medicines. For bioprocess engineers working in the pharmaceutical or biotechnology industry the primary concern is not reduction of manufacturing cost (although that is still a very desirable goal), but the production of a product of consistently high quality in amounts to satisfy the medical needs of the population.

Consider briefly the process by which a drug obtains FDA approval. A typical drug undergoes 6.5 years of development from the discovery stage through preclinical testing in animals. Human clinical trials are conducted in three phases. Phase 1 clinical trials (about 1 year) are used to test safety; typically 20 to 80 volunteers are used. Phase II clinical trials (about 2 years) use 100 to 300 patients and the emphasis is on efficacy (i.e., does it help the patient) as well as further determining which side effects exist. Compounds that are still promising enter phase III clinical trials (about 3 years) with 1000 to 3000 patients. Since individuals vary in body chemistry, it is important to test the range of responses in terms of both side effects and efficacy by using a representative cross section of the population. Data from clinical trials is presented to the FDA for review (about 18 months). If the clinical trials are well designed and demonstrate statistically significant improvements in health with acceptable side effects, the drug is likely to be approved. Even after this point there is continued monitoring of the drug for adverse effects. The whole drug discovery-through-approval process takes 15 years on the average and costs about $400 million (in 1996). Only one in ten drugs that enter human clinical trials receives approval. Recent FDA reforms have decreased the time to obtain approval for life-saving drugs in treatment of diseases such as cancer and AIDS, but the overall process is still lengthy.

This process greatly affects a bioprocess engineer. FDA approval is for the product *and* the process together. There have been tragic examples where a small process change has allowed a toxic trace compound to form or become incorporated in the final product, resulting in severe side effects, including death. Thus, process changes may require new clinical trials to test the safety of the resulting product. Since clinical trials are very expensive, process improvements are made under a limited set of circumstances. Even during clinical trials it is difficult to make major process changes.

Drugs sold on the market or used in clinical trials must come from facilities that are certified as GMP. GMP stands for *good manufacturing practice*. GMP concerns the actual manufacturing facility design and layout, the equipment and procedures, training of production personnel, control of process inputs (e.g., raw materials and cultures), and handling of product. The plant layout and design must prevent contamination of the product and dictates the flow of material, personnel, and air. Equipment and procedures must be *validated*. Procedures include not only operation of a piece of equipment, but also cleaning and sterilization. Computer software used to monitor and control the process must be validated. Off-line assays done in laboratories must satisfy *good laboratory practices* (GLP). Procedures are documented by SOPs (*standard operating procedures*).

The GMP guidelines stress the need for documented procedures to validate performance. “Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics” and “There shall be written procedures for production and process-control to assure that products have the identity, strength, quality, and purity they purport or are represented to possess.”

The actual process of doing validation is often complex, particularly when a whole facility design is considered. The FDA provides extensive information and guidelines