a vaccine, especially for LVV. The formulation and formulation process relies not only on the lot release assays, but the consistency in which the manufacturing process is completed and is a large part of establishing vaccine quality. This usually results in the formulation and formulation process defining the product.

Stage II

Vaccine Drug Product Optimization (Exploration of the pH, Excipients, Stabilizers, and Process Conditions)

After developing a formulation for safety assessment/toxicology and the initial phase I clinical development, the formulation scientist must begin to "optimize" the formulation for long-term commercialization.

Usually, experiments are completed to assess various stress conditions including thermal stress, agitation, impact of freeze-thaw, exposure to light, and interactions with formulation process conditions (i.e., mixing, pumping, tubing, filtration). These different stress conditions help determine the proper conditions to generate a robust formulation so that the product can be scaled and commercialized [19]. This is often achieved by further evaluating and optimizing various buffers, pH ranges, excipients, and ionic strengths to try and identify the ideal conditions for the vaccine target and achieve the stability profile necessary to support the GTPP.

As discussed earlier, vaccines usually consist of multiple antigens and the formulation scientist should examine both the combined final drug product as well as separate the multicomponent vaccine into monovalent vaccines during formulation screening and development. Since analytical methods are usually still often in development for the multicomponent vaccines, examination in a monovalent format will allow the formulation scientist the opportunity to better characterize the product and identify degradation mechanisms for each component found within the vaccine. By better understanding monovalent stability, the formulator can balance the stability profiles effectively to achieve the final multicomponent drug product. At times, there will be compromises on the stability of one or more of the multicomponents to ensure that a final drug product can support the GTPP. Additional CQAs may be required for conjugated or subunit vaccines where an adjuvant may be included and will be considered on a case-by-case basis.

The formulation scientist must also consider that any changes to scale, the formulation itself, or the formulation process requires ways to ensure comparability before and after that change. This comparability will help to ensure that there is no change to the safety and efficacy associated with the vaccine and is required by regulatory authorities to justify the changes. Comparability protocols and extensive analytical characterization must be put in place to justify the changes. Even when comparability has been established, regulatory agencies may still require additional clinical trials to show equivalency between the new and old vaccine.