in foreign countries, such as Ireland, Italy, India, and China, among others. It is a requirement that all manufacturers of APIs have modern production facilities that are staffed with well-qualified personnel and have implemented good quality systems that conform to the U.S. current good manufacturing practice (CGMP) requirements. Over the years, the foreign inspections branch of the FDA has done a truly outstanding job through vigorous inspections in enhancing the CGMP systems to the point that the foreign manufacturers offer high-quality APIs and an excellent value for the US as well as global markets. Through inspectional observations and, when/where necessary, warning letters, the FDA ensures that only manufacturers who have implemented adequate quality systems and manufacturing technology to comply with CGMP requirements can supply APIs to the U.S. drug product manufacturers.

Many APIs for generic drugs, however, are still not listed in the USP. Various API monographs are currently going through the review process in the Pharmacopeial Forum. CGMP requirements are nevertheless equally applicable regardless of whether the APIs are in the USP or not. The API manufacturers seem to be cognizant that demonstration of stability profiles of APIs are an essential component in meeting these requirements.

### Specifications and Test Methods

For those APIs with monographs published in the USP, the API manufacturers must ensure that their specifications are not wider than the pharmacopeial specifications. The specifications must be either identical or tighter than the respective pharmacopeial specifications. Historically, third-world countries in Asia and Africa have followed the USP. European countries and Japan have their own compendia, such as the European Pharmacopeia (EP) and Japanese Pharmacopeia (JP). Because foreign manufacturers are known to produce APIs for international markets, they have focused on developing a single set of specifications with the tightest limits to meet the requirements of the major pharmacopeias (USP, EP, JP). To assure that an API meets the stability specifications for international markets, the tightest specifications included in the major pharmacopeias should be selected. For example, if the USP has specifications of 98.0% to 102.0% for assay and 0.2% for a degradant and other pharmacopeias have specifications of 99.0% to 101.0% and 0.3%, respectively, the tightest specifications of 99.0% to 101.0% and 0.2% should normally be set as the stability specifications for the API.

For USP-grade APIs, USP test procedures should be followed. If an API manufacturer's test method differs from the USP procedure, crossover studies are required to demonstrate equivalency between these procedures. For example, if a titration procedure is employed by the manufacturer and a high-performance liquid chromatography (HPLC) procedure is described in the USP for an assay, the API sample should be analyzed by both methods. Another possible scenario is that an HPLC method may be used for the determination of impurities and degradants by the API manufacturer, which may be different from the HPLC method listed in the USP. Results from the two HPLC methods should be comparable within the experimental errors of the methods. This will allow the use of the titration procedure by the API manufacturer for assay and its HPLC procedure for stability testing and at the same time permit