and (iii) protein solutions (with no formulation additives) being freeze-dried in bulk. For the purpose of this chapter and ease of readers understanding, the term bulk freeze-drying shall be referred to as the first scenario only for practical reasons. Formulated protein solutions are rarely freeze-dried in bulk containers as compared to individual dosage units like vials/syringes/dual chamber cartridges; also, bulk freeze-drying of protein solutions without any additives is not feasible due to energy considerations in process development and protein stability limitations. Moreover, it would be appropriate to conclusively define bulk freeze-drying as an industrial process to bring down water/moisture limit to pharmaceutically acceptable levels, thereby permitting the long-term storage of active pharmaceutical ingredient (drug substance) until it is finally processed as a pharmaceutical product in an appropriate package/delivery device for commercial distribution.

Centrifugation in batch or continuous mode followed by repeated washings of protein crystals/precipitate to eliminate residual impurities and trace contaminants (buffers, salts, residual solvents noncrystalline protein impurities) is performed as a preceding step to bulk freeze-drying. Such a processing step provides uniform quality material for easy handling and transfer during a bulk processing step. Residual water content, total solids content in the slurry, slurry depth, and the uniform distribution/spreading of the slurry in a lyophilization tray are some of the important considerations for optimization and scale-up of bulk freeze-drying process. Slurry depth/fill is an important scale-up parameter necessary to be controlled for optimal drying and process performance. The otherwise important processing parameters like heat transfer, shelf temperature variation in a typical lyophilization process are equally important for bulk freeze-drying optimization. A major limitation of stainless steel freeze-drying trays is that they get warped over repeated use and hence have to be periodically replaced. Patel and Pikal have reviewed the development and scale-up issues with freeze-drying with a particular focus on the effect of load on process design and tray properties and considerations for freeze-drying [41].

Loading and unloading of a bulk tray lyophilizer typically take place under classified area and are important standard operating procedures in a typical manufacturing process. Recently, there has been considerable development towards finding an effective methodology for holding the product on the shelves for optimal freeze-drying. There are two possible ways to hold material.

Framed Structures This is a refined conventional approach for holding the product inside the freezer-dryer. In this approach, a low-density polyethylene (LDPE) sheet is sandwiched between two rectangular stainless steel frames. The LDPE sheet (appropriate pore size and thickness) then serves as the base for holding the crystal slurry. Once the product with optimal slurry concentration is spread uniformly on the sheet, a Tyvec sheet (appropriate pore size and thickness) is covered on top of this and fixed by means of the top frame. The Tyvec sheet avoids any product spilling before and after lyophilization.

Preframed Structures These structures typically are like the GORE® LYOGUARD® trays, their use in bulk freeze-drying has been discussed in sufficient details in subsequent parts of this chapter.