PLA 3.0

# CONTROL CHART PACKAGE
## GETTING STARTED GUIDE

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STEGMANN SYSTEMS

PLA 3.0

# Contents

# 1 Introduction

Welcome to the Getting Started Guide of the Control Chart Package.

This guide gives a general overview of this add-on and describes the basic concepts as well as standard use cases. It is intended for users who want to learn how to work with this add-on.

**Note:** It is assumed that users are familiar with the general handling of the PLA 3.0 user interface.

# 2 About the Control Chart Package

The Control Chart Package allows sophisticated statistical process control by plotting Shewhart I-Charts as recommended in the USP <1010>. It provides visualization options for intervals, subcharts and sidecharts, and allows you to define colors by a secondary characteristic. You can also define rules based on events and time frames.

The following list highlights the USP <1010> methods supported by the Control Chart Package:

- **Parameter statistics.** The Control Chart package automatically calculates the following parameter statistics for each data series: mean and median, standard deviation (SD), coefficient of variation (CV), 1st and 3rd quartile, min. and max. values, number of values, and missing values. The statistics are displayed on the Dashboard and in the reports.

  In addition, you can configure confidence intervals and sidecharts to deeply analyze your data.

- **Individual chart (I-Chart).** I-Charts monitor data such as measurements and regression parameters at regular intervals, with each data point within the chart representing a sample or an observation respectively.

  All charts generated by the Control Chart package are I-Charts. You can manually add the chart data, or aggregate it from other PLA 3.0 documents such as Quantitative response assays or Dose-response assays.

- **Control limits.** Control limits define a range of acceptable values, determined by an upper and a lower limit. Any value outside of this range is considered to be a rule violation and needs to be marked as such.

  Use the Control Chart Package to set up rule sets with independently defined upper and lower control limits. These rules will be drawn as horizontal lines on your control chart.

- **Nelson & Western Electric Company (WECO) rules.** These decision rules allow detecting out-of-control or non-random conditions on control charts, based on deviations from the mean. They are also capable of detecting patterns or trends. For example, you can apply Nelson rule 3 to detect when six (or more) points in a row are continually increasing (or decreasing).

  The Control Chart Package provides a set of predefined control rules (Nelson rules 1 to 8 and WECO rules 1 to 4) and also allows you to set up user-defined rules. You can also base control rules on parameter statistics of historical data. In contrast to control limits, where the limits can be defined independently, a control rule automatically applies to both the upper and the lower limits.

- **Calculation of the standard deviation.** USP <1010> recommends calculating the standard deviation using differences between consecutive data points instead of comparison to the overall mean.

  The Control Chart Package supports both methods for estimating the standard deviation.

To illustrate how you can use the Control Chart Package in connection with these methods, we provide sample documents you can download when activating the Control Chart Package add-on in PLA 3.0. Additional information about each sample document is provided in the document's Comment section.

# 3 Installation

The Control Chart Package is delivered as an add-on to the PLA 3.0.5 framework and does not require a separate installation. To make the functionality of the Control Chart Package available for use, you have to activate the add-on in your database.

**Important:** The current version of the package is a technology preview. It has not been released yet and has not been finally qualified for use in a productive system. We recommend activating the package in test environments only.

## Procedure

To activate the add-on:

1. Log in to PLA 3.0.5.
2. By default, you can use only components that have been released for use in a productive system. To activate a technology preview, you have to allow the use of draft components:
   - Open the **System** menu, and click **Database policies**.
   - On the **Advanced** tab, under **Development**, select the **Activate draft component** checkbox.
   - Confirm your selection with **OK**.
3. Open the **System** menu, and click **Add-on management**.
4. On the **Add-ons** tab, right-click the add-on you want to activate, and select **Activate**.

## Results

The add-on is added to the repository ( ) and activated in the database ( ).

# 4 Basic concepts

To support you in setting up your control mechanisms, the Control Chart Package utilizes some basic concepts, such as sidecharts, rule sets, and subcharts.

**Note:** By default, the observation data for the various methods is aggregated from referenced documents. However, you can also switch to user input and manually add the observation data.

To familiarize yourself with the concepts, you can use existing Control Chart documents from the Biological Assay Package. As structure upgrades are required for these documents in the context of the Control Chart Package, we recommend you work on copies of these documents.

## 4.1 Chart elements

Use chart elements to set up charts according to your requirements.

The following chart elements are available in this context:

- Data series
- Intervals
- Sidecharts

### Data series

Use data series to configure the observations you want to visualize in a chart. You can add several data series to the same chart, where each data series visualizes a different observation. Reference a column in the data table to depict the observation. You can also reference the same observation in different data series which allows you to highlight different aspects.

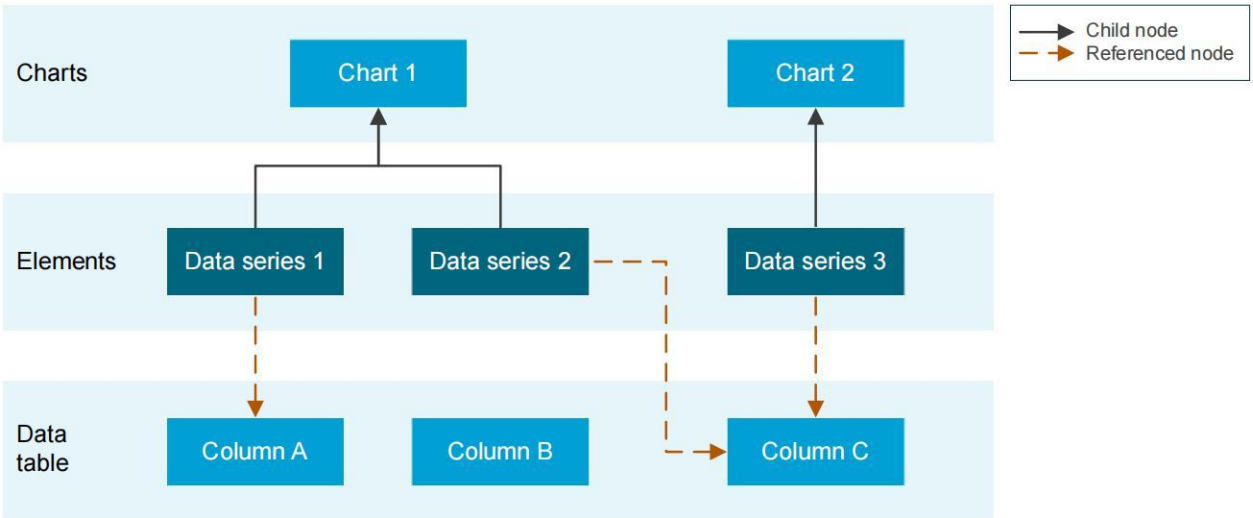



*Figure 1. Assignment of data table columns to data series*

### Intervals

Use intervals to quantify the uncertainty of your observations. Reference the data table columns you want to use as upper and lower boundaries to define the level of confidence and use bars or areas to visualize the results.

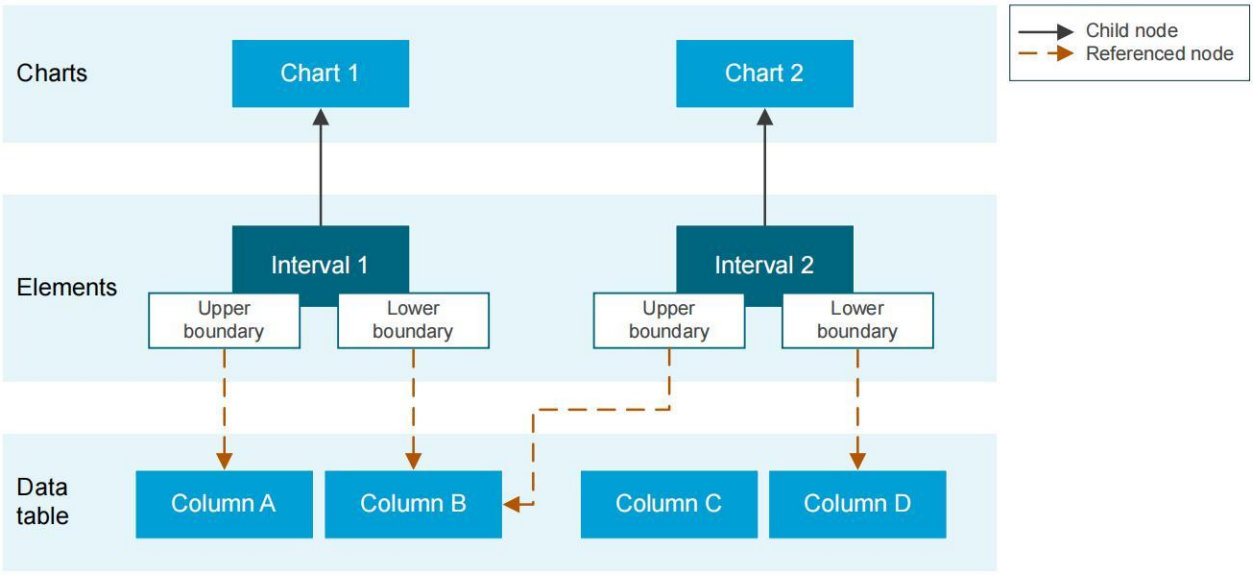



*Figure 2. Assignment of data table columns to intervals*

### Sidecharts

Use sidecharts to summarize statistical parameters in a data series and visualize them as box plots or using mean and standard deviation. Sidecharts can be created for all data series or a specific series as well as for the full chart or all subcharts. You can configure up to two sidecharts.

