Method Validation

Analytical methods for stability testing of APIs should be validated. USP contains a General Chapter <1225> on methods validation [9]. The FDA has also posted the ICH guidelines, Q2A and Q2B, on the validation of analytical procedures on its website [10,11]. These and other FDA guidelines [12,13] should be considered in developing and implementing a methods validation protocol for an API. In the USP, validation of an analytical procedure is defined as the testing process by which it is established that certain performance characteristics are achieved. Typical performance characteristics in the USP and ICH for the validation of analytical methods include the following: accuracy, precision, specificity, detection limit, quantitation limit, linearity, and robustness. The definitions for these analytical performance characteristics are provided in the USP and ICH guidelines and are not covered in this chapter. It should be noted that validation is a dynamic process and should be repeated when an analytical method has been revised or when an API is procured from a different manufacturer or produced by a different synthetic route.

Shelf-Life Development and Assignment

Stability testing should be conducted with the API packaged and stored under the ICH accelerated and long-term stability conditions, which are listed below

Accelerated stability condition: 40 ± 2°C/75 ± 5% RH
Long-term stability condition: 25 ± 2°C/60 ± 5% RH

For stability testing, samples may be stored in a smaller container/closure system that should be equivalent to the larger container used for storing larger quantities of the API. The smaller container/closure system must have the same composition, closure, and liners and include desiccants if they are also used in the larger container/closure system.

In a short time of 3 months, the accelerated stability studies provide valuable data on the degradation profile of an API and thus assist in validating a particular container/closure system for storage of the API. However, long-term stability studies are essential in developing a retest period and shelf-life for APIs stored in the warehouse under controlled room temperature conditions, which will be defined later in this chapter. A retest period is defined as the period of time during which the API is expected to remain within its specifications. Therefore, it can be used in the manufacture of the corresponding drug product, provided that the API is stored under appropriate environmental conditions. The shelf-life or expiration period for an API is the maximum allowable time period beyond which the API cannot be used in the manufacture of drug products and must be destroyed.

For APIs that exist as solids, a retest period of 1 year is generally supported by long-term stability data and accepted by the pharmaceutical industry. For stable APIs, a shelf-life of 5 years or longer derived from long-term stability and retest data are not uncommon. In the absence of an assigned shelf-life, the API can be retested again after 1 year and assigned a second retest date. This process of retesting can