

19. Application of Validation Principles to Other Analytical Techniques	376
19.1. Cleaning method	376
19.2. Physicochemical characterization method (dissolution)	378
19.3. Nonchromatographic methods	378
19.4. General considerations	380
References	381
Appendices	384

## Part I: Method Development

### 1. WHAT IS A STABILITY-INDICATING METHOD?

According to the regulatory definition (1), a stability-indicating method is one of a number of

Quantitative analytical methods that are based on the characteristic structural, chemical, or biological properties of each active ingredient of a drug product and that will distinguish each active ingredient from its degradation products so that the active ingredient content can be accurately measured.

Therefore a stability-indicating method is an analytical procedure that is capable of discriminating between the major active (intact) pharmaceutical ingredient (API) from any degradation (decomposition) product(s) formed under defined storage conditions during the stability evaluation period. In addition, it must also be sufficiently sensitive to detect and quantify one or more degradation products. A corollary may be added that the analytical method must be also capable of separating or resolving any other potential interfering peak such as an internal standard. With these criteria, then, the discriminating “nature” of the method indicates the method to be *stability-indicating* as well as *stability-specific*. Later in the discussion we will see that other methods may be stability-specific but not stability-indicating. Stressed testing may be used (1,2) to expedite the decomposition pathway(s) to generate decomposition product(s) for the API. However, stressed testing under forced conditions of oxidation, photolysis, hydrolysis, and varying pH values may form some decomposition products that are unlikely to be formed under accelerated or long-term stability storage conditions. The products generated nonetheless may be useful in developing and validating a suitable stability-indicating analytical method for the analysis of the drug substance and the drug product, expediting the availability of the completed analytical method.

It is paramount that the chosen analytical method used for stability evaluation be validated and discriminating to ensure efficacy of the subsequent stability evaluation. Confidence in the stability data is predicative on time invested up front to ensure a viable procedure as well as to conform to legal and regulatory requirements (2).

### 2. STRATEGY OF METHOD DEVELOPMENT

Development of a stability-indicating method should be predicated on the method's intended application as well as selecting a suitable technique designed to assess