Quality control of pharmaceutical drugs—Turning analysis and performance data into comprehensible charts

Application Note

Pharmaceutical

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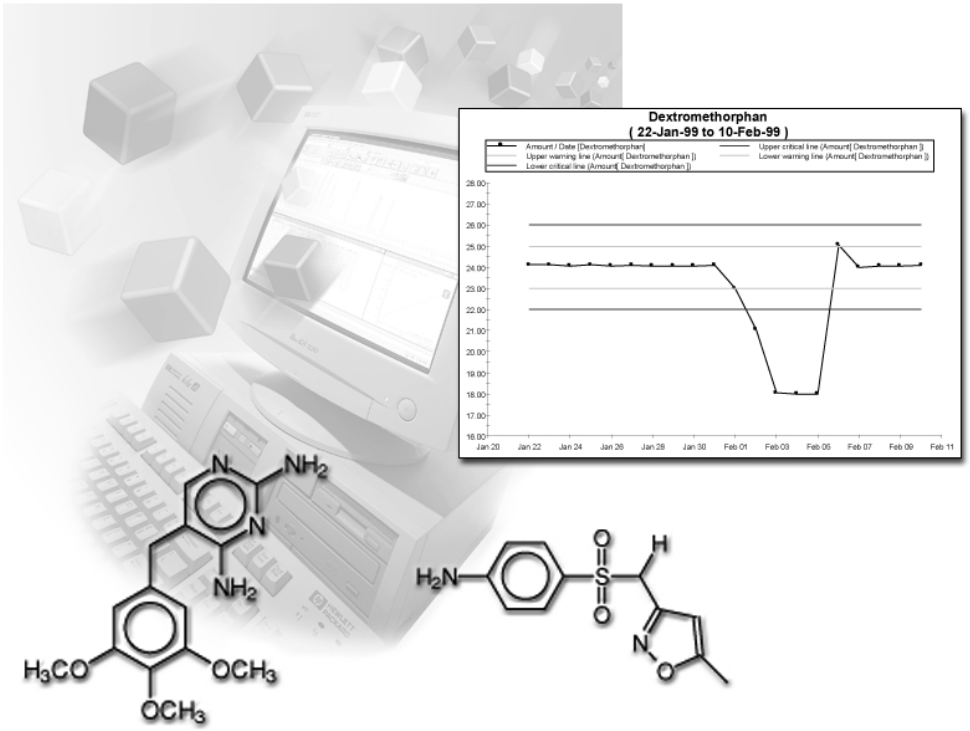

Abstract

Agilent ChemStore C/S, the database module of Agilent ChemStation Plus, offers a solution to evaluate, organize, manage and report chromatographic results imported automatically from LC, LC/MSD, CE, GC and A/D systems. In this application note we describe how Agilent ChemStation Plus helps turn chemical analysis data and peak and instrument performance data into clear and comprehensible results for a typical task of a pharmaceutical company—quality control of instruments and products.

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Introduction

Quality Control (QC) is an important task in the pharmaceutical industry. It not only protects the manufacturer against compensation claims, but also guarantees the patient a safe and effective product. QC measurements include stability testing of the drug formulation, dissolution testing[1] and analysis of raw materials and synthesis products.

A pharmaceutical company usually has to measure a large number of QC samples. They need to be evaluated and reviewed, and the data must be safely stored for quality and regulatory compliance. Furthermore, instrument performance has to be monitored to avoid erroneous results caused by column aging, for example. In this application note we demonstrate how Agilent ChemStation Plus1[1,2,3] in combination with the Agilent 1100 Series HPLC system can help increase lab productivity by turning chemical analysis data into clear and easily understandable charts.

Agilent ChemStation Plus

QC measurements generate a large amount of chemical data. To receive clear and understandable reports or charts analysts have to manually transfer the results of the collected data to a spreadsheet application. This is a slow, tedious and error-prone process. Agilent ChemStation Plus provides the capability to transfer, manage and report the QC data automatically and error-free. Furthermore, it provides secure data storage and a consistent link between analytical method, raw data and final results. Therefore, it is easy to show auditors how the results were generated.

Other features include:

- Review of the retrieved data online to inspect analysis results. The results can be approved or rejected and sent back to the Agilent ChemStation Plus.
- Data is organized by setting up studies containing custom fields, which map the studies' structure to the results.
- Data sets can be retrieved quickly and easily using an intuitive query function.
- Summary or regression statistics can be performed on the analytical data. The results can be displayed in tables or charts.

