labeling the API as conforming to USP. The situation becomes complicated if the different pharmacopeias employ different methods of analysis. In that case, multiple crossover studies should be conducted to allow the use of a single test method by the API manufacturer for the analysis of a given test attribute such as assay.

To harmonize development of specifications for impurities and degradants in ANDAs and DMFs, the FDA has published a guidance [3] to provide recommendations on the identification and qualification of impurities in APIs produced by chemical synthesis, which are applicable for both pharmacopeial and nonpharmacopeial APIs.

FDA and ICH Guidelines

Both FDA and ICH (i.e., International Conference on Harmonisation) guidelines [4–8] require stability-indicating assay procedures for analysis of drugs. The HPLC assay procedure is the preferred method for stability testing. For demonstration of stability, an API sample is purposely degraded [6] by stressing it under harsh conditions of temperature, humidity, oxidation, ultraviolet (UV) light, acidity, and basicity. Evidence for the stability-indicating property of the assay procedure is demonstrated by adequate separation of the degradants from the active ingredient peak. To assure that no degradants are coeluting with the active peak, it is advisable to conduct peak purity studies by multiwavelength scans of the chromatographic peak using a photodiode array detector (PDA). With this technique, the purity of the main peak can be established only if the UV chromophores of the API and the coeluted degradant are sufficiently different. However, if the UV chromophores are similar, this technique will not succeed in establishing peak purity. In such cases, the more powerful hyphenated technique of HPLC analysis coupled with mass spectrometric detection (known as liquid chromatography-mass spectrometry or LC-MS) should be considered.

Issues for Multisource APIs

Spurred by the growth of the generic industry, multiple manufacturers of APIs have arisen. With time, many more API manufacturers will gain FDA approval and join the ranks of producers of quality APIs. Because they will all compete for essentially the same generic market for a given API, their success will be governed by their ability to deliver quality APIs at the least possible cost. This will require creativity for the API manufacturers to survive and succeed in a highly competitive business. For that to happen, they will have to cut costs in the production of the APIs. The different manufacturers will employ different syntheses for the same API. In all cases, the final product, the API, must be chemically identical. The starting chemicals, intermediates, final intermediates, synthetic pathways, and residual solvents detectable in the API will usually differ from one manufacturer to another. Although the API produced by different manufacturers must be chemically indistinguishable, its physical properties such as bulk density, particle size profile, its crystalline or amorphous character, and its rate of degradation may differ. Therefore, in addition to cost, its stability as well as its processing characteristics in the manufacture of finished products should be considered in selecting the manufacturers of the APIs.