continue as long as the degradation levels and other quality attributes remain well within specifications. Stability studies to justify assigned retest and expiration dates should be repeated by the drug product manufacturer if the API is repackaged in a different container than that used by the API manufacturer.

Packaging

The FDA guidance [14] entitled "Container Closure Systems for Packaging Human Drugs and Biologics" includes information on container/closure systems for packaging of APIs. In general, APIs are solids; for such APIs, the container/closure system for storage or shipment of APIs usually consists of a fiber drum containing double low-density polyethylene liners that are closed with twist ties. For protection from moisture and thus to assure stability, a desiccant may be placed between the bags if necessary. In that event, the stability samples should also contain appropriately placed desiccants to simulate the configuration of the larger container/closure system.

Shipment

API manufacturers should evaluate test results for critical test attributes such as assay and degradants when they are near specification limits before shipment of batches to drug product manufacturers. Existing stability data should be studied to ensure that such batches will remain within specifications, allowing for analytical measurement errors when initially tested at the API manufacturer's site and also at the assigned retest or expiration dates. If stability data are not available for a batch with test results approaching the specification limits, the particular API batch representing the worst case for its closeness to the specification limits should be studied under long-term stability conditions to develop the stability profile to justify quality-control release and shipment of such batches.

Because the vast majority of APIs are imported from foreign countries, Customs and the FDA require verification of the integrity of the container/closure system's labeling information and the manufacturer's analytical documentation to rule out pilferage or tampering. If the container was opened during transit and the API was exposed to the atmosphere, even for a brief duration, the stability profile of the API could be affected and the possibility of contamination could arise. Therefore, at the minimum, assay, impurities, and degradant profile of the API should be determined at the finished product manufacturer's site. The results should be compared with the API manufacturer's certificate of analysis to verify that the quality of the API has not been compromised.

INTERMEDIATES FOR DRUG PRODUCTS

In general, the manufacturing process for both immediate-release (IR) and modified-release (MR) solid oral dosage forms begins with the mixing of the required APIs and excipients, then proceeds through stages of intermediates, and finally ends with the production of finished products, such as capsules and tablets. These intermediates are known as blends, intermediate pellets, cores, etc.