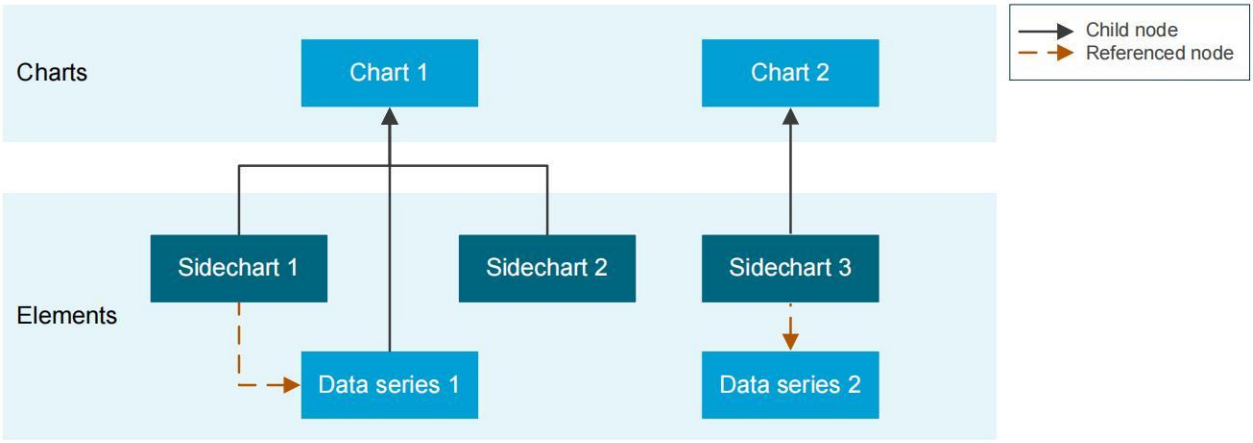



*Figure 3. Assignment of data series to sidecharts*

## 4.2 Rule sets

Use rule sets as a unified control system to apply the same visualization options to multiple rules, adjust periods of validity using events, and monitored data series for multiple rules based on control limits and control rules.

### Control limits

Control limits define a range of acceptable values, determined by an upper and a lower limit. Any value outside of this range is considered to be a rule violation and needs to be marked as such. Use the Control Chart Package to set up rule sets with independently defined control limits. These rules will be drawn as horizontal lines on your control chart.

### Control rules

In statistical process control, conspicuous data such as pattern anomalies and extreme values need to be detected and marked as rule violations in the related control chart. Control rules support you during this process in that they allow you to configure as of when data is considered to be out-of-control. Use them to monitor critical attributes, detect out-of-control data, and visualize rule violations in control charts.

Select one or more of the predefined rules (Nelson rules 1 to 8 or Western Electric rules 1 to 4), and fine-tune your process control by defining your own rules based on mean and standard deviation. Limits can be set manually or derived automatically from a specified subset of the data.

### Assigning rule sets to charts

Setting up a unified control system employing rule sets is a two-step process. In the first step, you configure the rule sets by defining control limits and control rules. In the second step, you set up the charts, add the required data series and assign the rules sets to the data series they should monitor. One chart can plot several data series and the same rule set can be assigned to multiple data series of multiple charts.

In the following example, rule set A monitors data series 1 of chart 1 as well as data series 2 of chart 2. Rule set B also monitors data series 2 of chart 2 and in addition data series 3 of chart 2.

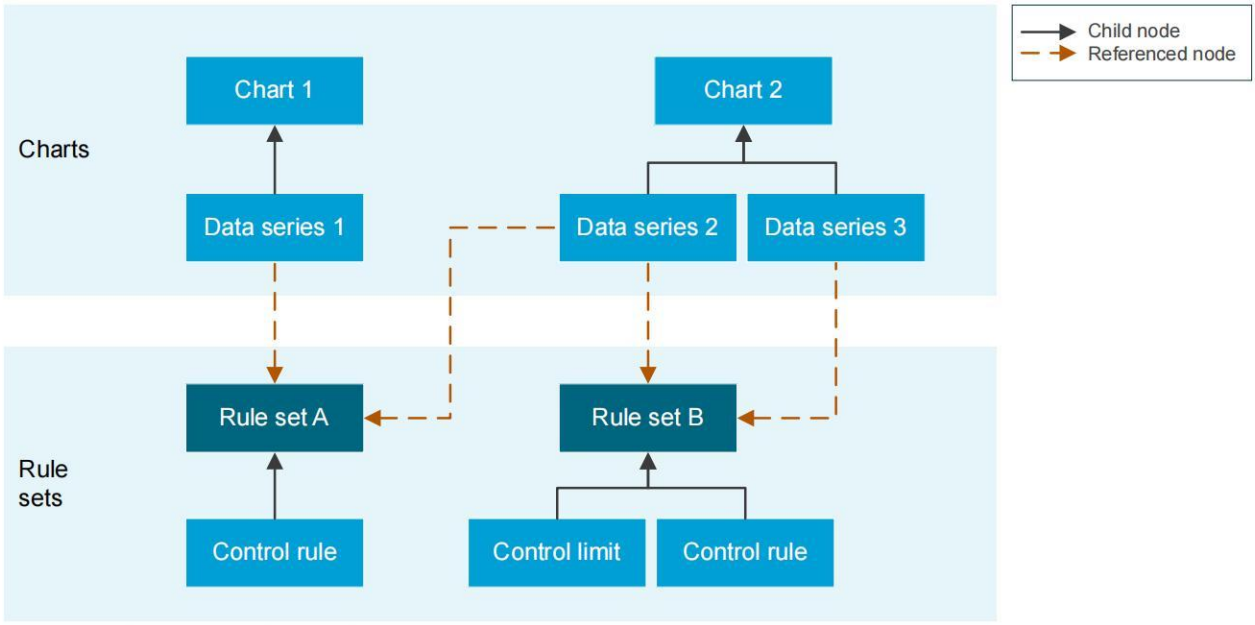



*Figure 4. Assignment of rule sets to data series and charts*

## 4.3 Events

Use events to set a marker on the x-axis of your chart. Events can be anything you want to visualize in a chart, such as the replacement of a reagent, an adjustment to an SOP, or the recalibration of an instrument.

Specify a date and time for the event, add a remark to describe the event, and use colors to distinguish between different events. In the resulting chart, you can quickly ascertain if and how your process was impacted by the change.

The following image from the '02 Plotting Manual Input' sample document shows how an event can be used when working with non-assay data. The event indicates the recalibration of a machine that is used to produce screws.

