

Continued Performance Verification of Analytical Procedures Using Control Charts of Empower Chromatography Data Software

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INTRODUCTION

Analytical procedures (methods) are a critical element of the overall quality control to ensure the identity, quality, purity, and efficacy of drug substances and drug products. A method that is used for quality testing of the manufactured product must be validated to demonstrate it is suitable for its intended purpose by meeting the proper standard of accuracy, sensitivity, specificity, and reproducibility. After implementation in a QC laboratory, a validated method should be monitored during its lifecycle to continually assure that it remains fit for its intended purpose.¹

The United States Pharmacopeia (USP) proposed a new general chapter: *The Analytical Procedure Lifecycle* <1220>. It is to introduce a holistic approach to controlling an analytical procedure throughout its lifecycle.² The approach starts with establishing predefined performance requirements for the analytical procedure or the analytical target profile (ATP). Depending on the intended use of the method, the ATP requirements may include the performance criteria such as accuracy, precision, specificity, and linearity. In addition, the quality of the reportable value produced by an analytical procedure, based on the product acceptance criteria, may also be a requirement specified in the ATP.¹

The overall analytical procedure lifecycle approach is based on three stages that include design and development, performance qualification, and continued verification. The first stage, design and development, is built around a series of steps that include procedure development, risk assessment, experimental robustness studies, and knowledge gathering. The design of experiments (DoE) approach is often applied to investigate variables that may affect the performance characteristics of the procedure. The output of the DoE study may be a design space of operational conditions, within which the procedure performance is ensured. In the second stage, performance qualification, method validation is performed to show that the procedure is suitable for its intended use. This is done by conducting a validation study to confirm the procedure generates results that consistently meet the performance criteria defined in the ATP. In the final stage, procedure performance continues to be verified during routine use in the quality control (QC) laboratory to assure that the method remains fit-for-purpose and meets the ATP criteria throughout its lifecycle. Overall, the ATP is a reference point for assessing the fitness of a method throughout all stages of its lifecycle, starting from the development to continued verification.

This white paper describes the use of Empower™ 3 Control Charts to facilitate the continued procedure performance verification stage of the analytical procedure lifecycle approach. Trend analysis of the system suitability results of replicate injections, as well as of the assay results for the related substances of metoclopramide drug substance, are demonstrated using Empower 3 Control Charts. Data from separate chromatographic runs are compared against the predefined performance goals and assessed for any adverse trends. Utilizing system suitability calculation and control charts of the Empower Software streamlines trending analysis of the method

performance characteristics to assure that the method continuously meets the predefined goals, or to predict performance issues before they happen.

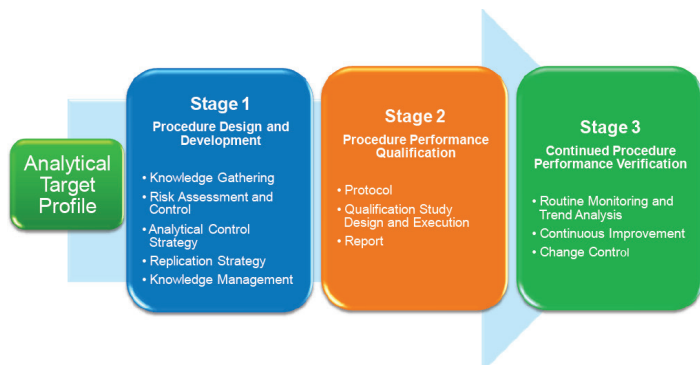


Figure 1. The analytical procedure lifecycle approach as illustrated in the USP proposed chapter <1220>.²

CONTINUED PROCEDURE PERFORMANCE VERIFICATION

Continued performance verification of the lifecycle approach evaluates how the method operates during routine use in a QC laboratory and confirms that the generated data continues to meet the requirements defined in the ATP.

