cal properties, and due to target dose (e.g., high concentrations) or drug delivery (e.g., subcutaneous). Lyophilization (freeze-drying) has been widely utilized (almost ~50% of marketed proteins products) for stabilization of biological drug products, which are, unstable in the liquid form or preferred over the frozen solutions. During lyophilization process development and scale-up using quality-by-design (QbD) principles, these differences should be carefully considered for a successful process validation and commercialization of each product. In this chapter, we focus on recent advances in lyophilization and scale-up of therapeutic protein products in vials. Also, advances in QbD approaches and a case study will be presented in detail.

Lyophilization Scale-Up

The delicate nature of protein molecules generally results in their poor long-term storage stability in aqueous solution, and thus lyophilization (Lyo) is often used to stabilize protein therapeutics as a solid-state dosage form. The lyophilization process depends heavily on the protein molecule and excipient components used in the formulation [5], and readers can refer to previous chapter for more details about the impact of formulation on lyophilization process design. In addition, the container–closer system also plays an important role in lyophilization process development. Among the many different primary containers available, a glass vial is the most commonly used container in the lyophilization field mainly because of long history of use and the inert nature of glass as well as the effective barrier to moisture relative to plastic containers. At the early stage of a product development, a lyophilization process in a vial container is initially developed in a small laboratory freeze-dryer, and then scaled up to a pilot-scale lyophilizer for early-stage clinical trial manufacturing. At the late-stage clinical phase III and commercial stage, the lyophilization process generally needs to be further scaled up to a large manufacturing-scale lyophilizer to meet the supply requirement.

The lyophilization scale-up process is quite challenging due to multiple differences between the small- and large-scale dryers. There is some guidance to facilitate the development of an efficient lyophilization cycle in the laboratory [50]. However, even an optimized cycle from the laboratory freeze-dryer may not transfer smoothly to manufacturing scale. In addition to the scalability differences, there are several other differences between laboratory- and manufacturing-scale lyophilizers, which may pose a serious challenge for scale-up. These challenges are discussed below.

Ice Nucleation Differences During Freezing

One important goal of freezing is to produce a homogeneous product in terms of ice crystal size so that variation in drying behavior within the batch is minimized and an efficient drying process can be easily developed. However, the random nature