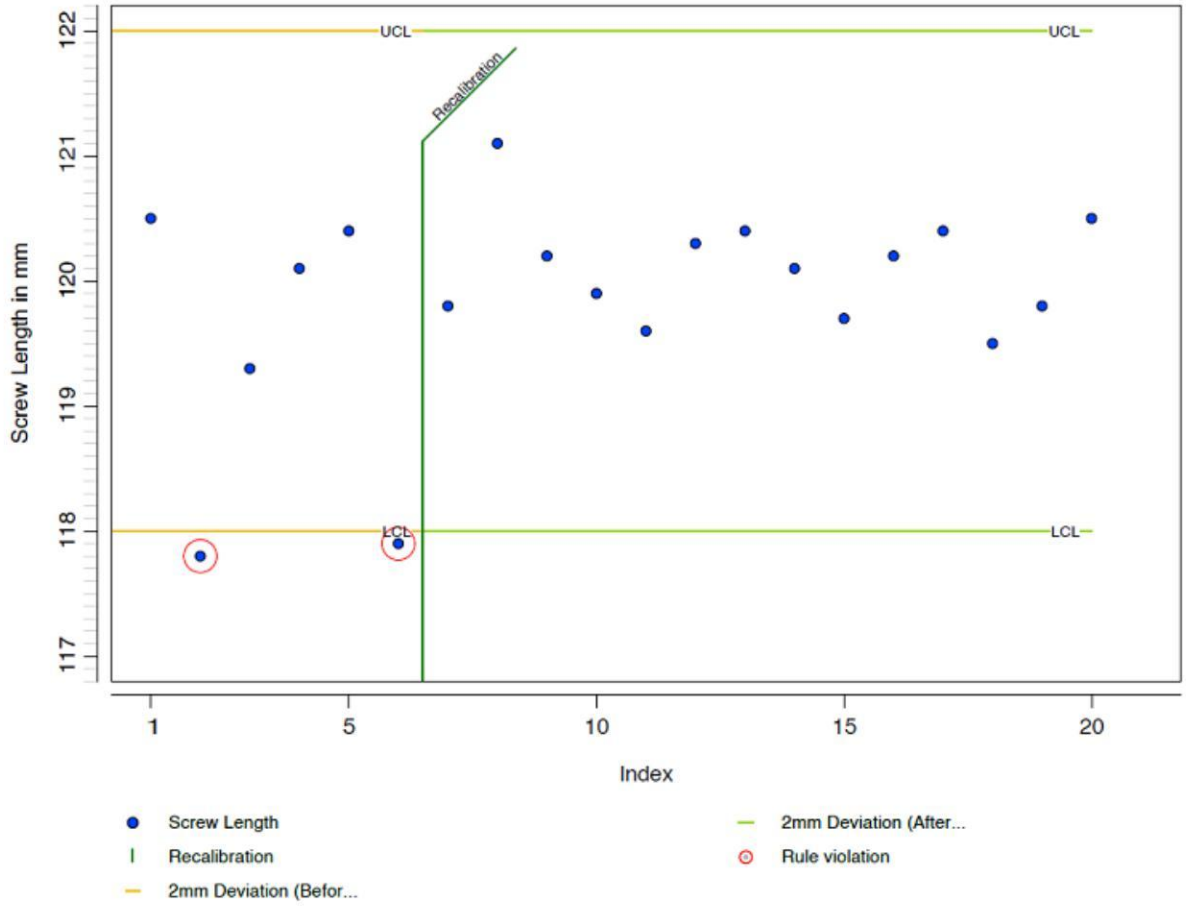



*Figure 5. Event marking the recalibration of a machine*

**Note:** You can also reference events in rule sets to make sure that accompanying changes to control rules stay synchronized.

## 4.4 Document status

Configure severity levels for your rules and use the resulting document status to quickly ascertain the criticality of a rule violation.

### Severity levels

You assign severity levels to control limits and control rules. If a rule is violated, the most critical status is propagated to the next level in the document structure, according to the following logic:

The status of control limits and control rules is propagated to the rule set they belong to. The rule set status is propagated to the chart that references the rule set. The chart status is propagated to the document itself, the highest level in the document structure.

Table 1. The following severity levels are available:

| Severity level | Description |
|---|---|
| Alarm | If the rule is violated, the status is set to red. |
| Warning | If the rule is violated, the status is set to yellow. |
| Information | If the rule is violated, the status is set to green. |

**Example**

In the following example, two charts are set up for a document. Chart 1 uses one rule set, Rule set A. Chart 2 uses two rule sets, Rule sets B and C. Rule set A uses Nelson rule 1 as control rule, with 'Alarm' set as the severity level. For each of the rule sets of chart 2, a control limit and a control rule are configured. The severity levels of the control limits are set to 'Alarm'. The severity level of Nelson rule 3 is set to 'Information', the severity level of WECO rule 4 to 'Warning'.

Rule violations are detected for three rules and are propagated to the document as follows:

- For Chart 1, Nelson rule 1 is violated. The 'Alarm' status is propagated to Rule set A. Chart 1 is set to 'Alarm'.
- For Chart 2, Nelson rule 3 and WECO rule 4 are violated. The status is propagated to their respective rule set. As the status of Rule set C is more critical, this status is propagated. The status of Chart 2 is set to 'Warning'.
- For the document, the status of Chart 1 is more critical and is propagated. The document status is set to 'Alarm'.

The following figure visualizes the process:

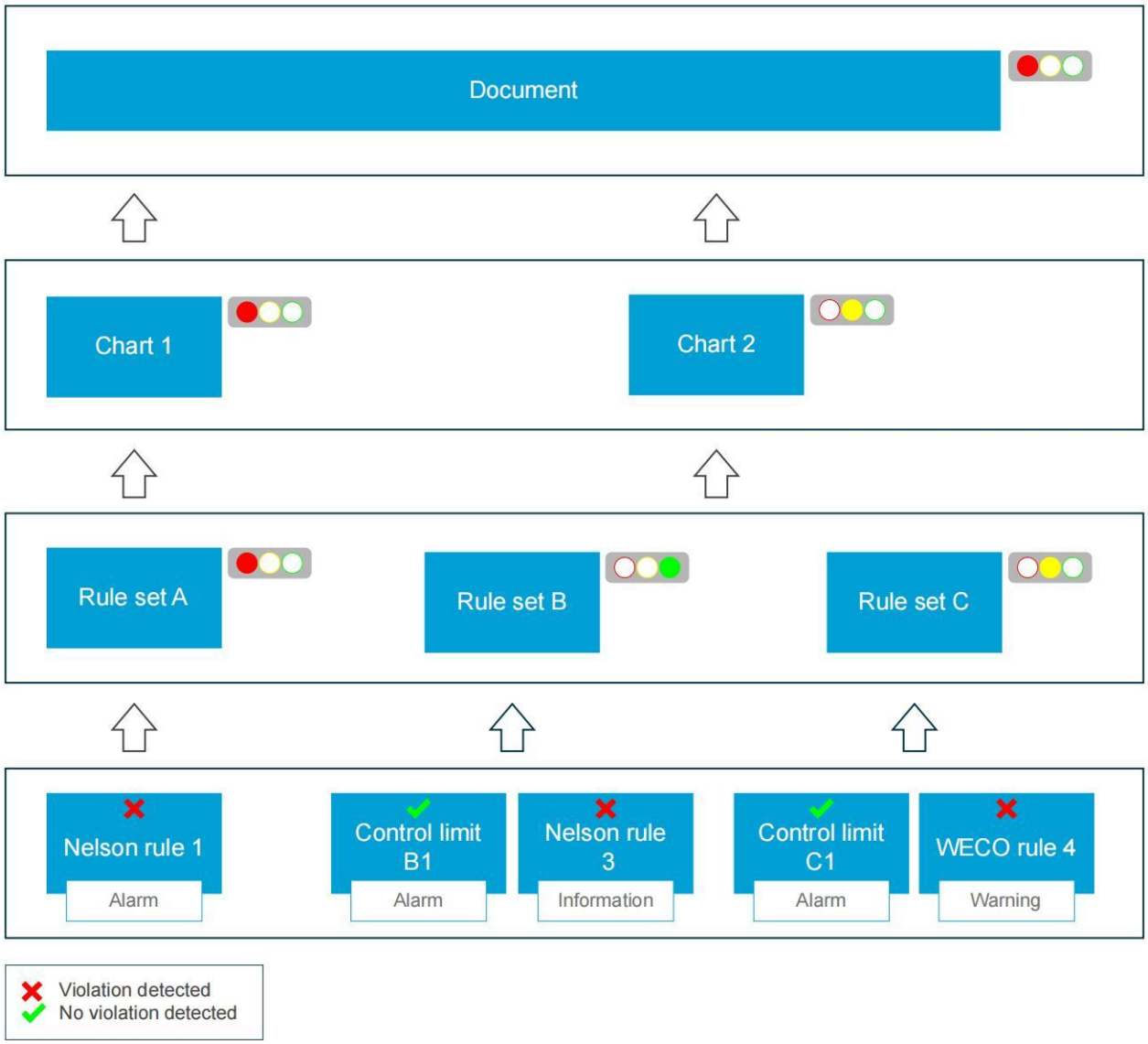



*Figure 6. Status propagation from rule to document level*

## 4.5 Subcharts

By default, all observations of a data table column are plotted in the same chart. You can split one chart into several subcharts or plot only a subset of data in subcharts.

