Summary - Analytical Test Method Validation - Robustness

This procedure provides guidance for the validation of analytical test methods. These analytical test methods include those tests which evaluate API Raw Materials, In Process samples (e.g. reaction monitoring) and early intermediate materials (prior to the introduction of the first critical intermediate).

Critical parameters effecting response factors, if used in the method, should be identified and characterized during robustness testing.

Parameters that can be used for test method robustness:

Solution Stability Experiments:
It is recommended that sites perform solution stability experiments.

Approach 1:
As directed by the test method, prepare standard and sample aliquots and analyze them. The test samples are allowed to stand, under normal conditions of test (e.g., at room temperature), for a minimum length of time equivalent to the maximum expected use time, (typically 24 hours to one week). Sample and/or standard stability are demonstrated for more than 24 hours if applicable. If possible, analyte stability is demonstrated over a time period that slightly exceeds the stability time period indicated in the test method.

Approach 2:
For standard stability for a low level impurity method, two different stock preparations of equal concentration are prepared (a_1 and b_1) and diluted separately to the same solution concentration (a_2 and b_2). Six (6) injections of standard check solution "a_2" and three (3) injections of standard check solution "b_2" are performed. From each set of injections calculate the mean peak area response for the analyte main peak then calculate the standard check using the following equation.

Check = Mean Area STD "a_2" x Concentration STD "b_2"(µg/ml) x 100
Mean Area Std "b_2" x Concentration Std "a_2"(µg/ml)

Approach 3:
For a chiral HPLC method, solution stability is assessed using an injection and analysis of the sample of the appropriate test material at the following times after preparation.

Approach 4:
For TLC where the sample is required to be analyzed immediately, the standard only is analyzed and the intensity should be the same as at t=0 and the plate should not have new spots.

Approach 5:
For an HPLC method where the standard peak is a retention time marker only, the criteria for solution stability is for the main peak to be present and no new ones eluted. Repeatability studies cover the range of typical sample preparation time therefore sample solution stability is combined with repeatability studies.