Routine monitoring may include trending of the system suitability data, tracking analytical results of real samples or standards, out-of-specification or out-of-trend investigations, stability trends, or other parameters as appropriate.^{2,3}

The trend analysis of the method performance should be conducted on a regular basis to assure conformance with performance requirements in the ATP. When a method is demonstrated to generate data that meets the performance requirements, it is considered acceptable. However, if frequent modifications of the operating conditions are required to meet the performance goals, or adverse trends are identified, it may be an indication that the procedure is not in control. In this case, an investigation should be performed with a goal of identifying the root cause and taking corrective action. Changes to the method or the control strategy may be required to improve operational performance. Therefore, the method should be reevaluated, revalidated, or amended, as appropriate.¹

SYSTEM SUITABILITY TREND ANALYSIS

System suitability is a regulatory requirement to verify that the chromatographic system is performing as intended at the time of use. As stated in the USP General Chapter, <621> Chromatography, system suitability tests are used to verify that the resolution and reproducibility of the chromatographic system are adequate for the analysis to be done.⁴

Acceptable criteria for the system suitability test are defined as a quality check to ensure that the system functions as expected on a given day and typically include repeatability of the retention times and peak areas, USP resolution between peaks (if there are multiple peaks), and peak symmetry. The peaks of interest are often identified using retention time, therefore it is important that the retention time for a peak is constant throughout the chromatographic run. Setting up a retention time window ensures correct peak identification, while allowing for some variations in mobile phase, batch-to-batch compositions or change in column characteristics. Precision measures the closeness of repeated measurements; therefore, it is an important parameter of the system suitability test to assure confidence in the generated data. Resolution confirms acceptable separation between closely eluting peaks under method operating conditions. For some applications, tailing peaks can have a negative impact on the separation, and decrease sensitivity. Therefore, including tailing factor will ensure that the method performs acceptably over routine use.

Measuring system suitability parameters provides assurance that the method is running as expected at the time of use. The system suitability option of the Empower 3 processing method calculates system suitability parameters according to the guidelines defined by the United States, European, and Japanese Pharmacopeias (Figure 2).

PDA Processing Method

Default Amounts/Purity | Named Groups | Timed Groups | **Suitability** | Limits | Noise and Drift

☒ Calculate Suitability Results

☒ Calculate Suitability Results for Unknown Peaks

System and Separation Efficiency

Void Volume Time (min) 0.300

☐ US Pharmacopoeia ☐ European Pharmacopoeia ☒ All

☐ Japanese Pharmacopoeia

Tangent Percent for USP Resolution 50

Tangent Percent for USP Plate Count 61

☒ Calculate USP, EP, and JP s/n

☒ Use noise centered on peak region in blank injection

Half Height Multiplier for USP s/n Noise Region 5

Half Height Multiplier for EP s/n Noise Region 5

Half Height Multiplier for JP s/n Noise Region 20

Noise Value for s/n

Baseline Noise and Drift Measurements

Maximum Allowable Noise Maximum Allowable Drift

% Run Time Over Which to Average 5.0

Baseline Noise Minimum 30 Seconds

Baseline Start Time (min) Baseline End Time (min)

☐ Calculate Peak Statistical Moments

Figure 2. System suitability option in the processing method of the Empower 3 Software.

System suitability test for each chromatographic run should be conducted as per specifications defined in the individual analytical procedure. When such specifications are not available, performance can be verified according to the system suitability recommendations listed in the USP General Chapter, <621> Chromatography.⁴

In case of a UPLC™ method for related substances analysis of metoclopramide,⁵ the system suitability parameters with the predefined performance goals or acceptance criteria include:

- %RSD of peak areas ≤ 2.0
- %RSD of retention times ≤ 0.5
- USP resolution of ≥ 2.0 between the peaks
- USP peak tailing of ≤ 1.5

Example of the system suitability determination for five replicate injections of a standard solution for a single chromatographic run is shown in Figure 3. The repeatability of retention times and peak areas are excellent. The USP resolution between all components and tailing for each peak pass the system suitability acceptance criteria.