**Note:** Using subcharts is optional. The Subcharts element is therefore not available by default; you have to manually add it from the Createable elements pane.

### Creating subcharts

You can configure subcharts based on a specific number of observations (Observations per subchart) or a specific number of days (Days per subchart). The system automatically calculates the required number of subcharts.

Examples:

- Observations per subchart: If the total number of observations is 1000 and you configure 100 observations per subchart, ten subcharts are generated.
- Days per subchart: If your observations comprise one week, you can create one subchart for each day by entering '1' as the value.

### Plotting a subset of data

Instead of plotting all your observations, you can plot only a subset of data. You can plot the most recent observations in your data table (Most recent observations) or the observations with the most recent date (Most recent days).

The following example shows six observations. If you plot the three most recent observations, the subchart contains observations 4 to 6. If you plot the three most recent days, the subchart contains observations 1 to 3.

**Important:** This feature is based on the sort order of the data table. Make sure the Sort data option for your charts is set according to your requirements.

| | Identification | Date/Time | A Parameter - D Parameter |
|---|---|---|---|
| 1 | Simulated Assay (1 of 1000) | Mar 12, 2021, 8:48:17 AM | 4315.611464 |
| 2 | Simulated Assay (2 of 1000) | Mar 11, 2021, 8:48:17 AM | 4349.653186 |
| 3 | Simulated Assay (3 of 1000) | Mar 10, 2021, 8:48:17 AM | 4391.591726 |
| 4 | Simulated Assay (4 of 1000) | Feb 26, 2021, 8:48:17 AM | 4328.490556 |
| 5 | Simulated Assay (5 of 1000) | Feb 26, 2021, 8:48:17 AM | 4341.526102 |
| 6 | Simulated Assay (6 of 1000) | Feb 26, 2021, 8:48:17 AM | 4404.020158 |

**Tip:** You can also combine both options. For example, if the total number of observations is 1000 and you configure 100 observations per subchart and 500 most recent observations, five subcharts are generated with 100 observations each.

### Dashboard

On the Dashboard, the Results overview displays one tab for each chart you configure. On each chart tab, the most recent subchart, as well as the full chart, are displayed. The full report shows all available charts.

The following figure shows the Dashboard of the '03 Splitting the Chart into Subcharts' sample document, with the Current data chart in focus.

**Note:** The full chart is always plotted.

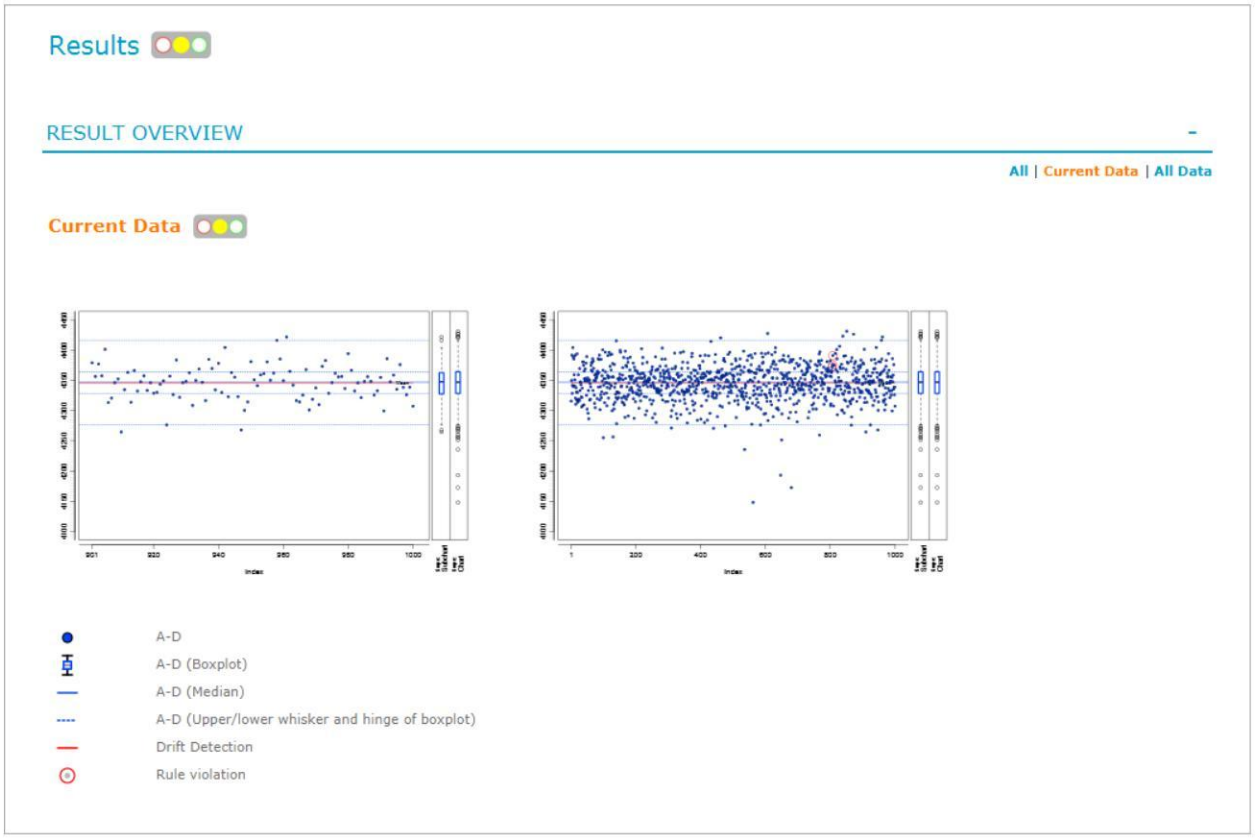



*Figure 7. Result overview displayed on the Dashboard*

## 4.6 Coloring by secondary characteristic

Associate observations with a secondary characteristic, for example, the operator who performed the assay, to evaluate at a glance which additional factors might be influencing your results.

Define the secondary characteristic by adding a floating-point number or a single line text to your data table, and use this characteristic in a data series to assign a color to the characteristic.

In the following example, a column 'Operator' is added to the data table and referenced in the data series to distinguish between the operators Alice and Bob. The monitored parameter (in this example the potency) is referenced in the same data series

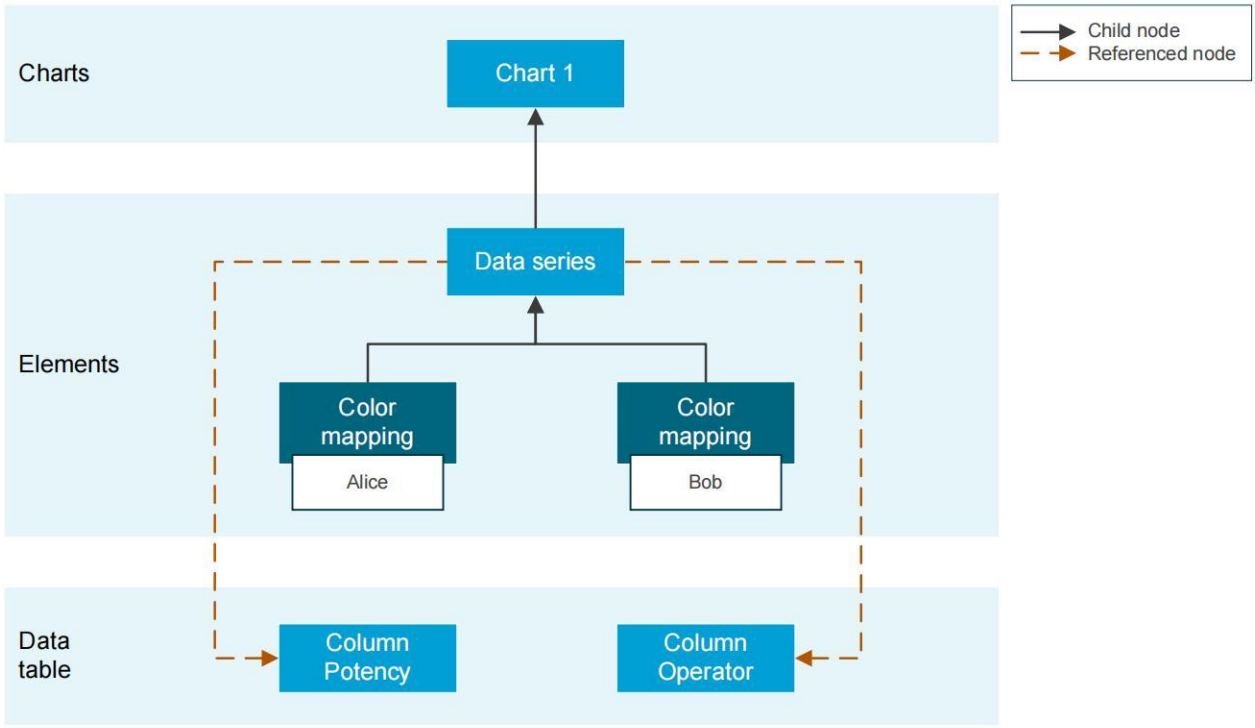



*Figure 8. Assignment of data table column to data series for use as a secondary characteristic*

**Note:** Secondary characteristics are for visualization purposes only. They do not change the parameter statistics of a data series or chart.

