overall development time for the product as well as development cost. Thus, it is important that most of the formulation development and optimization has been completed before entering phase II.

Developing good quality control for vaccines has been a challenging task. One of the main reasons around this is the ability to define the CQAs associated with