Equipment

The system consisted of an Agilent 1100 Series quaternary pump, an Agilent 1100 Series autosampler, an Agilent 1100 Series thermostatted column compartment and an Agilent 1100 Series variable wavelength detector. It was controlled using the Agilent ChemStation (version A.06.04) software. Data was stored using the Agilent ChemStation Plus database client software (version B.01.01). *Extended Performance* was set up as report style in the *Specify Report* window and the settings were saved with the method.

The chromatographic conditions are listed below.

Column:	Zorbax SB-C18 4.6 x 75 mm, 3.5 µm
Mobile phase:	A = 0.025 M KH_2PO_4 in water, pH=3 (H_3SO_4) B = acetonitrile
Gradient:	at 0 min 10 % B at 10 min 30 % B at 11 min 10 % B
Flow rate:	1 ml/min
Stop time:	11 min
Post time:	5 min
Column temperature:	40 °C
Injection volume:	5 µl
UV detector:	variable wavelength detector 204 nm, standard cell

Results and Discussion

Model scenario

A pharmaceutical company produces a cystits tablet containing sulfamethoxazole and trimethoprim. Five batches are produced daily and sent to the analytical lab for QC analysis with the Agilent 1100 Series HPLC system controlled by the Agilent ChemStation Plus. *Sample Type* is set to *Sample* in the *Sequence Table* of the Agilent ChemStation Plus. In addition to the five samples a control measurement with a standard is performed every day. It is set up as *Control Sample* in the sequence table. The measured data are transferred automatically to the Agilent ChemStation Plus to manage, report and store them securely.

Monitoring analysis results and analysis performance parameters

The chemist in the analytical lab performs measurements and sends the result to the supervisor. If a result is beyond the QC limits the analyst has to find the reason for the erroneous result. This can either be a process problem or an analytical problem such as low instrument performance or column aging. To minimize the second possibility it is very helpful to monitor analysis and instrument performance parameters over a certain period of time. If, for example, an analysis result is beyond the QC limits but all instrument and analysis performance parameters for the same measurement are within the specified ranges it is very likely that a low quality synthesis product is the reason for the measurement. If the analysis results and the performance parameters are beyond the limits, the problem is probably caused by the instrument or the column.

Another advantage of monitoring analysis results, analysis performance and instrument performance parameters offers, is the possibility to recognize trends. If, for example, column performance decreases the tailing factor increases. The column can now be replaced before a complete column breakdown occurs. This helps prevent instrument downtime.

For these reasons the following parameters are monitored over a certain period of time:

- Analysis results containing lower and upper limits for the amounts of the two compounds.
- Analysis results for the control samples with mean value and relative standard deviations.
- Performance results for analyses such as peak performance parameters, tailing factor and selectivity. These results are used to monitor the system and the column to ensure they are working properly.
- Instrument parameters, for example, pump pressure. Instrument parameters are monitored to make sure the system is working properly. If the pump pressure increases, it may be necessary to exchange the PTFE frit in the purge valve.

Presentation of analysis results

To perform the analysis of the QC measurements the results are loaded into the Agilent ChemStation Plus by a query including the whole study. To separate the samples from the control samples two filters are created. The filter condition of the first filter is set to *Sample* in the result field *Sample Type*, and for the second filter it is set to *Control Sample*. By turning on the appropriate filter, it is easy to analyze the results for either the samples or the control samples respectively.

The charts shown in figures 1a and 1b are generated for the two active compounds in *Chart Layout* of the *Compound* view.

The compound amounts are shown on the y-axis. Upper and lower warning lines and critical lines are also displayed for easy control. The limits are fixed values given by the QC requirements. On May 25, for example, the amount of trimethoprim almost reached the upper warning limit of 45 mg/l. For the x-axis, the time axis, a custom field *Date* in the format *Date/Time* was used. Other time fields, such as *Injection Time*, could also have been used.