# 5 Use cases

## 5.1 Monitoring the effect of a cell culture change

Create events for the dates on which you changed the cell culture and reference the events in rule sets to define the periods you want to monitor.

### Setting up events and rule sets

The following image from the '03 Performing Statistical Process Control with Events' sample document shows how you can use events to mark the dates on which you changed the cell culture. To refine the setup, the events are referenced in rule sets.

- Scope: Time interval: The events are referenced as end events of a time interval to create four consecutive periods. This allows you to restrict the application of a rule set to the specified time interval.
- Mean and SD: defined by data: The events are referenced as end events in a control rule. This allows you to calculate the mean and standard deviation based on observations from the specified time interval.

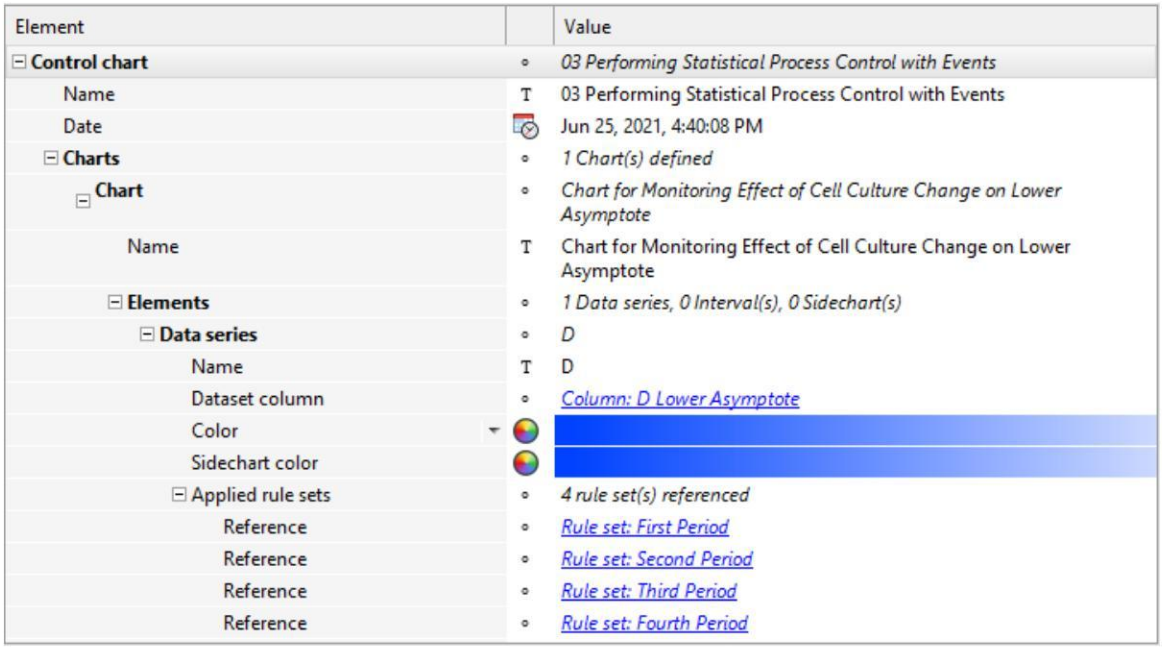
| Element | | Value |
|---|---|---|
| **Control chart** | | *03 Performing Statistical Process Control with Events* |
| Name | T | 03 Performing Statistical Process Control with Events |
| Date | | Jun 25, 2021, 4:40:08 PM |
| **Charts** | | *1 Chart(s) defined* |
| **Events** | | *3 Event(s) defined* |
| **Event** | | *2/15/21 - New Cell Culture , 2021-02-15 07:00:00 UTC* |
| **Event** | | *3/05/21 - New Cell Culture, 2021-03-05 07:00:00 UTC* |
| **Event** | | *3/17/21 - New Cell Culture, 2021-03-17 07:00:00 UTC* |
| **Rule sets** | | *4 Rule set(s) defined* |
| Color of rule violation marker | | |
| **Rule set** | | *First Period* |
| Name | T | First Period |
| Color of limits | | |
| Scope: Time interval | | *-∞ - 2/15/21 - New Cell Culture* |
| End event | | *Event: 2/15/21 - New Cell Culture* |
| Control rules | | *1 predefined rule(s) and 0 advanced rule(s) applied* |
| Mean and SD: defined by data | | *-∞ - 2/15/21 - New Cell Culture* |
| End event | | *Event: 2/15/21 - New Cell Culture* |
| Estimate SD based on | | Mean observation |
| Predefined rules | | *1 predefined rule(s) applied* |
| **Rule set** | | *Second Period* |
| Name | T | Second Period |
| Color of limits | | |
| Scope: Time interval | | *2/15/21 - New Cell Culture - 3/05/21 - New Cell Culture* |
| Control rules | | *1 predefined rule(s) and 0 advanced rule(s) applied* |
| **Rule set** | | *Third Period* |
| **Rule set** | | *Fourth Period* |

*Figure 9. Setup of events and rule sets*

### Selecting the monitored parameter

The monitored parameter (in this example the lower asymptote or D parameter of the four parameter logistic regression) is set in the data series of the chart by adding a reference to the floating-point number column 'D Lower Asymptote' of the data table to the Dataset column.

**Note:** In the same data series, the Applied rules sets node references the configured rule sets.



| Element | | Value |
|---|---|---|
| **Control chart** | | *03 Performing Statistical Process Control with Events* |
| Name | T | 03 Performing Statistical Process Control with Events |
| Date | | Jun 25, 2021, 4:40:08 PM |
| **Charts** | | *1 Chart(s) defined* |
| **Chart** | | *Chart for Monitoring Effect of Cell Culture Change on Lower Asymptote* |
| Name | T | Chart for Monitoring Effect of Cell Culture Change on Lower Asymptote |
| **Elements** | | *1 Data series, 0 Interval(s), 0 Sidechart(s)* |
| **Data series** | | *D* |
| Name | T | D |
| Dataset column | | *Column: D Lower Asymptote* |
| Color | | |
| Sidechart color | | |
| Applied rule sets | | *4 rule set(s) referenced* |
| Reference | | *Rule set: First Period* |
| Reference | | *Rule set: Second Period* |
| Reference | | *Rule set: Third Period* |
| Reference | | *Rule set: Fourth Period* |

### Result

In the resulting plot, the events are indicated as vertical lines. Nelson rule 1 is set as the control rule in all rule sets. But as each period references a different set of observations, the control limits vary.

