- Loading and unloading of lyophilizers requires either direct human intervention for manual loading, or complex, high-precision automatic loading and unloading equipment. The presence of humans in such close proximity of open sterile product is a concern for sterility assurance, and has high costs associated with training, gowning, airlocks, room pressure differentials, and microbial monitoring support.
- Reconstitution of some lyophilized products such as antivenoms [12] and highly concentrated therapeutic proteins [4] can take an hour or more. There is some evidence in the literature that spray-drying can yield powders that reconstitute faster than the lyophilized version [7].
- Free-flowing powders produced by some alternatives to lyophilization are more versatile than lyophilized cakes because they can be filled into a wide variety of containers for innovative reconstitution/injection technologies [9].

This chapter covers the following alternative drying methods with current or emerging capability to serve as alternatives to lyophilization: sterile spray-drying, bulk tank freeze-drying, aseptic crystallization and drying, vacuum-drying, and drying on a fiber matrix. Most of these generate flowable powders, so we have included information on aseptic powder filling into vials as well as innovative reconstitution-injection technology under development. Finally, we offer some insight into reformulation as a liquid.

Sterile Spray-Drying

Spray-drying is a manufacturing technology that has a long history in the production of dry powder forms of foods, chemicals, pharmaceutical excipients, and active pharmaceutical ingredients (APIs). A comprehensive review of biopharmaceutical spray-drying can be found in [19] and [20].

Sterile spray-drying is an emerging technology, in that it is close to commercialization in the pharmaceutical industry. It offers the potential to generate sterile powders that can be filled into vials as a direct replacement for lyophilization, with the promise of higher throughput/lower cost [10, 11].

Several vendors are having success in delivering integrated production equipment over a range of sizes, and the authors understand that some pharmaceutical companies are developing sterile spray-dried products. And while there are contract manufacturers that offer sterile spray-drying, we know of no sterile injectable drugs or biologics produced by sterile spray-drying that have been approved by the regulatory body of a large market. The coming decade will certainly see regulatory approvals of such products, and a rapid proliferation of equipment and process parameters that have been "proven" as fully GMP.

Spray-drying is a mechanistically simple, continuous process, in which two streams are pumped simultaneously into a drying chamber: a fine spray of the solution to be dried (usually aqueous), and a drying gas. What exits the other end of the