Before packaging of the batch(es), the necessary Packaging Documentation needs to be prepared. This describes the actual packaging disposition of each batch. It is customary to package each batch (in its entirety) into equal quantities (taking the actual batch "yield" into account) of each packaging configuration to be utilized after initially removing sufficient quantity for "large pack" evaluation under controlled warehouse conditions. For example, if 50,000 tablets/capsules are removed for "large pack" evaluation, the balance can be packed into various sizes such as 50s, 100s, 250s, 500s, and 1000s. Each of the container closure systems must be of identical material/chemical composition as the large storage container for the 50,000 batch. The packaging operation must be carried out under cGMP conditions using large-plant equipment.

Once the product has been packaged, samples of each pack size are incorporated into formal stability programs (usually 40°C/75% RH, 30°C/65% RH, and 25°C/60% RH) [86,87] according to a Stability Protocol, which outlines the pack sizes and types to be evaluated, the manufacturer(s) of the packaging components and actual composition thereof, the predetermined times at which samples must be drawn, the necessary testing that needs to be undertaken, and the predetermined acceptance criteria that are required to be met. Refer to Chapter 6 for further details on stability testing and stability protocols.

Drug product(s) containing APIs sensitive to light should be tested in appropriate photostability chambers according to an approved protocol. Samples of innovator product(s) should be included as controls for each accelerated condition specified.

It is generally considered that the formulation of tablets is somewhat more complex than capsules; hence, the manufacturing processes required to produce tablets are necessarily more rigorous than those required to manufacture capsules. The foregoing processes have thus focused on the development of tablet dosage forms, while at times occasional references were made to capsules. Nevertheless, similar considerations apply to the development of a capsule dosage form.

Appendices A4.1 and A4.2 are provided herewith to outline the processes and sequences involved in the development of a generic tablet dosage form.

Quality-by-Design Approaches

The introduction of the concept of "Quality-by-Design" (QbD) marks a fundamental shift in the drug product development process. The FDA cGMP document envisioned a modern, efficient, and flexible pharmaceutical manufacturing sector for the 21st century to ensure the reliable production of high-quality drug products without the need for extensive regulatory oversight [88]. However, the drug product development approach commonly used by industry relies on empirical formulation development followed by postmanufacture testing of the quality of the dosage form. Therefore, the goal of the FDA was to address major issues related to the state of pharmaceutical manufacturing, such as the inability to predict the possible effects of scale-up on the final product, inability to analyze or understand reasons for manufacturing failures, and the achievement of reasonable product quality at a great effort and cost, among other issues. After a decade, this goal is still a challenge for most pharmaceutical companies. However, the FDA will require that companies in