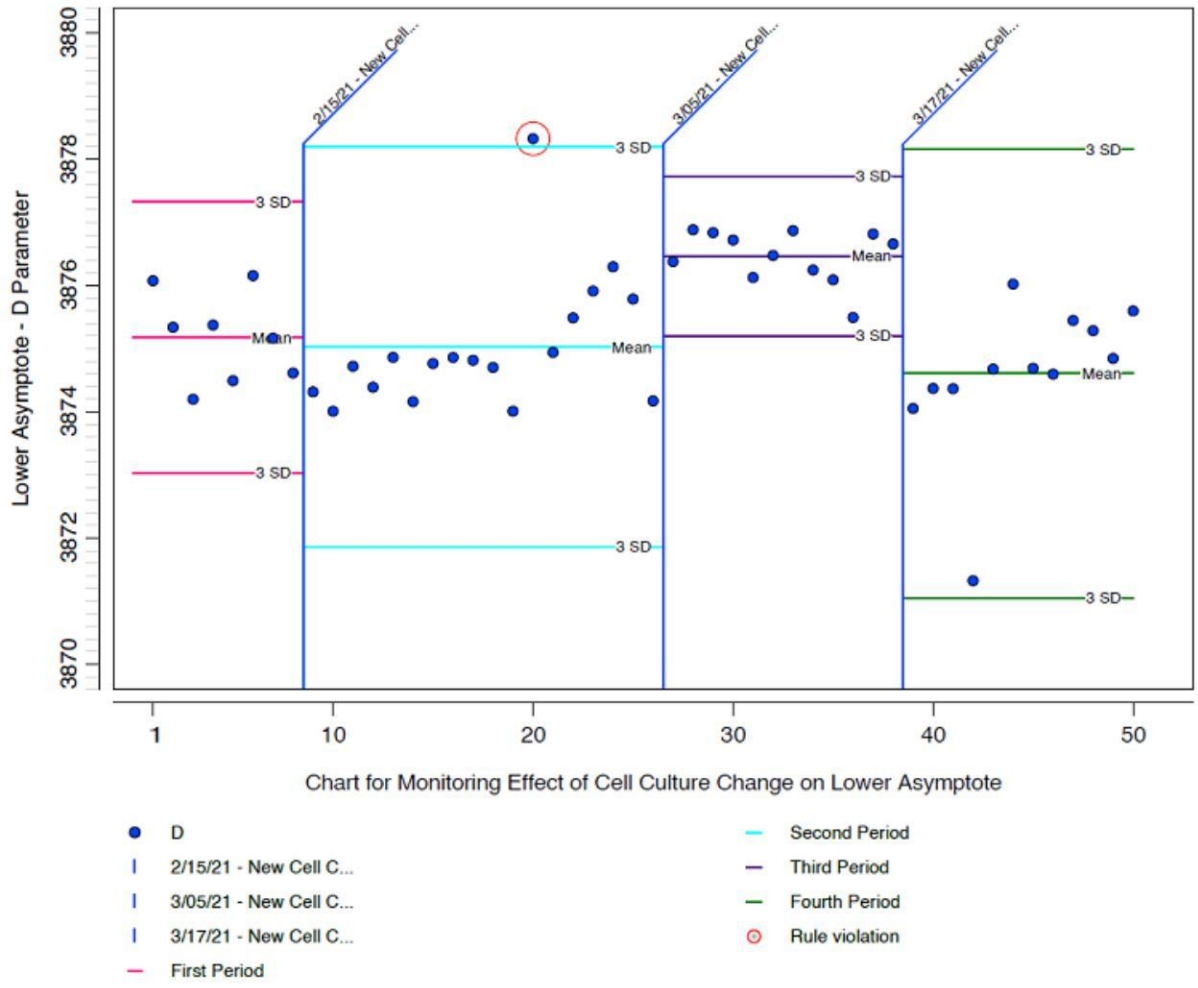



*Figure 10. Visualization of events, including the detection of out-of-control data based on Nelson rule 1 (beyond 3*SD)*

# 5.2 Applying colors based on secondary characteristics

Color your observations depending on a secondary factor not shown in the plot. You can apply colors based on thresholds or utilizing an independent text column.

The following images from the '01 Coloring by Secondary Characteristic' sample document show how you can use a secondary column to map colors to a monitored parameter. The monitoring is set up by referencing the respective parameter in the Dataset column of the data series. In the following examples, the Relative Potency' floating-point number column is monitored.

The colors are applied based on a threshold value or utilizing a manually added text column.

### Applying colors based on a threshold

This setup uses the Color: defined by threshold option. The Weight Relative Potency floating-point number column of the data table is used as the color-related parameter and is set by adding a corresponding reference to the Dataset column of the Color: defined by threshold node.

Individual colors are defined for values above and below the threshold.

| Element | | Value |
|---|---|---|
| **Control chart** | ∘ | *01 Coloring by Secondary Characteristic* |
| Name | T | 01 Coloring by Secondary Characteristic |
| Date | | Jul 1, 2021, 12:39:50 PM |
| **Charts** | ∘ | *2 Chart(s) defined* |
| **Chart** | ∘ | *Color by Operator* |
| **Chart** | ∘ | *Color by Relative Potency Weight* |
| Name | T | Color by Relative Potency Weight |
| **Elements** | ∘ | *1 Data series, 0 Interval(s), 0 Sidechart(s)* |
| **Data series** | ∘ | *Relative Potency Series* |
| Name | T | Relative Potency Series |
| Dataset column | ∘ | *Column: Relative Potency* |
| Color: defined by threshold | ∘ | *Threshold: 6000* |
| Dataset column | ∘ | *Column: Weight Relative potency* |
| Threshold | ℝ | 6000 |
| Color above threshold | | |
| Color below threshold | | |
| Sidechart color | | |
| Applied rule sets | ∘ | *1 rule set(s) referenced* |

*Figure 11. Setup of color mappings employing thresholds*

In the resulting plot, the values above and below the threshold value are plotted in the corresponding color.

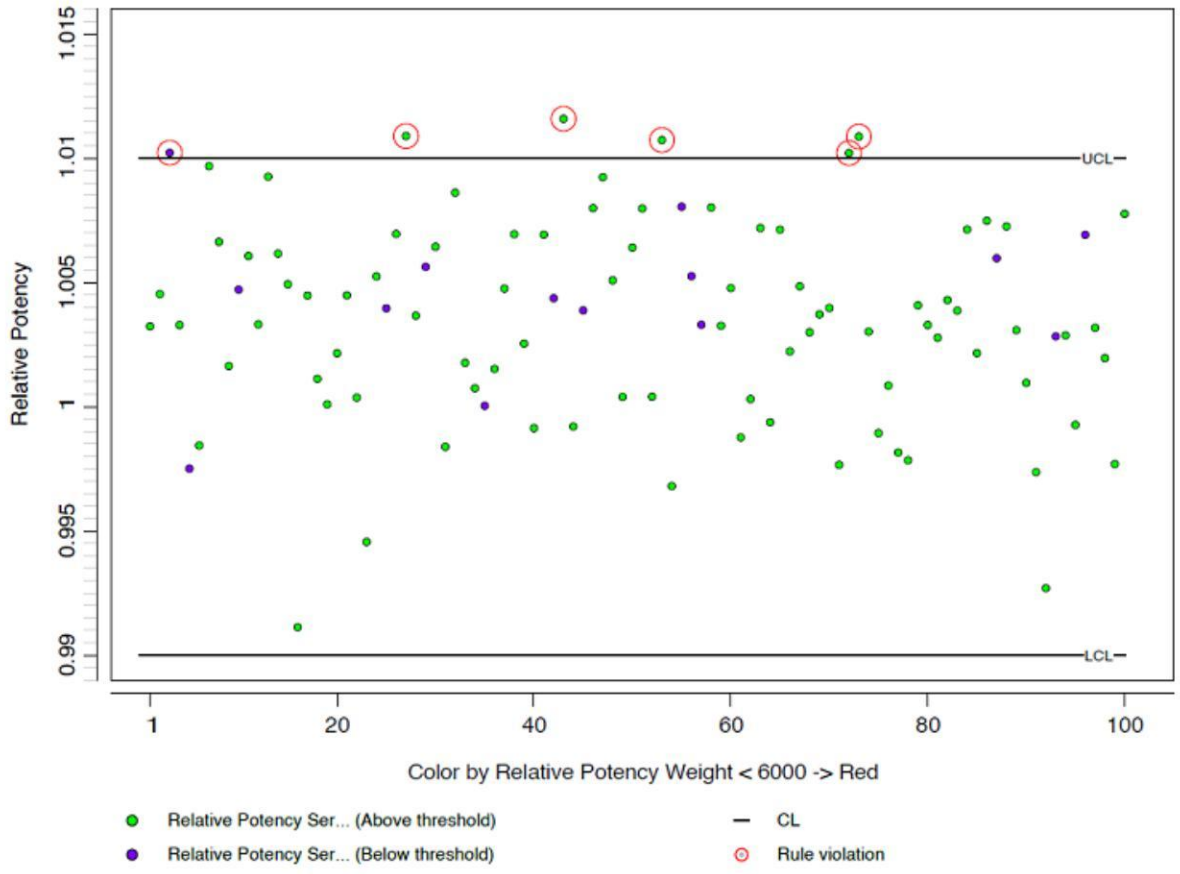


*Figure 12. Visualization of colors based on threshold values*

### Applying colors based on a text column

This setup uses the Color: defined by Value option. The Operator single line text column of the data table is used as the color-related parameter and is set by adding a corresponding reference to the Dataset column of the Color: defined by value node.

