QbD Approach

These differences between laboratory- and manufacturing-scale lyophilizers can pose a serious challenge for scale-up, and a systematic approach is needed to ensure a robust scale-up. Recently, "QbD" concept has become quite popular in guiding the development of protein formulation and lyophilization processes. The term "quality-by-design, QbD" stems from the perspective of building the quality into the product by a rational design, meaning quality is assured, rather than dependence of analytical testing of produced batches to detect individual defects and possibly reject batches. One might argue that the concept of designing the formulation and process in a way that assures quality, such that testing of the batch is superfluous, is hardly a new concept. What is perhaps new in the current QbD focus is the commitment to actually take the time to execute the required scientific and engineering studies that indeed will assure product quality, and to perform these studies with full consideration of the risk to product quality in each aspect of product and process design. This means that aspects that pose little risk to product quality will receive minimal attention, but aspects that may pose serious risk to critical product quality attributes (normally, safety and efficacy) will be systematically and completely studied. Thus, the QbD concept is a scientific and risk-based approach for drug development and the term "design space" is its key element [22].

QbD: Elements and Protein Modality Considerations

In recent years, industries have adopted the US Food and Drug Administration (FDA) International Conference on Harmonization (ICH) Q8, Q9, and Q10 guidelines at different stages of lyophilized product development and commercialization [7–10]. Some of the key elements include: defining a quality target product profile (QTPP), prior knowledge, risk assessment, design of experiment (DoE) studies, defining design space and control strategy utilizing PAT, identifying critical quality attributes (CQA), critical process parameters (CPP), process qualification/validation, and continuous verification of process.

During early stages while defining the QTPP and design space, a special consideration should be made to differences in modality of proteins (e.g., monoclonal, domain, fused antibodies, antibody drug conjugate, or peglyated proteins). Each modality of protein along with differences in dose (e.g., high vs. low concentrations) or drug delivery route (e.g., subcutaneous vs. intravenous) may require quite a different approach towards defining which key quality attributes and what steps in lyophilization are critical for controlling and hence assuring QbD principles [14]. For example, freezing step in case of one modality of protein might be more crucial than controlling primary drying step [15, 37]. The use of statistical methods (univariate statistical process control (SPC)- or multivariate statistical process control (MSPC)-based models) has been used to evaluate the process parameters and develop the design space [1]. In addition, there have