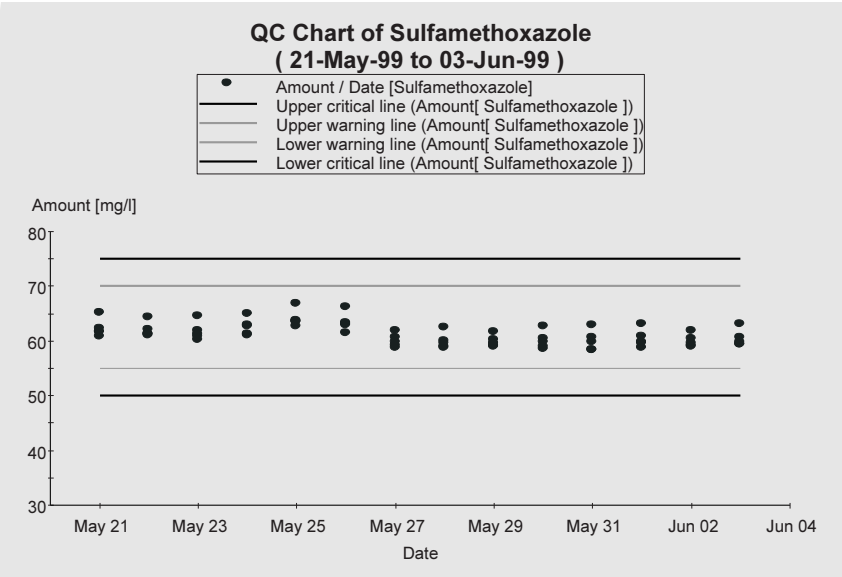

Figure 1a
Amount of sulfamethoxazole–daily analysis results for five batches

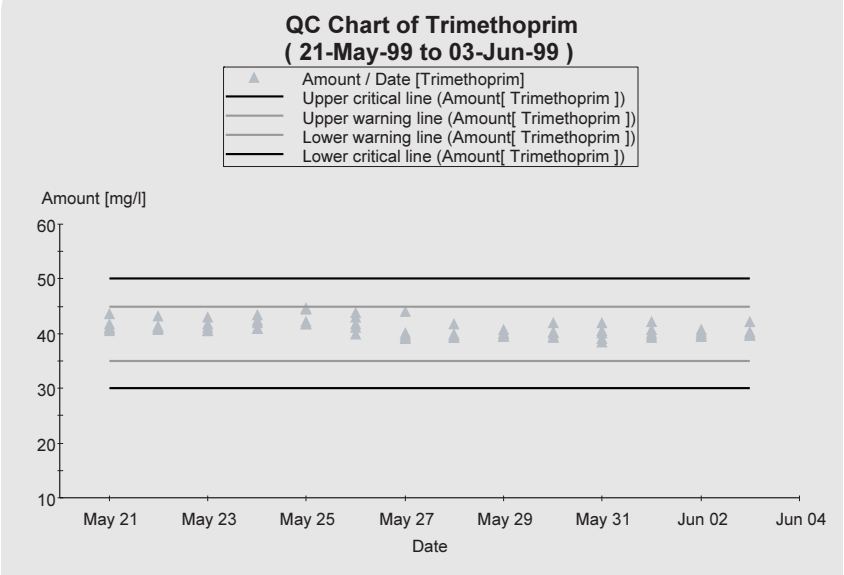

Figure 1b
Amount of trimethoprim–daily analysis results for five batches

To check the performance of the analysis the next two charts are generated for the control samples (figures 2a and 2b).

For the control charts the control sample amount is displayed against the measurement date. The center line is the mean value of the measurements. The lower and upper warning limit is the mean value ± 2 σ, which is twice the relative standard deviation. The upper and lower critical limits are ± 3 σ. These limits are again given by the QC requirements of the company.