For each operator, a color mapping is applied based on the name of the operator.

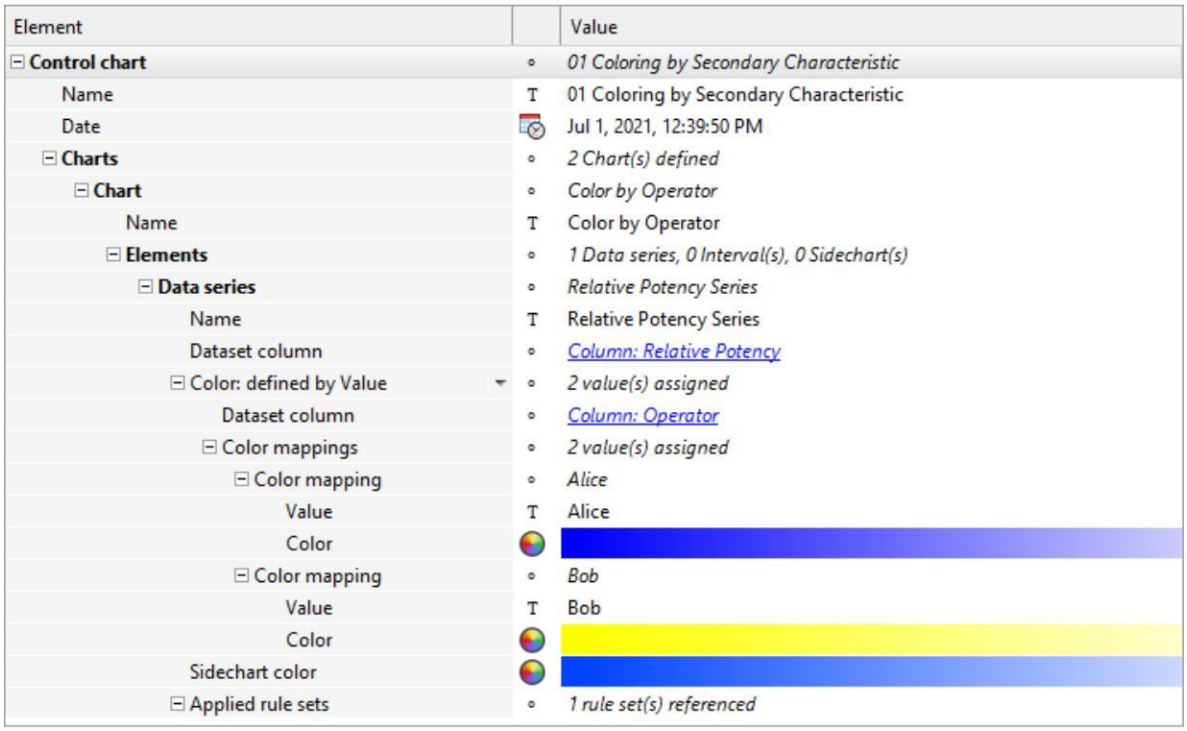



*Figure 13. Setup of color mappings employing a text column*

In the resulting plot, the observation values are plotted in the color according to the operator who performed the assay.

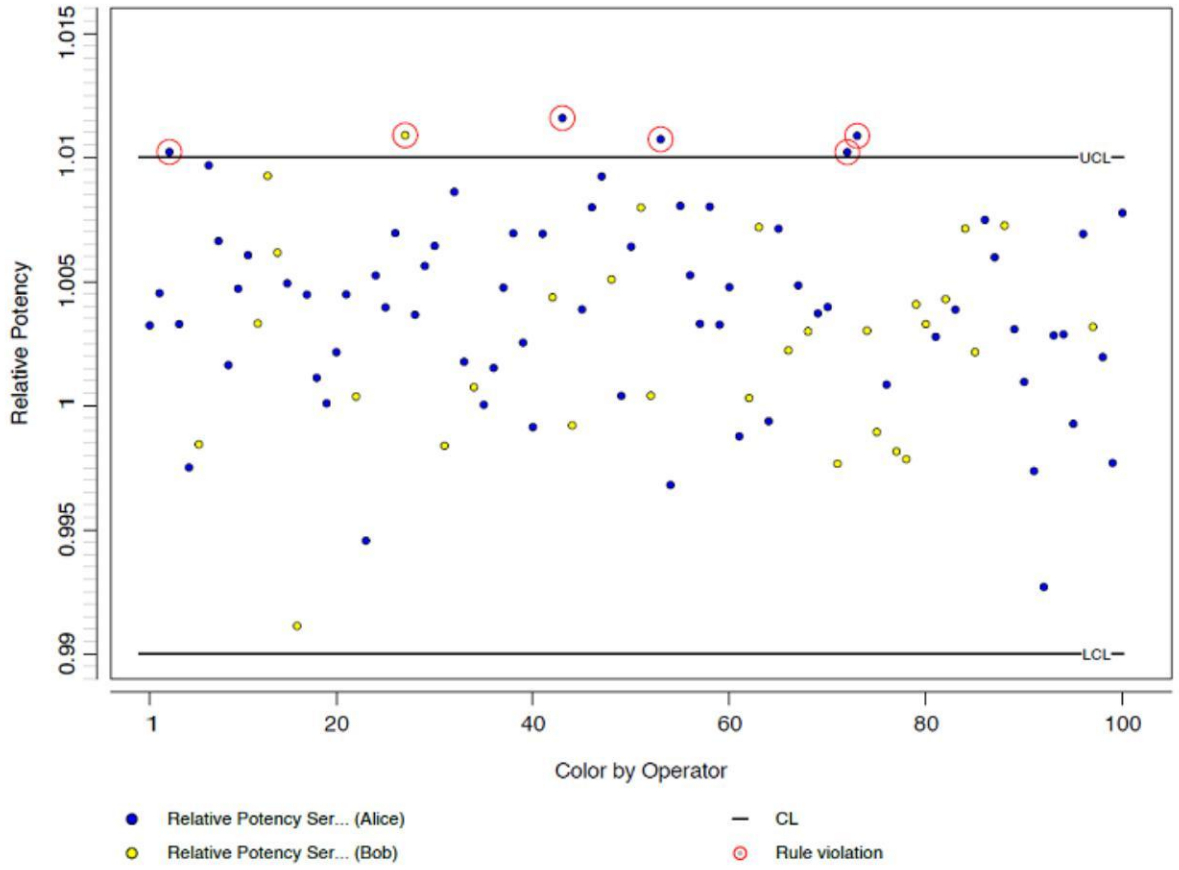



*Figure 14. Visualization of colors based on text values*

## 5.3 Monitoring effective and interpolated concentrations

Monitor the EC50 of a dose-response analysis together with the interpolated Test sample concentrations. Monitor the effective and interpolated concentrations for individual days, and employ a sidechart that provides the mean EC50 and a three-sigma interval for the EC50.

The following images from the '06 Monitoring EC50 And Sample Results from DRA Assays' sample document show how you can employ the chart elements data series, intervals, and sidecharts to compare the interpolated concentrations of Test samples with each other and with the EC50 estimate of the Standard sample.

### Setting up the data series

Two data series are set up. The first data series monitors the interpolated concentration of each Test sample and applies a different color to each Test sample. The second data series monitors the EC50 value.

