Annual Stability

After the expiration dating has been verified with three production batches, an ongoing stability testing program for an approved drug product should be implemented in accordance with the postapproval stability testing protocol in the ANDA application. The protocol should include the commitment to place at least one batch of every strength in every container/closure system, such as bottles or blisters, in the annual stability program for the subsequent years. If the manufacturing interval for a drug product is greater than 1 year, a batch of drug product released next year should be added to the stability program. Approved bracketing and matrixing designs should be implemented to reduce the stability testing workload.

Intermediate testing time points may be reduced for annual batches on a case-by-case basis through a prior approval supplement (PAS) [5]. The proposed reduction must be justified based on a history of satisfactory long-term stability data. The reduced testing stability protocol should include a minimum of four time points, including the initial and expiration time points and two time points in between. For example, for an expiration dating period of 36 months or longer, batches should be tested annually. It should be noted that the reduced testing protocol applies only to annual batches and does not apply to batches used to support a postapproval change that requires long-term stability testing at all time points. However, bracketing and matrixing designs may be included in the PAS, which will optimize testing efficiency.

Extension of Expiration Dating Period

An extension of the expiration dating period based on full long-term stability data obtained on at least three production batches in accordance with a protocol approved in the ANDA application may be implemented immediately and does not require prior FDA approval. 21 CFR Part 314.70(d) (5) allows implementation of the extended expiration dating through an AR submission only if the criteria set forth in the approved stability protocol were met in obtaining and analyzing stability data.

Bulk Holding

Upon completion of manufacturing, the finished products, such as capsules and tablets for solid oral dosage forms, are usually held for a period of time, often called the bulk holding time, before packaging. The length of the bulk holding time is usually governed by scheduling of packaging operations and inventory requirements. In the interest of saving development time during routine production, it is advisable to establish the bulk holding time by monitoring the controlled room temperature stability of a sample of the ANDA submission batch, which is stored in a smaller container equivalent in composition to the larger container used for storage of unpackaged bulk finished tablets. For example, to simulate the larger cardboard containers used for storage in the warehouse, suggested dimensions of the smaller containers would be $4'' \times 4'' \times 4''$ cardboard containers, double lined with low-density polyethylene bags that are closed with twist ties. The stability study of samples stationed in the warehouse, maintained at the controlled room temperature condition,