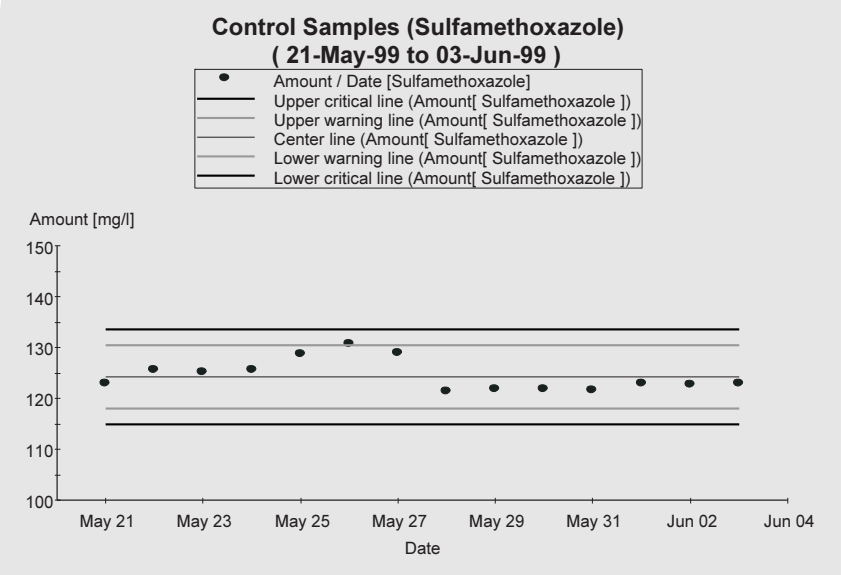

Figure 2a
Amount of sulfamethoxazole control samples

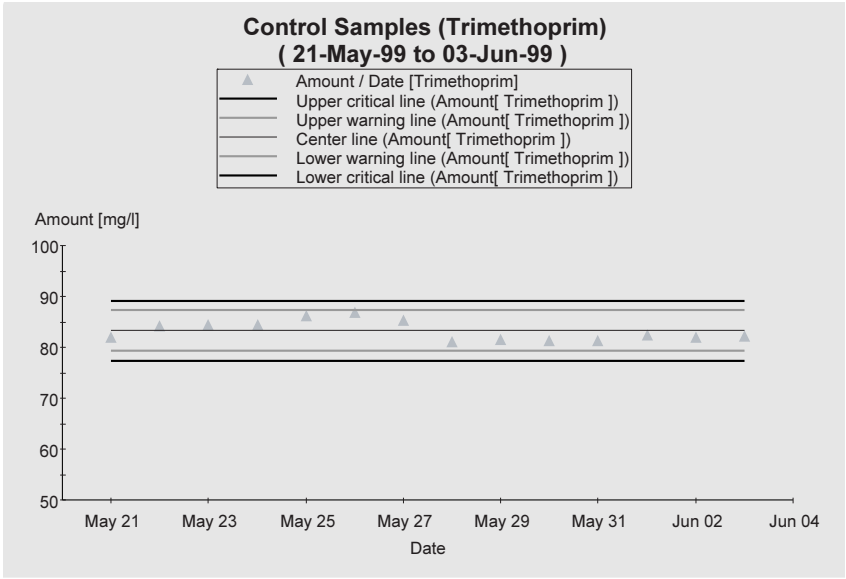

Figure 2b
Amount of trimethoprim control samples

Peak performance results

For the performance results of the analysis the following peak performance parameters are displayed in charts:

- peak symmetry
- tailing factor
- resolution
- selectivity

The symmetry of a peak should be around one. For a tailing peak it is higher than one, for a fronting peak it is lower than one. An unsymmetrical peak can indicate bad column performance. Figures 3a and 3b show the symmetry of the two peaks in the analysis

Figure 3a shows that the symmetry factor for the sulfamthoxazole peak is around 0.75. The peak is fronting but the values are relatively constant over the monitored time period. The symmetry factor for trimethoprim shown in figure 3b is around 1.05, which means the peak is slightly tailing. Some values are beyond the warning limit of 1.15. The warning and critical limits are compound specific fixed values.

