

The following example approaches may be considered. The acceptance criteria should be based on the limits' range. The extent of change should not significantly affect the final result. The change should also not affect the decisions made from the data.

#### **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. During this study, solutions are analyzed against freshly prepared solutions. For acceptance a minimum discernible trend in analyte response from initial and final analyses is observed and analyses should agree within reproducibility found for the system precision.

#### **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<sub>2</sub>" and three (3) injections of standard check solution "b<sub>2</sub>" 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.

$$\text{Check} = \frac{\text{Mean Area STD "a}_2\text{"} \times \text{Concentration STD "b}_2\text{"}(\mu\text{g/ml}) \times 100}{\text{Mean Area Std "b}_2\text{"} \times \text{Concentration Std "a}_2\text{"}(\mu\text{g/ml})}$$

Approximately 50ml of standard check solution A is decanted into a flask clearly labeled and stored in a refrigerator (+2 to +8 degrees C). The remaining volume is stored at room temperature. A fresh standard check solution is prepared on the day of analysis and the standard check procedure is repeated for each of the stored standard A solutions against the freshly prepared check solution after a period of 24, 48, 72 hours and 7 days storage. For acceptance criteria, the standard check is between 95% and 105% (any acceptance criteria applied must consider the concentration of the standard solutions under test, for example the acceptance range may vary from a 10ppm solution (0.001%) to a 0.1% solution). Standard stability may be performed over a longer period if necessary.

#### **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.

- 0 hours (i.e., within 1 hour of preparation)
- 24 hours
- 48 hours

Use one of the samples prepared for the precision or robustness studies for the sample stability study, i.e., the first sample injected for the precision study may be used to obtain the  $t = 0$  data-point. Extra time points may be added and some of the tests may fail the expected criteria. However, this is recommended to be explained in the protocol ahead of time. These extra time points are examined to determine at which point the solutions are no longer stable.

#### **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.