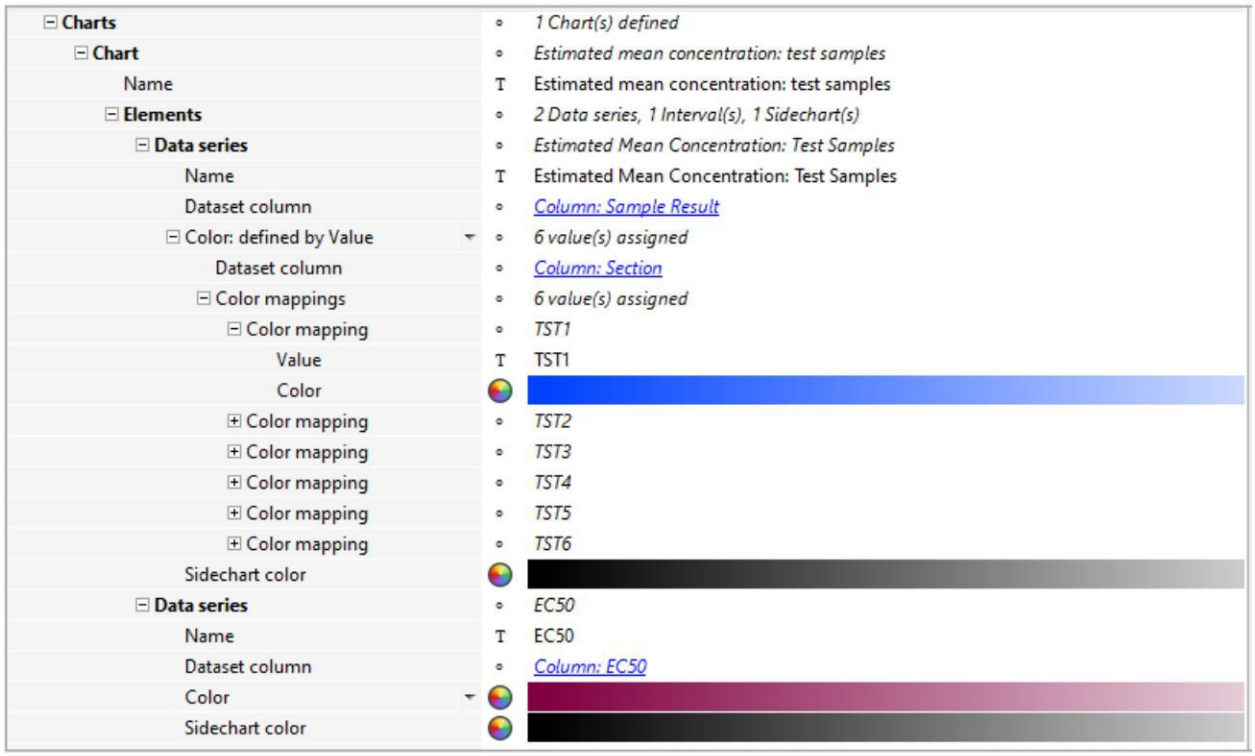



*Figure 15. Setup of data series for Test and Standard*

## Setting up the interval

Interval boundaries for effective concentrations of 20 and 80 are added to visualize the distribution of the interpolated Test sample values in the resulting chart, employing bars.

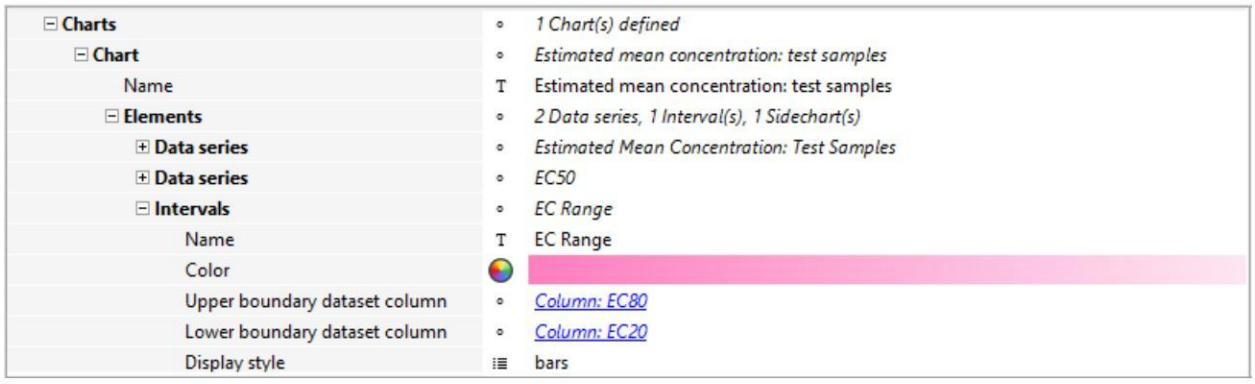



*Figure 16. Setup of upper and lower interval boundaries*

## Setting up the sidechart

A sidechart provides the mean and standard deviation of the EC50 values.

| | | |
|---|---|---|
| **Charts** | ∘ | *1 Chart(s) defined* |
| **Chart** | ∘ | *Estimated mean concentration: test samples* |
| Name | T | Estimated mean concentration: test samples |
| **Elements** | ∘ | *2 Data series, 1 Interval(s), 1 Sidechart(s)* |
| **Data series** | ∘ | *Estimated Mean Concentration: Test Samples* |
| **Data series** | ∘ | *EC50* |
| **Intervals** | ∘ | *EC Range* |
| **Sidechart** | ∘ | *Mean and SD for EC50* |
| Type: Mean and SD | ∘ | *Mean and 3 SD* |
| SD factor | ℝ | 3 |
| Select data series | ∘ | *1 data series* |
| Data series | ∘ | *Data series: EC50* |
| Scope | ≣ | Chart |
| Draw horizontal lines | ≣ | yes |

*Figure 17. Setup of sidechart for the EC50 data series*

## Result

In the resulting plot, the interpolated concentrations of Test samples and EC50 values are plotted as shown below. Intervals are added for improved readability.

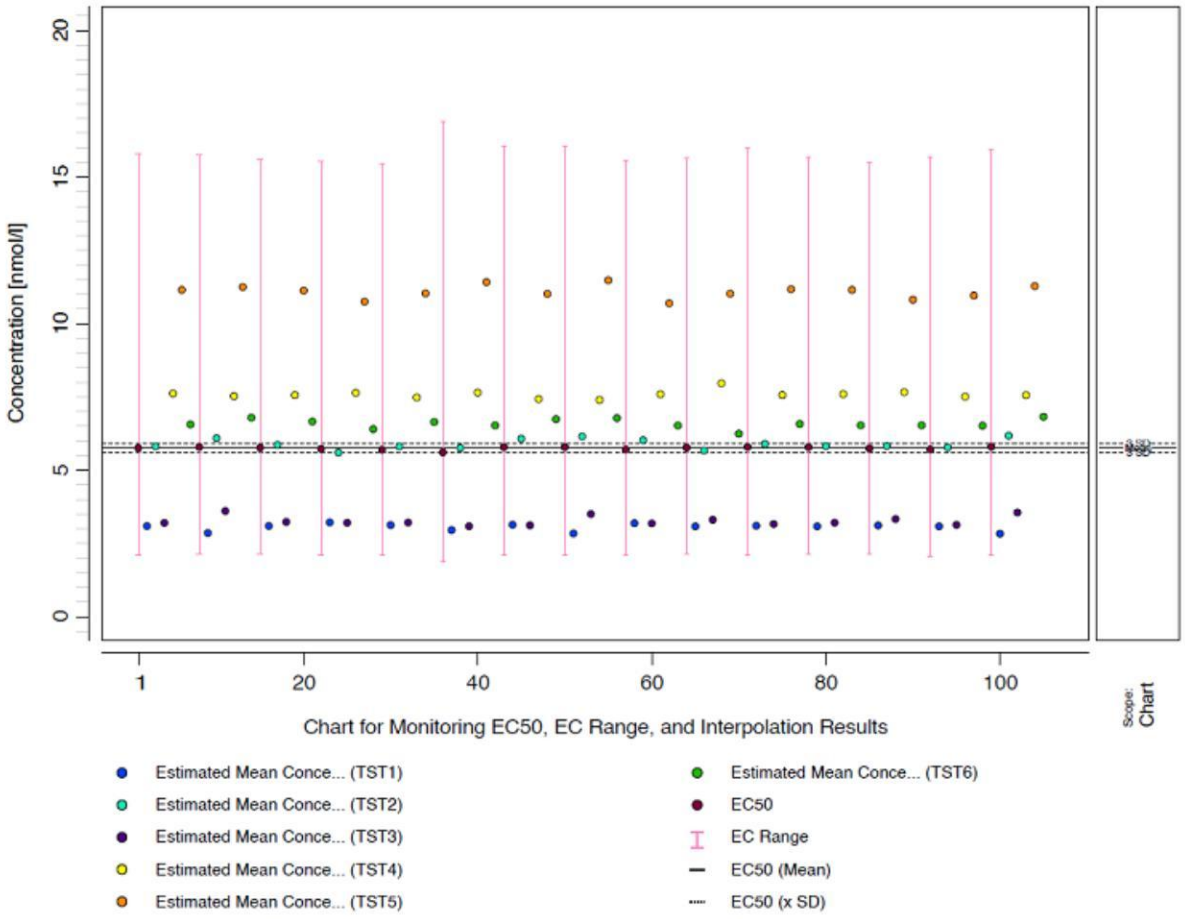



*Figure 18. EC50 values and interpolated concentration values of the Test samples over consecutive days*