An example of a GTPP for a new vaccine is shown in Table 1.

The GTPP allows the formulation scientist to define the potential CQAs for the product. ICH Q8 (R2) defines a CQA as "A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality."

Input from preformulation and formulation development as well as prior knowledge from similar vaccines are essential in establishing the initial CQAs associated with the vaccine candidate. During formulation development, the CQAs are further explored and optimized. It is commonly accepted that risk assessments are essential to understand which processes within the vaccine product are considered critical.

Quality by design (QbD) within the vaccine development space, as well as other modalities, has been evolving. QbD approach requires that the quality is built into the process and not into the final drug product. This requires the formulation scientist to understand variability associated with raw materials, equipment changes between scale, and correlation of CQAs between product and process [31]. As mentioned above, QbD approaches are not applied holistically to vaccines due to their complexity and inherent variability, especially LVV. As a result, a combination/hybrid approach will be the norm in regulatory filings for vaccine products. For example, lyophilization is one unit operation where QbD can be applied for vaccines. It should be noted that although QbD is being applied more routinely to vaccine product, regulatory agencies do not expect to give the manufacturers regulatory relief when applied. It is assumed that this is building better quality into the product, but does not ensure comparability when minor changes within the design space occur.

End-to-End Development for Vaccine Lyophilized Products

Early in preclinical development, the availability of bulk (DS) is limited for formulation, analytical, and DP process development. Lack of well-established stability-indicating assays, limited knowledge on factors impacting product quality (CQAs), the inability to utilize platform formulation approaches for vaccines, especially LVV, and the ability to establish a LOS (line of sight) to clinical and manufacturing facility limits the DP scientist in how to optimize the formulation and process while documenting the corresponding risks.

Due to the poor stability profiles, vaccines suffer from substantial losses during the formulation and filling processes. These include bulk thaw yields, time out of refrigeration losses, liquid degradation, and lyophilization yields. This results in an overall process yield from the DS to the final DP. Additionally, the DP scientist must account for losses during routine shipping and storage following release of the product. Given the complexity of LVV, the use of accelerated stability to determine final DP characteristics likely will lead the scientist astray. Real-time statistically powered stability is key to choosing the optimal formulation for a vaccine product. This is due to the lack of following Arrhenius kinetics and the high variability associated with the analytical methods to determine stability.