

Guidance 003 Analytical Test Method Validation - System Suitability

- Peak symmetry, as measured by the tailing factor, may be of importance to report, especially in impurity testing. If tailing is too extensive, it may mask other impurities. When the tailing factor increases, integration becomes less reliable and precision can be compromised. Peak fronting may also cause integration problems and may become a factor as columns age.
- It is considered that repeatability is normally used as an essential criterion for system suitability testing but this may not be possible for all types of IPC test methods. For example, Area % methods do not require repeatability. System repeatability is regarded as the contribution of the instrumental variability to the precision.
- Demonstration of specificity may be required for certain applications and may involve resolution between two significant peaks, peak efficiency by theoretical plates or peak symmetry by tailing factor. It is recommended that the specificity be demonstrated as part of the SST criteria where variability of sample make up is possible (e.g. for a chromatographic method or TLC method, the sample diluent is prepared on day of analysis or may be of a different batch/lot of solvent to that used during validation). It may be of benefit to demonstrate adequate specificity between the diluent (blank solvent) and the sample solution. This is particularly useful when investigating low-level impurities as the detection and attribution of a novel impurity to the sample may be discounted by its presence in the sample diluent.
- For non-chromatographic testing, the use of control samples or day/ time of use calibration may sometimes be appropriate for some technologies. Examples include but are not limited to KF, LOD (day/time of use calibration), and particle size (control samples).

Other pharmacopoeias should be consulted if required, however, the US Pharmacopoeia recommends that to determine system suitability % RSD, 5 replicate injections if the % RSD is 2.0 or less and if the % RSD is greater than 2.0, six replicate injections are recommended. While the USP recommends the above % RSDs, these criteria may not be adequately low to assure method performance (e.g. when the %RSD of the assay is 1% or when the specification is tight such as 99.0 – 101.0%). Therefore, it may be relevant to consider using the EP Pharmacopoeia recommendation for a tighter % RSD of 1/3 of the specification range to have a 95% confidence that the result is within the limit. The EP recommends that system suitability for repeatability is based on the limit range and number of standards used in the test, where n can vary from three to six.

Recommended SST Criteria:

The acceptance criteria used should assure adequate precision and specificity for the intended use. One approach is to set chromatographic SST criteria based on data collected during a validation exercise. Equivalency may be demonstrated as follows,

- If resolution is no less than 0.8 times of the average typical value; tailing is no greater than 1.3 of typical value; and efficiency is no less than 0.8 times of the average typical value. It is recommended that a sensitivity standard at the 0.05% level for API impurity and degradation methods be utilized.