extraneous peaks from the main analyte peak is required for submission. The origins of extraneous peaks in drug substance are process impurities (which include isomeric impurities) from the synthesis process, residual solvents, and other extraneous components from extracts of natural origins. For the drug product, sources of extraneous peaks include any impurities, degradation products, interaction of the active drug with excipients, residual solvents from both the active drug substance and the excipient, and so on.

17.4. Forced Degradation

In previous sections, we have defined specificity as discussed by USP Chapter <1225>, the ICH Guidance, and the FDA Reviewer Guidance. The discussion was limited to specificity studies in the presence or absence of impurities and excipients. A question that arises if nothing (i.e., no extraneous peaks) is observed is, What approach one might use to show the specificity and stability-indicating nature of the proposed method?

Both the FDA and the ICH recommend forced degradation/or stress testing of the drug substance and drug product. For these studies, acid and base hydrolysis, temperature, photolysis, and oxidation are recommended. Neither the ICH nor the FDA guidelines specify how to perform these forced degradation studies. Experimental conditions and the design of these studies have been left to the discretion of pharmaceutical companies. A generic protocol for these studies is shown in Table 2.

To demonstrate that the analyte chromatographic peak obtained after forced degradation or stress studies is a single entity, peak purity tests are recommended by the FDA and the ICH. Photodiode array detection can be used to demonstrate peak purity. The spectra collected across a peak are compared mathematically to establish peak homogeneity.

It is generally recommended that about 20–30% of analyte degradation, at least, in one medium be achieved. For some compounds, severe degradation conditions may be required.

17.5. Detection Limit (DL)

The detection limit (DL) is the lowest concentration of the analyte that can be detected, but not necessarily quantitated, under the stated experimental conditions. It is a parameter of limit test and specifies whether or not an analyte is above or below a certain value. In the current USP General Chapter <1225>, determination of limit of detection is described for instrumental and noninstrumental methods. For instrumental methods, one determines the signal-to-noise ratio by comparing test results from samples with known concentration of analyte with those of blank samples and establishes the lowest concentration at which analyte can be reliably detected. A signal-to-noise ratio of 2:1 or 3:1 is required. Another approach is to calculate the standard deviation for analysis of a number of blank samples. The standard deviation multiplied by a factor, usually 2 or 3, gives an estimate of limit of detection.

For noninstrumental methods, DL is determined by the analysis of samples with known concentrations of analyte. The minimum concentration at which the analyte can be reliably detected is the limit of detection. The ICH has recognized