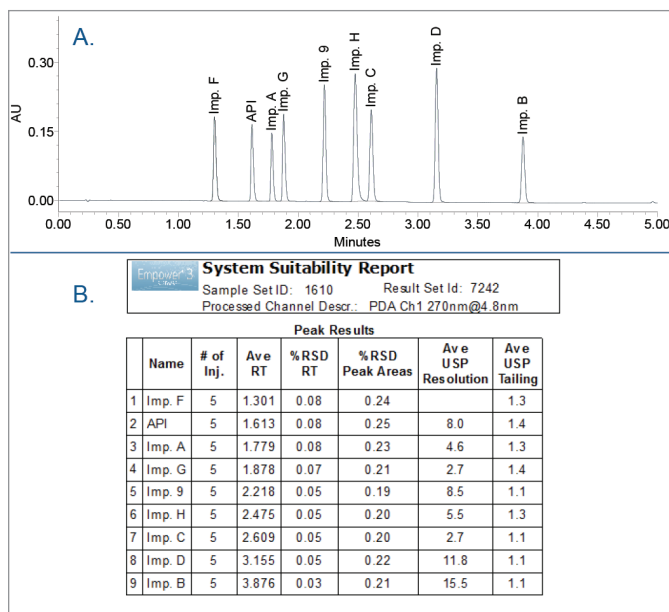


Figure 3. UPLC method for analysis of related substances of metoclopramide drug.. Five replicate injections standard solution at 0.06 mg/mL (A) and system suitability results (B).

When an analytical procedure is implemented in a QC laboratory for quality testing of the manufactured product, it should be monitored during its lifecycle to assure that it continuously meets the predefined performance goals, in this instance, system suitability requirements. The control charts of the Empower Software enable quick and easy data

trending over time against the performance characteristics for any analytical procedure. The Empower Software compares the processed data against the system suitability acceptance criteria defined by the user, flagging any out-of-trend results.

For related substances of the metoclopramide method, control charts of the Empower 3 Software are used to monitor system suitability trending over 20 separate chromatographic runs. Performance target goals for each parameter, lower and upper limits, as well as the warning limits are entered in the "Limit" tab of the Empower 3 Software processing method (Figure 4). These limits include %RSD of peak areas, %RSD of retention times, average USP resolution, and average USP peak tailing for five replicate injections of standard solution. The control charts are then used to evaluate system suitability trending against the predefined limits. Example of trend analysis of %RSD for impurity A peak areas from five replicate injections over 20 separate chromatographic runs is displayed in Figure 5. The performance target, lower and upper limits, as well as warning limit lines are displayed in a plot. The trend plot shows that the repeatability of impurity A peak areas is below the target performance goal, but two of the chromatographic runs reached the upper warning limit. Approaching a warning limit may be an indication that some preventative and corrective action might be needed to prevent getting out-of-specification results. A complete system suitability trend analysis of %RSD of peak areas, %RSD of retention times, average USP resolution, and average USP peak tailing for impurity A (Figure 6) show that all results meet the target performance goals. Using control charts, system suitability trending displayed in a plot enables quick data examination for any out-of-trend results over the lifetime of the analytical procedure.

System Suitability Limits									
Field Name	Target	Error %	Lower Error Limit (LCL)	Upper Error Limit (UCL)	Warning %	Lower Warning Limit	Upper Warning Limit	Ignore Blank Values	Check Limits
1 RSD_PeakAreas	0.000			2.000			1.000	<input checked="" type="checkbox"/>	Always
2 RSD_RetentionTimes	0.000			1.000			0.500	<input checked="" type="checkbox"/>	Always
3 Ave_USP_Resolution			2.000					<input checked="" type="checkbox"/>	Always
4 Ave_USP_Tailing	1.000		0.850	1.500				<input checked="" type="checkbox"/>	Always

Figure 4. Limits for the system suitability parameters defined in the processing method of the Empower Software.

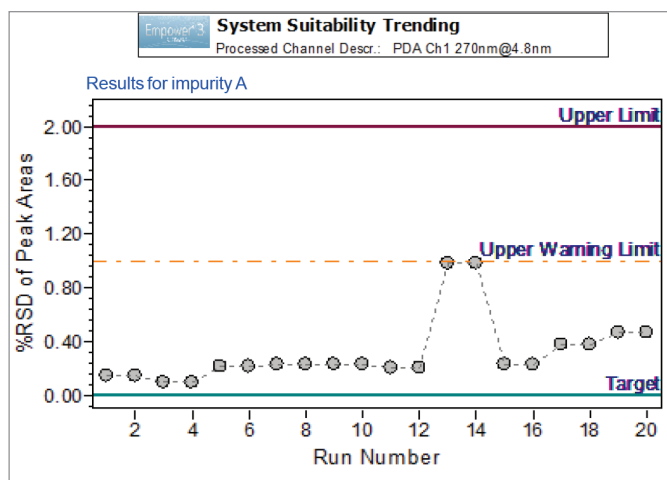


Figure 5. Trend analysis using control chart of the Empower 3 Software showing %RSD for impurity A peak areas from five replicate injections over 20 separate chromatographic runs.

