

Attribute/Technique	Robustness Considerations
	Effects of particle size between standards and samples.
Titration Methods or KF	Different electrodes Varying amounts of sample Temperature and Humidity of test environment

Solution Stability Experiments:

It is recommended that sites perform solution stability experiments. The results should be analyzed for signs of degradation to determine if the solution is stable for the period that is studied.

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 "a₂" and three (3) injections of standard check solution "b₂" 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)

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- Here repeatability is addressed across different typical sample amounts, intermediate precision is addressed by different analysts and equipment and robustness is shown across typically allowed variations in the method.
- If the method is shown to be reliable across all of these variations, each factor alone does not need to be demonstrated.

Recommended Robustness Criteria:

Changes within the test range whether allowed explicitly or implicitly by the assay should not exceed the previously defined validation parameters for accuracy, precision or specificity. This may be accomplished by evaluation of system suitability parameters that are relevant to the change.

- For example, robustness for limits tests should confirm that variations still cause a pass/fail decision to be unaffected by the change. Multiple preparations below and above the specification can be used to demonstrate the ability of the method to reliably distinguish passing and failing results.

Increased robustness testing during development may provide additional support for an abbreviated System Suitability Testing (SST). If robustness testing is not adequately performed and documented during development and/ or validation, there is more of a reliance on detailed SST, which should be included during the run. A full SST at the beginning of a campaign could be performed, and then repeated periodically throughout the campaign. As a working practice, some sites allow 24 hours validity between SST and running a sample (provided no major changes in instrument operating conditions have been performed within the time period). This allows the laboratory to analyze a series of samples within that 24 hour period without repeating the SST and provides the advantage of allowing a quicker sample turn around in cases where analysis of many samples may be required over a short time period (e.g. when monitoring residual solvent by hourly sampling during drying). The choice of taking this approach should be carefully weighed with the risk of implicating a large amount of data if a system suitability failure were to occur.