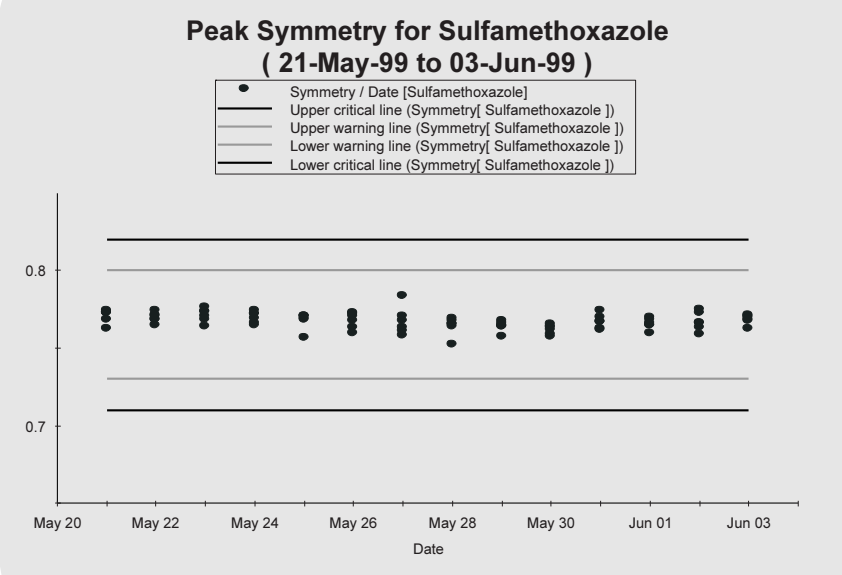

Figure 3a
Peak symmetry of sulfamethoxazole peak

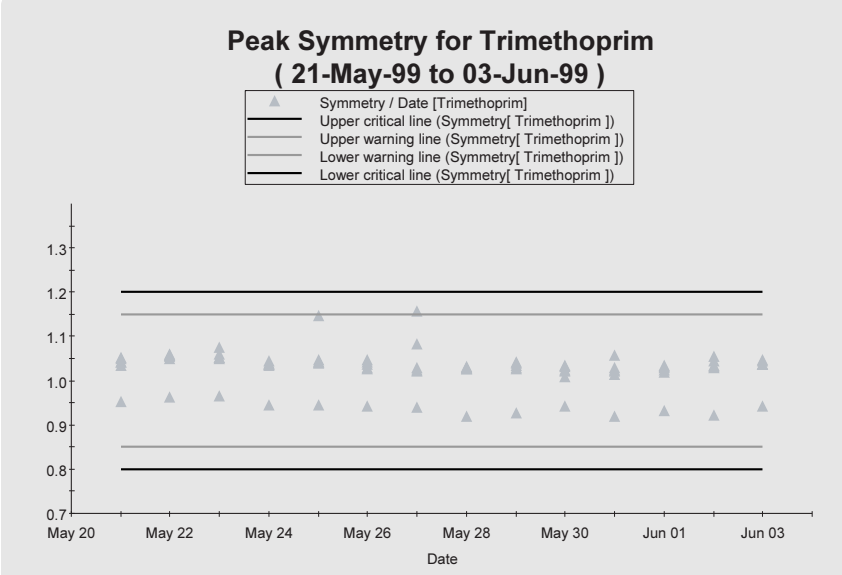

Figure 3b
Peak symmetry of trimethoprim peak

The tailing factor also describes the symmetry of a peak. It can be calculated by a formula given by the USP. Figures 4a and 4b show the tailing factors of the two peaks in the analysis.

The tailing factors of sulfamethoxazole and trimethoprim are about 1.3 and 1.1, which means the peaks are only slightly tailing. An absolutely symmetrical peak would have a tailing factor of 1. The warning and critical limits are fixed values given by the QC requirements of the company.

