QUALITY CONTROL REFERENCE MATERIAL AND BENCHMARKING INSTRUMENT PERFORMANCE

Use of Quality Control Reference Materials

The purpose of this paper is to address the use of a specific type of Reference Material called Quality Control Reference Materials (QCRMs). The rationale for using these QCRMs is establishing quantitative benchmarks for a particular analytical system. The proper use of these materials provides documenting mechanisms to track variances of a analytical and chromatographic system. One of the strongest tools for a chemist is control charting. Control charting can be performed using specific sets of reference materials designed, by Waters, per instrument, to help chemists identify and understand the significance of variances in their data. From previous papers we established the following important definitions surrounding "reference materials":

Reference Material – (RM) material, sufficiently homogeneous and stable with reference to specified properties which has been established to be fit for its intended use in measurement or in examination of nominal properties.

Certified Reference Material – (CRM) reference material, accompanied by documentation issued by an authoritative body and providing one or more specified property values with associated uncertainties and traceabilities, using valid procedures.

Quality Control Reference Material – (QCRM) reference material that is precisely formulated, accurate, consistent from lot to lot, and specifically designed for instrument performance checks including control chart analysis of chromatographic indicators. May be documented as a Certified Reference Material.

WHY YOUR REFERENCE MATERIAL CHOICE MATTERS

Reference Material analyses provide information about the performance of analytical instruments. Control charting of the data associated with Quality Control Reference Materials analyses allows for quick visibility of instrument performance and prevents the use of arbitrary criteria in determining whether or not the performance indicators are in control. In addition to providing real-time instrument performance data, control charting provides visibility into potential problems and allows for proactive maintenance and the implementation of preventive actions.

One of the keys to generating valuable control charting data is using a reference material that is accurate, consistent from lot to lot, and appropriate for the analyses being conducted. The quality of the reference material is paramount to the evaluation of the analytical data and the instrument performance. It is critical to understand the uncertainty for the parameters of interest of the reference material. This will allow you to understand whether or not an observed variance originates from the tolerances of the reference material or, more often, from an unexpected system variance. When observed system variability well exceeds any variation associated with the manufactured reference material, investigation of the system is warranted.

The most powerful way to use these Quality Control Reference Materials is analyzing them routinely on an analytical or chromatographic system and then control charting the critical results.This current and historical data and identifies areas of excess variability warranting concern.

DEVELOPING A CONTROL CHARTING PROGRAM

The first step in establishing a control charting program is defining the performance indicators to be tracked and sourcing an appropriate reference standard. Using high performance liquid chromatography (HPLC) as an example, common instrument performance indicators are peak width or peak area, retention time, and peak resolution. Each of these parameters can be tracked and evaluated in real time by control charting the results of the analysis of an appropriate reference standard. In the case of retention time monitoring, Waters' Neutrals Quality Control Reference Material (P/N 186006360) is appropriate for most analytical chromatographic systems using UV detection.

Establishing the frequency for reference material control charting is a function of risk analysis and understanding the stability of the analytical system being monitored. When control charting identifies an out of control situation, all data generated back to the last documented in-control point on the control chart is in jeopardy.[1] If many analyses have been conducted between the two sets of reference material data, all of that data may have to be recalculated or even invalidated, which can be a very expensive proposition. Control charting in analytical chemistry is a fairly easy and inexpensive process, as compared to the destructive testing of a product in a manufacturing environment, many labs will analyze and control chart reference standards on a daily basis. At a minimum, control charting should be done after each calibration or maintenance to the instrument.

A control charting program should be established for each instrument and set of analytical conditions. Comparing data from multiple instruments that may have different operating conditions and are undergoing maintenance at different times can lead to a loss of sensitivity in the control charting process and potential unrecognized problems. Additionally, where multiple analysts are routinely operating an instrument it is ideal to have a control chart for each analyst. If personnel-specific control charts are unfeasible, it is critical to use multiple analysts' data to establish initial control limits.

Control Charting Process

Control charting data is generally collected in a spreadsheet software program such as Microsoft Excel. Each time the reference material is analyzed, the data for the performance indicator(s) being tracked should be entered into the spreadsheet along with the analysis date. Figure 1 shows an example table of retention time data being tracked over a period of five consecutive days at three injections per day.

Figure 1: Reference Material Retention Time Data Example

		Acetone	Naphthalene	Acenaphthene
Day	Injection	Retention Time		
day1-1	7	0.33	1.63	2.89
day1-2	8	0.32	1.62	2.86
day1-3	9	0.33	1.64	2.89
day2-1	16	0.32	1.64	2.90
day2-2	17	0.32	1.64	2.90
day2-3	18	0.32	1.64	2.90
day3-1	25	0.32	1.63	2.90
day3-2	26	0.33	1.64	2.90
day3-3	27	0.33	1.64	2.91
day6-1	34	0.32	1.64	2.88
day6-2	35	0.32	1.64	2.88
day6-3	36	0.32	1.62	2.86
day7-1	43	0.32	1.62	2.88
day7-2	44	0.32	1.62	2.90
day7-3	45	0.32	1.63	2.89

Using the data contained in the table, the mean and standard deviation of the data should be calculated.

