biological activities of proteolytic enzymes. Another advantage of lyophilization is the potential to modify the formulation after manufacturing prior to administration, such as introducing volatile additives, preservatives, or salt; changing pH, viscosity, or volume; initiating reactions, adding adjuvants, or diluting with buffers or non-aqueous diluents for special applications.

Among biopharmaceuticals, different issues have been observed in lyophilizing different modalities, e.g., antibodies, enzymes, hormones, cytokines, peptides, vaccines, viral vectors, and nonviral vectors. Therefore, general approaches in optimizing any specific class of biologics have been different from lyophilizing other modalities. To achieve successfully lyophilized formulations, specific issues were addressed by employing relevant excipients, including stabilization during freezing, dehydration, or storage, and formation of an elegant cake with an efficient cycle.

While lyophilized formulations offer multiple advantages over liquid formulations, they also bear substantial disadvantages, like the inconvenience of reconstitution for end users, additional steps for cycle development and optimization, expensive equipment, and high costs for manufacturing. The choice of implementing lyophilization, therefore, requires an intelligent strategy to maximize the advantages and minimize the disadvantages.

In this chapter, challenges and practical solutions associated with the development and commercialization of lyophilized biopharmaceutical formulations are discussed along with examples of relevant industrial practices and the list of currently commercialized lyophilized protein therapeutics.

Lyophilization Design and Stability Considerations of Various Biologics

As the primary purpose of utilizing lyophilization is enhancing product stability, the best product candidates for lyophilization go beyond considerations of pharmaceutical modality. Generally, the products with the following attributes are good candidates for lyophilization:

- Products with limited stability in a liquid state, even after formulation optimization, are obvious candidates. Extensive research has been conducted to predict the intrinsic stability of biopharmaceuticals based on structural information. However, accurately determining product stability profiles without real-time stability data remains a challenge, as stability relates to complex relationships of many different variables. Although it is difficult to generalize, many nonglycosylated proteins, interferons, hemophilia factors, and vaccines requiring biological function are good candidates for lyophilization.
- Intravenous infusions, among various routes of parenteral delivery, are generally better suited for lyophilization primarily due to the experience of health-care professionals in reconstituting lyophilized formulations.