be derived by comparing the formulations of antibodies, Fc-fusion proteins, antibody drug conjugates (ADCs), peptides, and general proteins including enzymes, cytokines, antihemophilic factors, etc.

A list of commercialized antibodies, Fc-fusion proteins, and ADCs is shown in Table 3. A majority of antibody products are formulated with sucrose or trehalose as a bulking agent or tonicity modifier with surfactants. This particular trend primarily results from general experience with antibodies; most antibodies are reasonably stable in a liquid state and do not require additional stabilization beyond water-replacing sugar(s). These products contain higher concentrations of proteins and, consequently, can form good cakes without the need for additional bulking agents.

This trend changes significantly for Fc-fusion products or ACDs (Table 3). Fc-fusion products have demonstrated inferior stability compared to naturally existing antibodies and thus require additional stabilizers in their lyophilized formulations. The structural compatibility between Tc and Fc regions has been discussed among possible sources of instability [6, 19]. Likewise, the conjugation of antibodies with small molecule pharmaceuticals results in less stable molecules than the original antibodies. Due to this stability issue, more product-specific stabilizers are generally included in these commercial products.

Table 4 lists other general protein therapeutics. As the advantages of antibody products, i.e., high stability and high concentration, do not generally apply for other protein therapeutics, more customized formulations include additional crystalline bulking agents like mannitol or glycine and product-specific stabilizers such as amino acids, salts, etc. As some of the necessary ingredients are relatively difficult to lyophilize, additional formulation components, e.g., crystalline bulking agents or polymeric excipients are added to overcome the low collapse temperatures of such stabilizers. For example, antihemophilic factors generally require high ionic strength as well as specific stabilizers like calcium chloride, both of which have very low collapse temperatures [7] and can be difficult to lyophilize. To address these challenges, additional excipients like sugars or mannitol are commonly used in the formulation. In addition to formulation optimization, the development of an appropriate lyophilization cycle is critical for products containing such additives.

Commercial peptide products and their formulations are outlined in Table 5. Unlike other protein therapeutics discussed above, peptides are formulated with a simple crystalline bulking agent such as mannitol, without the need for other stabilizers like surfactant or sugars. The primary reason behind a simple formulation is that peptide products do not typically possess a complex three-dimensional structure, so the stabilization of a delicate conformation may be not necessary. On the other hand, peptide products are relatively more vulnerable to chemical degradations during storage in liquid state which can be readily eliminated by lyophilizing the product.

Table 6 shows a list of commercial vaccine products which are available in lyophilized forms. Just as there are various modalities even within vaccine preparations, there are complicated and diverse formulations presented to the market. Unique stabilizers like gelatin, HSA, and glutamate commonly appear in vaccines