- Products with a strong intellectual property positions that do not anticipate strong competition in the market are good candidates for lyophilization, as the convenience factor of a liquid formulation may not be necessary.
- Products that are globally distributed, especially to areas where a cold chain is not well established, generally benefit from the added stability of lyophilization.

In order to maximize the benefits of a dry powder formulation, the following topics should be addressed during a general formulation development process.

Stabilization by Lyophilization

For all lyophilized formulations, adequate short-term stability of the product in a liquid state needs to be established during manufacturing, handling, storage, transportation, and administration, to accommodate formulation and filling operations as well as stability after reconstitution. However, the major focus of the development process should be to achieve sufficient stability during long-term lyophilized storage. In order to develop a stable formulation, various formulation factors need to be optimized.

Protein degradation rates are heavily dependent on formulation pH. As different proteins are susceptible to various degradation pathways, it is crucial to identify the optimal pH range where the protein of interest is most stable. A proper buffer with a sufficient buffering capacity should be selected in order to maintain this pH range.

An efficient lyophilization cycle is an ideal attribute of a lyophilized formulation, which is discussed in further detail in Sect. 5.1.2. As part of this design, bulking agents are often introduced to the formulation to achieve an elegant cake. The physical properties of the bulking agents, especially their characteristics in a frozen state, need to be understood for successful optimization [2]. Various classes of bulking agents such as crystalline, amorphous, ionic, nonionic, polymer-based, or protein-friendly sugars can be considered during lyophilized formulation development. As the physical properties of the selected bulking agents would directly affect product stability as well as the lyophilization cycle, careful compatibility studies will need to be conducted. Bulking agents that have a tendency to crystallize during lyophilization, e.g., mannitol or glycine, are commonly used to achieve an elegant cake. However, the large surface areas generated by crystalline structures often enhance undesirable degradations of proteins, so they need to be selected with these considerations. Other commonly used tonicity modifiers with low collapse temperatures like sodium chloride or monosaccharides, e.g., glucose or sorbitol, can be challenging to lyophilize without cake collapse unless they are formulated with other excipients or with a high concentration of protein.

Another inactive ingredient often crucial for successful lyophilized formulation development is a surfactant. Surfactants have been used to maintain the integrity of proteins against surface-induced degradations derived from agitation, filtration, filling, freeze-thawing, etc. [10]. Nonionic surfactants like polysorbates or poloxamers have been successfully used in protein formulations. Some optimization is required