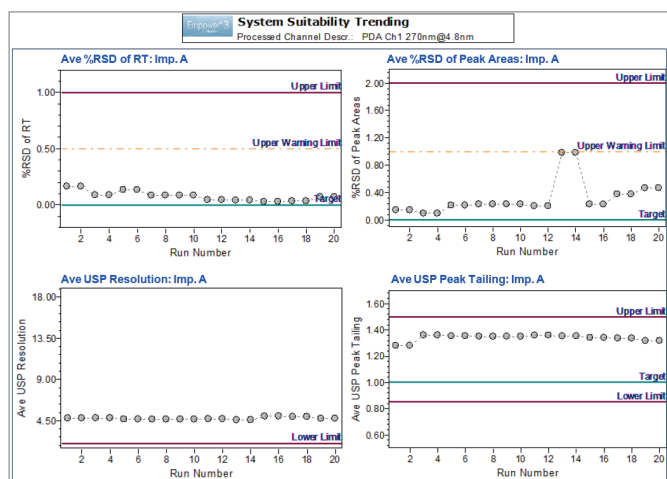


Figure 6. Control charts of the Empower 3 Software for system suitability trend analysis for impurity A from five replicate injections of standard over 20 separate chromatographic runs.

ASSAY RESULTS TREND ANALYSIS

Reportable values generated using qualified analytical procedures via laboratory testing provide the basis for key decisions regarding compliance of the test article with the regulatory, compendia, and manufacturing limits.¹ The laboratory testing is necessary to ensure that the components, containers and closures, in-process materials, and finished products conform to the specifications. Hence, reportable assay results are used to confirm whether the manufactured product meets the prescribed standards for identity, quality, safety, purity, and potency.

Trend analysis of reportable values over the lifetime of the drug product enables a quick identification of out-of-trend results or deviations from the acceptance criteria. Charts visually display the data, which helps to examine patterns, predict likelihood of future out-of-specification results, and suggest corrective measures.

Control charts of the Empower 3 Software facilitate trend analysis of the reportable assay results over separate chromatographic runs against the product specification or acceptance criteria. Trend analysis of the reportable results is demonstrated using assay results for related substances analysis in a metoclopramide tablet sample.⁵ An example of a related substances analysis (% impurity) in a spiked metoclopramide tablet sample is shown in Figure 7. Using the control charts of the Empower 3 Software, the trending is performed over 20 chromatographic runs to examine how the assay results compared to the predefined acceptable limit or specification (Figure 8). For this analysis, the specification includes related substance content (or % impurity) of less than 0.1% (the upper limit) with a warning limit of 0.075% in sample injection. The trend plot clearly indicates results that meet and exceed the allowable limits, respectively. Using control charts, trending reportable results helps to identify results that deviate or exceed specifications over the lifetime of the drug product.

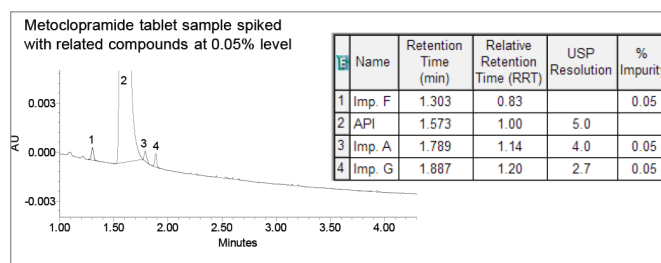


Figure 7. Results for related substances analysis in metoclopramide tablet sample.