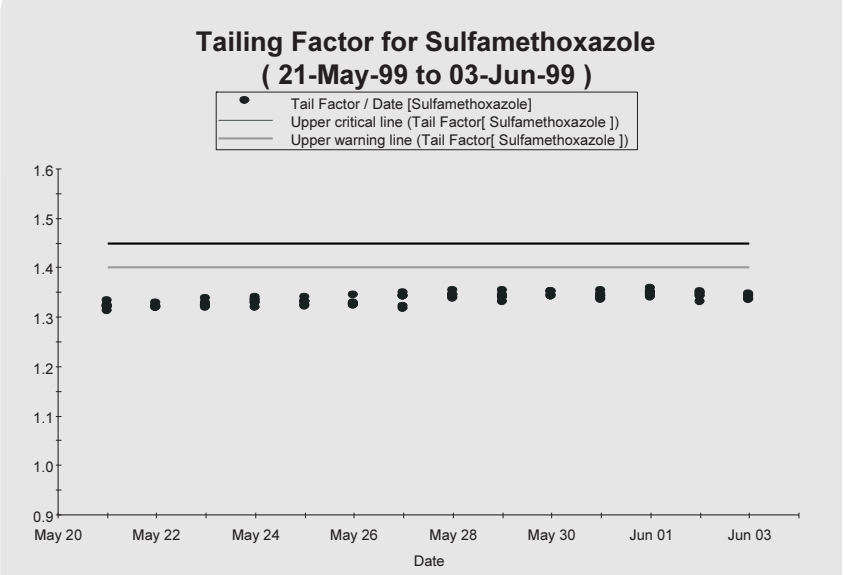

Figure 4a
Tailing factor of sulfamethoxazole peak

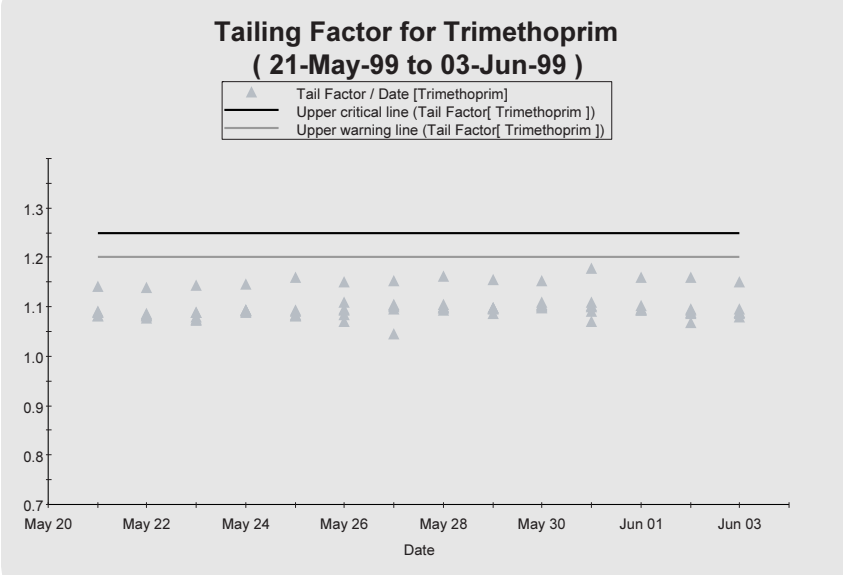

Figure 4b
Tailing factor of trimethoprim peak

The resolution describes how well two compounds are separated from each other. Figure 5 shows the resolution at the peak halfwidth of sulfamethoxazole.

Another parameter for the separation of the peaks is selectivity. Figure 6 shows the selectivity of sulfamethoxazole.

The selectivity for sulfamethoxazole is about 1.9. If it falls below a certain value (1.85 in figure 6), this may indicate that column performance is decreasing.