Mean is calculated as: $\bar{x} = \frac{\Sigma x}{n}$

Where n = the number of measurements, and

x = results of each individual measurement

The formula for the sample standard deviation is: $s = \sqrt{\frac{\Sigma(x\text{-}\bar{x})^2}{n\text{-}1}}$

Once at least seven data points have been collected, the mean and standard deviation of the data should be calculated for each performance indicator. Using the mean and standard deviation, warning and control limits can be calculated. The data used to initially calculate limits can be gathered over a condensed time frame to speed up the use of the control chart, but the data should be collected over at least a few days, and using multiple analysts unless analyst-specific control charts will be generated.

Warning limits are generally set to the mean plus and minus two standard deviations and control limits at the mean plus and minus three standard deviations. The formulas for calculating upper and lower warning limits (UWL and LWL) and upper and lower control limits (UCL and LCL) are shown below.

$UWL = \bar{x} + 2s$

$LWL = \bar{x} - 2s$

$UCL = \bar{x} + 3s$

$LCL = \bar{x} - 3s$

Using the data in figure 1, the following results are calculated.

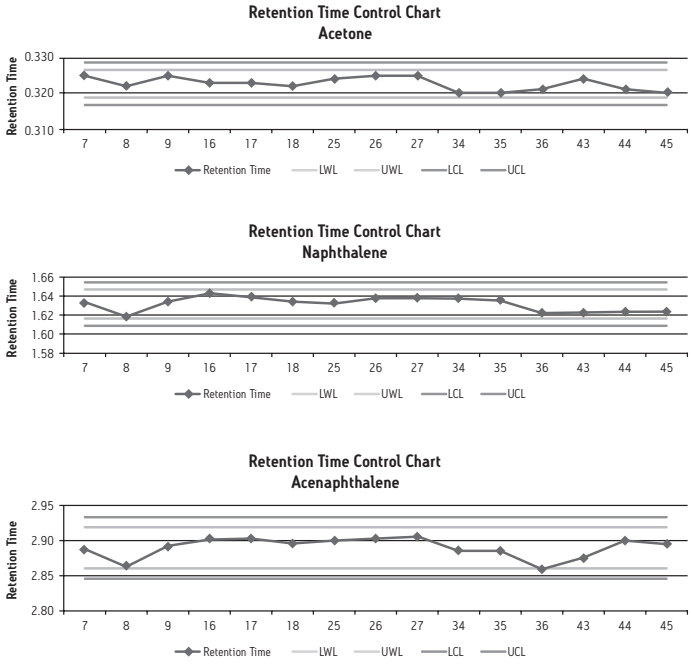
Figure 2: Example Control Chart Limit Calculations

	Acetone	Naphthalene	Acenaphthene
	Retention Time (minutes)		
Mean	0.32	1.63	2.89
Standard Deviation	0.00	0.01	0.01
%RSD	0.58	0.45	0.49
LWL	0.32	1.62	2.86
UWL	0.33	1.65	2.92
LCL	0.32	1.61	2.85
UCL	0.33	1.65	2.93

Data Evaluation

A graph with time as the independent variable and instrument response as the dependent variable should be created using the data generated by the analysis. Lines should also be added to indicate the warning and control limits calculated from the data. The control chart created using the data from this example, with its associated limits, is shown in figure 3.

Figure 3: Retention Time Control Charts for each component



Each time a new data point is added to the spreadsheet, the graph should be updated to show its location relative to the limits. If the newest data point is within the warning limits, this is an indication that the instrument is in control. When a data point falls outside of the warning limits, but is still within the control limits, this is an indication that the data is beginning to trend toward being out of control. A single data point between the warning and control limits does not generally require corrective action, but an investigation into possible causes should be completed. The data may be indicating, for example, that the analytical column, or some other replaceable item, is nearing the end of its useful life, and being able to anticipate this based on the control chart data can save time and money. If there are two consecutive points between the warning and control limits, an investigation should always be performed and corrective action implemented. If a result falls outside of the control limits, all data generated back to the last in-control data point needs to be reviewed to have its validity determined and corrective action must be implemented and verified prior to using the instrument again.

SUMMARY

Control charting the results of Quality Control Reference Materials specifically designed for the analysis of critical instrument performance indicators allows for real-time evaluation of instrument performance. By frequently monitoring their analytical instruments in this way, labs can significantly reduce system down time and prevent costly data errors. Choosing an appropriate frequency, selecting a reference material that is consistent from sample to sample and lot to lot, and appropriate for the analysis being conducted, are all critical aspects of a successful control charting program.

The power of using standards of known traceability and uncertainty as part of this process allow the variations to be documented with confidence and defensibility. When the parameters of interest are well defined and consistent, decisions to continue analysis, to review data or to abandon an analytical run can be made quickly with supporting information to justify the prompt decision.

This concept can be expanded beyond a single instrument to multiple instruments in a single laboratory or to multiple facilities so long as the same source of reference material is used. Using single source reference materials opens the door for making intra and inter-laboratory data comparisons. In today's global manufacturing environment these data comparisons become more important and now with Quality Control Reference Materials designed only for this purpose, possible.

References

1. Taylor, J.K., "Quality Assurance of Chemical Measurements", Lewis Publishers, 1987
2. Smith, G.M., "Statistical Process Control and Quality Improvement", 3rd edition, Prentice Hall, 1998
3. Ahuja, S. and Dong, M.W., "Handbook of Pharmaceutical Analysis by HPLC", Elsevier Inc., 2005

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