been great advances in the freeze-drying theory and computational methods, which allow modeling the drying process in vials for a design space construction and avoid many trial-and-error experiments [18, 22, 38]. Also, scale-up and scale-down models are used towards freeze-drying process optimization, keeping in mind the manufacturing equipment capabilities, towards successful technology transfer, process validation/qualification batches.

QbD: Quality Risk Management

It is important to identify potential risks and their criticality during early development of product and process, which is an essential part for applying QbD principles. Definition of risk is the combination of the probability of occurrence of harm and the severity of that harm. During the entire product life cycle, quality risk management (QRM) provides a systematic process for assessment, control, communication, and quality risk review of product. Three main pillars of the QRM are risk assessment, risk control, and risk review.

Risk assessment involves risk identification, risk analysis, and risk evaluation, where risk identification utilizes prior knowledge, historical data, flow charts, cause-and-effect diagrams (e.g., Fishbone or Ishikawa), and fault tree analysis. Next step is the risk analysis that involves risk ranking (high–medium–low, quality attributes, and process impact scores); failure modes and effects analysis (FMEA); failure mode, effects, and criticality analysis (FMECA). This leads to a risk evaluation by various tools such as DoE, control charts, Pareto charts, and process capability analysis.

Second major pillar is the risk control that involves risk reduction and risk acceptance, which enables a robust QRM process providing control strategy, improvement, data flow optimization, and achieves overall risk management goals. Finally, a risk review of events is conducted, which provides continuous improvement opportunities. Such an effective QRM approach can provide confidence in the decision-making process and biopharmaceutical company's capabilities to handle potential risks to ultimately provide right quality and regulatory assurance.

The scope of this chapter is to explore the latest development and scale-up of the lyophilization process for protein therapeutics in the vial using a QbD approach. First, the fundamentals of lyophilization process in vials are briefly presented in terms of the heat transfer theory and vial heat transfer coefficient measurement. Then, the applications of QbD concepts to lyophilization processes are discussed for the freezing and drying steps, and the latest developments for designing robustness into the cycle, based on the theoretical modeling specifically for primary drying, are presented. A case study is presented for a protein product using both theoretical modeling and experimental scale-down model approach to obtain a wide design space. Finally, the application of QbD to facilitate the process development and scale-up is summarized.