lyophilization stress but will also be useful to predict the long-term stability of the dry powder formulation.

General Development Approaches

Due to limited time and drug substance availability, it is typically difficult to develop a formulation at an early stage of product development that is feasible for commercialization. For this reason, most biopharmaceutical companies adopt a two-step formulation approach: formulation development for a formulation suitable for preclinical and early clinical trials, followed by formulation development for a commercially feasible formulation before phase III clinical trials. An efficient alternative approach would be to develop a lyophilized formulation with the possibility of reaching the market without further modifications followed by an amendment after licensing approval. General formulation development approaches can include:

- A frozen formulation for the initial formulation followed by a liquid or lyophilized formulation, depending on product stability
- A lyophilized formulation for the initial formulation followed by a liquid formulation, if feasible, for commercialization
- A liquid formulation with limited expiry for the initial formulation followed by an extension of the expiry for commercial purposes

After receiving approval for commercialization, additional formulation optimizations can be performed for competitive purposes and to manage the life cycle of the product.

A rough diagram of various formulations and steps in formulation development that occur during product development and commercialization is shown in Fig. 1.

Strategy for Initial Formulations

The development of an initial formulation can be initiated as early as the process development stage, as the establishment of a good formulation would also benefit upstream purification processes. A pre-formulation characterization can be conducted with minimal drug substance to establish the following basic formulation parameters: pH, ionic strength, and the necessity of a surfactant. In general, pH and ionic strength conditions can be determined by a simple accelerated stability study. An effective surfactant can be identified through an agitation or shear stress study. When these three formulation parameters are optimized, the formulation is often stable for about 6 months in refrigerated storage or frozen state, which may be sufficient to support preclinical studies and early clinical trials. This “initial formulation” will most likely differ from the “commercial formulation,” which is discussed later in this chapter. After the product is introduced to the market, there will be a continued effort to improve the formulation through life-cycle management.