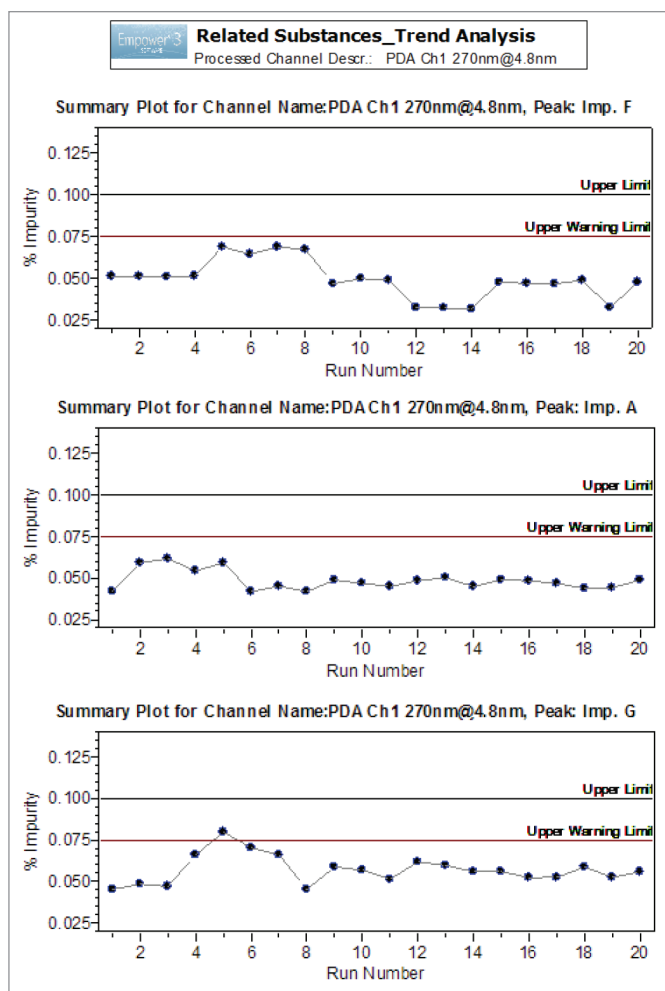


Figure 8. Trend analysis of assay results for related substances content (% impurity) in metoclopramide tablet sample over 20 chromatographic runs.

COLUMN ROUTINE USE

The performance of the LC column may deteriorate over long-term use due to the stress applied by the separation conditions or samples analyzed. When the LC column is used for a specific assay, tracking the injection count and column pressure will help to decide if a corrective action is needed to prevent issues before they happen or when the column is approaching end of life so that a new column should be installed. This may subsequently prevent failures of the sample assay runs or a need to start a new chromatographic run.

As demonstrated in a routine use study of a UPLC assay method for Telmisartan Tablets, a control chart in the Empower Software is used to display system pressure trending over 3000 injections of standard and tablet preparation solutions on a single column lot.⁶ The system pressure monitored for a routine use study shows slight increase in overall system pressure at approximately 2100

injections (Figure 9). This increase indicated a need to wash the column, which regenerated and returned it to the original operating conditions.

Monitoring other parameters such as column theoretical plates, USP resolution, and peak tailing in control charts may also help to predict whether a corrective action is needed to prevent problems or for how many injections is a column expected to last. Overall tracking column performance characteristics over routine use will help to reduce instrument downtime caused by column failures, hence improve routine QC laboratory efficiency.

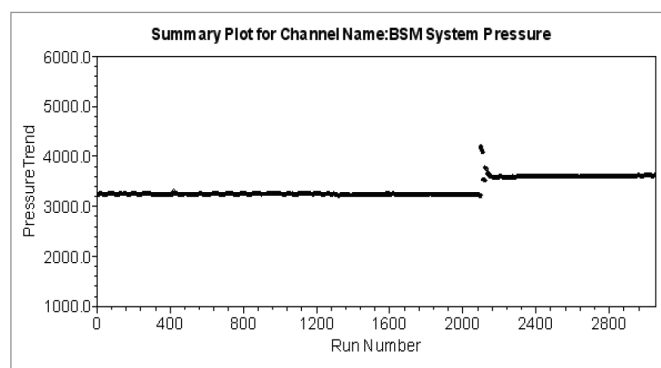


Figure 9. System pressure trend analysis for routine use over 3000 injections on the ACQUITY™ UPLC HSS T3 Column.⁶

CONCLUSION

Continued performance verification of the analytical procedure lifecycle approach routinely examines performance data of a method over its lifecycle. Therefore, large amounts of data must be reviewed to confirm that the method continuously meets the performance goals. Trending using control charts visually displays the data and the target performance goals, which helps to quickly identify patterns and out-of-trends results that may go unnoticed when using summary reports.

Control charts from the Empower 3 Software provide graphical representation of the performance characteristics data trends over time. They provide an easy way to perform trend analysis of data generated by a method, which allows quick identification of any out-of-trend results or deviations from the performance goals. This helps to predict any potential performance problems or take preventive and corrective actions before a major problem occurs. Whether examining system suitability trending, column performance characteristics, or reportable results for a specific product, Empower control charts will help to assure that a method continuously generates fit-for-purpose results.

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