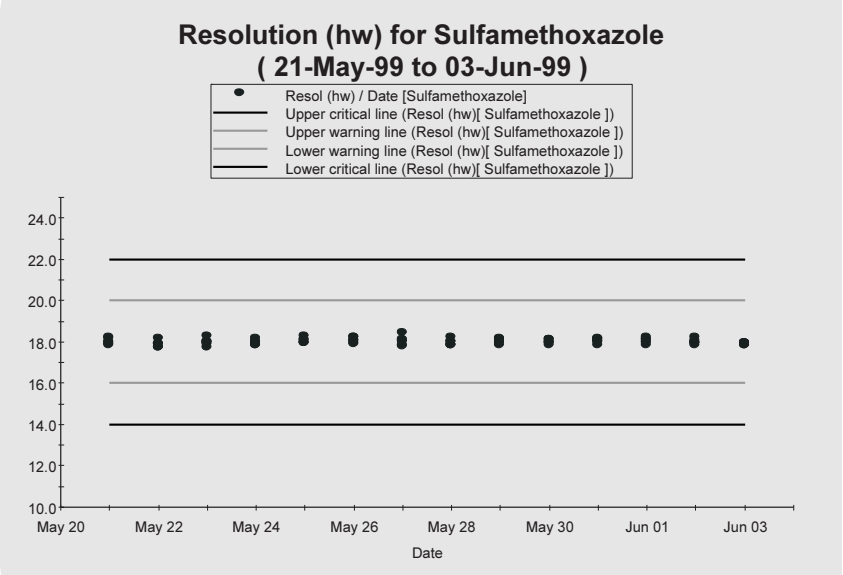

Figure 5
Resolution of sulfamethoxazole peak

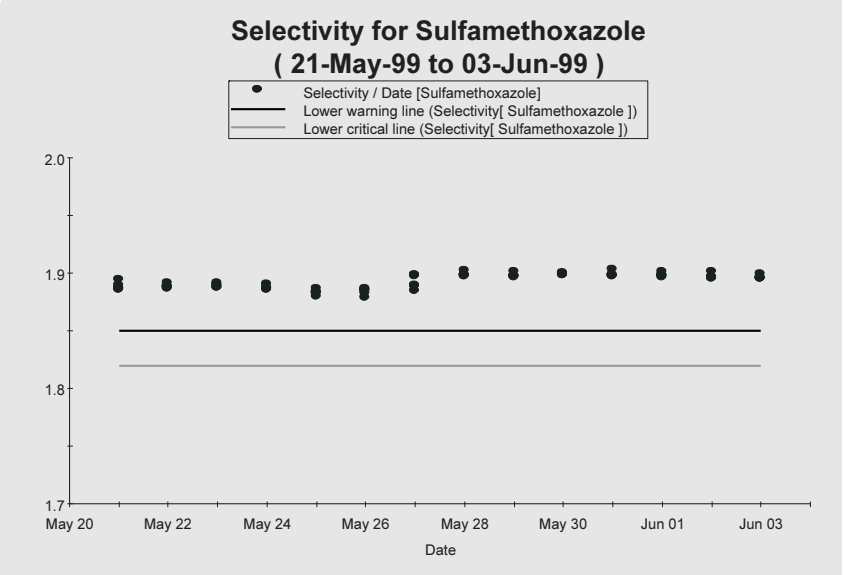

Figure 6
Selectivity of sulfamethoxazole peak

Instrument parameters

The instrument parameters should be in a certain range over all analyses to make sure that no instrument errors lead to wrong analysis results. Instrument parameters selected for instrument performance control are:

- pump pressure
- pump flow
- column temperature

Figure 7 shows the pump pressure for each analysis.

An increasing pump pressure may indicate that a filter, for example, the PTFE frit in the purge valve, the solvent inlet filter or the frit of the column needs to be cleaned or replaced.

Another instrument performance parameter is the pump flow as shown in figure 8.

A decreasing or increasing pump flow could indicate a defective pump. Figure 8 shows that the pump flow for the Agilent 1100 Series quaternary pump is very stable.

