Process design, control, and qualification are the focus of the Guidance for Industry Process Validation: General Principles and Practices issued by U.S. FDA in November 2008. According to this guidance, each step of a manufacturing process has to be controlled to ensure that the finished product meets all design characteristics and quality attributes including specifications.

This chapter is intended to address these issues, and, to this purpose, it is structured as follows: The first section points out how equipment design can affect product quality and batch heterogeneity during operation (mainly during primary drying), through pressure gradients in the drying chamber and temperature gradients over the various shelves, besides the well-known effect of radiation. The use of computational fluid dynamics (CFD) can be very effective, especially if dual-scale modeling approaches are adopted, to improve the design not only of the drying chamber but also of the condenser, and for a selection of duct size and valves that assure the required performances. Recipe development in pilot units is discussed in the second section, showing that the recipe can be obtained *in-line*, by using some tools to monitor the process, and then manipulating the operating variables to achieve the desired goals, or can be designed *off-line*, by using mathematical models to build the *design space*, and then validating it. The third section discusses how process transfer or scale-up can be made easy and robust either using specific software tools after a process identification step or using a monitoring and control system, if available in the large-scale equipment. Finally, future perspectives concerning further improvement in the performance of monitoring systems and the possibility of using more sophisticated control systems, which can take into account batch heterogeneity, is discussed; a short account about the use of model predictive control (MPC) in freeze-drying is also given.

EQUIPMENT DESIGN

When designing a freeze-dryer, a number of critical issues must be properly addressed. These can be grouped into two categories. The first category is related to the problem of batch heterogeneity; as it is well known, especially at the industrial scale, it is challenging to design an equipment capable of guaranteeing the very same operating conditions for the entire batch. It is very common, in fact, that the product contained in vials positioned in different points of the chamber experience different temperature and pressure histories, resulting, for example, in significant variations for the drying time and the final residual water content (as well as other important characteristic properties). Typical design and operating parameters affecting the final batch heterogeneity are chamber geometry, clearance between shelves and number of shelves, position of the duct leading to the condenser, number and position of the inert gas injection nozzles, as well as temperature gradients of the heating fluid circulating through the shelves (14–16). An example of the effect of these factors on the drying of a pharmaceutical product in vials is shown in Figure 1.

The second category of critical issues concerns the capability of the freeze-drier to evacuate the requested water vapor flow rate to operate under the desired operating conditions (i.e., specific sublimation rates and thus batch drying times and chamber pressure). Typical design parameters that affect the overall performance of the freeze-drier with respect to these issues are mainly the geometry of the condenser and, for freeze-driers with condensers separated