validation in an article titled "How good is your method?" In Sec. 17, definition of validation parameters is based on requirements stipulated in the ICH Guidelines Q2A, Q2B, the FDA Reviewer Guidance, and USP General Chapter <1225>.

Though many types of chromatographic techniques are available, the most commonly submitted method in NDAs and ANDAs is reversed-phase HPLC with UV detection. Therefore this method is selected here to illustrate parameters for validation. The criteria for the validation of this technique can be extrapolated to other detection methods and chromatographic techniques. For acceptance, release, or stability testing, accuracy should be optimized, since the need to show deviation from the actual value is of great concern.

17.1. Accuracy

Accuracy is the measure of how close the experimental value is to the true value. It is measured as the percent of analyte recovered by assay or by spiking samples in a blind study. For the drug product, this is performed by analyzing synthetic mixtures (placebos) spiked with known quantities of drug. Accuracy should be established across the specified range (that is, line of working range) of the analytical procedure. For the assay of the drug substance, accuracy measurements are made by comparison of the results with the analysis of a standard reference material or to compare the results obtained from a second well-characterized independent procedure, the accuracy of which is stated and/or defined. For quantitation of the impurity, accuracy is determined by spiking drug substance or drug product with known amounts of available impurities. In case it is impossible to obtain impurities or degradation products, comparison of results to a second well-characterized independent method is acceptable. The response factor of the drug substance can be used. Another approach is to perform specificity studies by forced degradation. This will be discussed under specificity. It should be decided up front how the individual or total impurities are to be reported, e.g., percent weight/weight or area percent, in all cases relative to the major analyte.

The FDA recommends that recovery be performed at the 80, 100, 120% of label claim as stated in the Guideline for Submitting Samples and Analytical Data for Method Validation (2). Recovery data, at least in triplicate at each level (80, 100, and 120% of label claim) is recommended. The data should be calculated as percent label claim, and the mean of the replicates along with % RSD for each level is reported to demonstrate accuracy and sample analysis precision.

ICH Guidelines Q2B recommend assessment of accuracy at three concentration levels covering the specified range (i.e., three concentration levels and three replicates at each level of the total analytical procedure). The data should be reported as the percent recovery of the known amount added or as the difference between the mean and true values with confidence intervals.

17.2. Precision

Precision is the measure of how close the data values are to each other for a number of measurements under the same analytical conditions. In USP 23/NF 18, General Chapter <1225>, precision is defined as "the degree of agreement among individual test results obtained by repeatedly applying the analytical method to multiple samplings of a homogeneous sample." Thus precision refers to the distribution