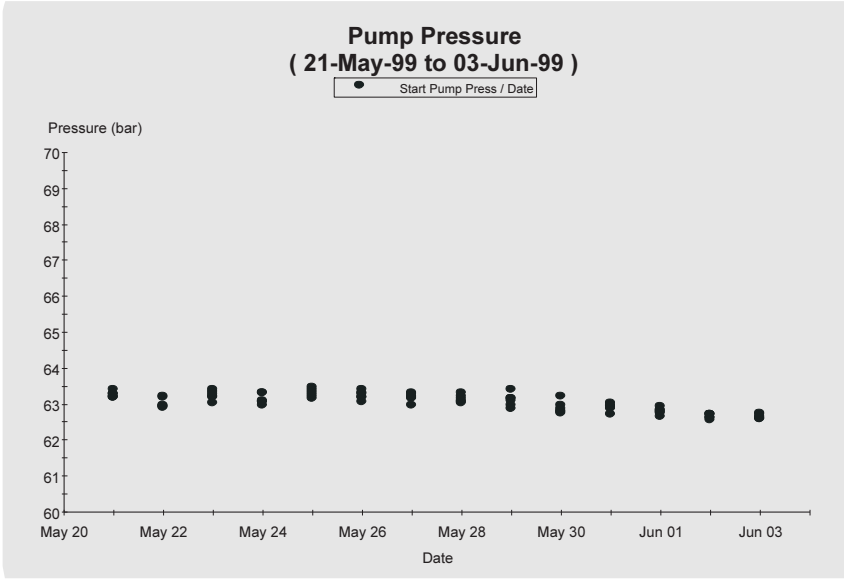

Figure 7
Pump pressure

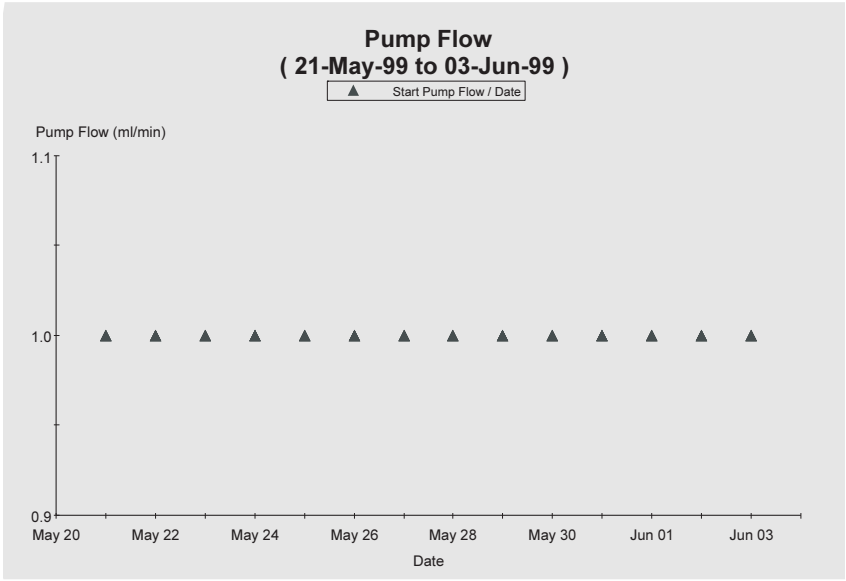

Figure 8
Pump flow

The last monitored instrument parameter was column temperature.

Column temperature has an influence on other instrument parameters, for example, pressure, and analysis parameters, such as retention time or peak width. Although the Agilent 1100 Series thermostatted column compartment provides an excellent temperature stability it is always recommended to monitor this parameter to prevent erroneous analysis results (figure 9).

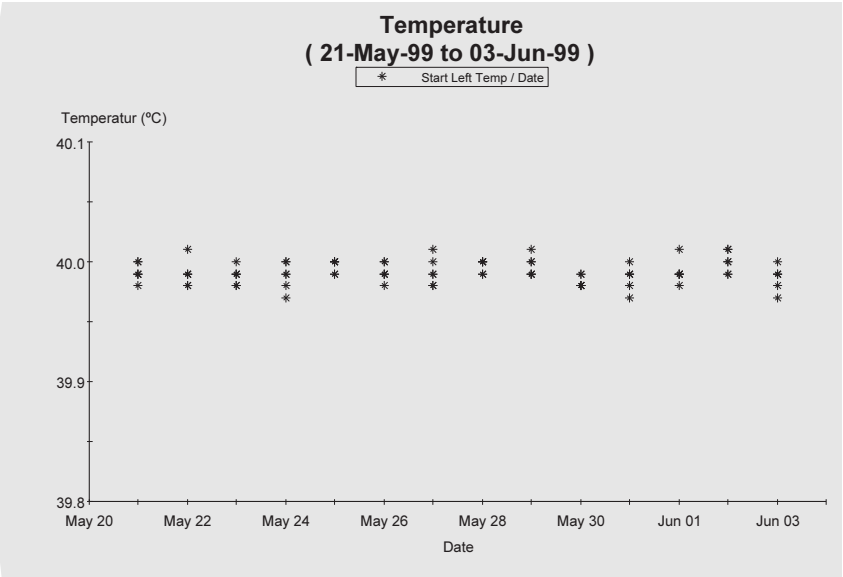

Figure 9
Column temperature

Conclusion

In combination with the Agilent 1100 Series the Agilent ChemStation Plus is an optimal tool for QC measurements for the pharmaceutical industry. It allows simultaneous monitoring of the analysis results and instrument performance during an analysis, without tedious and error-prone manual result transfer to a spreadsheet application.

With *Extended Performance* set up as *Report* in the Agilent ChemStation Plus, it is no longer necessary to change the method or perform multiple runs to get all results. The results are displayed in a clear format as tables or charts, which can be either copied to other Microsoft Windows® applications or can be implemented into customized reports. The results can be stored safely and are always traceable which is a big advantage in case of an audit.

Literature

1
"Drive down costs and raise productivity" *Agilent Technologies Brochure Brief*, **1999**, publication number 5968-4782E

2
"Agilent ChemStation Plus" *Agilent Technologies Specifications*, **1999**, publication number 5968-4782E

3
"From data to decisions" *Agilent Technologies CD-ROM*, **1998**, publication number 5968-1713E

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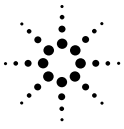

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