JMP047: Manufacturing Excellence in Pharma – Part 1

Statistical Process Control, Control Chart, Process Capability

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Manufacturing Excellence in Pharma – Part 1

Statistical Process Control, Control Chart, Process Capability

Key ideas

This case study requires the use of control charts to understand process stability and to analyze the patterns of process variation. It also explores process capability in light of external requirements. All these concepts support a better process understanding and guide the development of improvement strategies.

Background

FVM Pharmaceuticals is an international drug manufacturer, specializing in manufacturing finished formulations that cater to the most demanding global needs. FVM delivers contract manufacturing of tablets, capsules, and liquids.

A typical manufacturing process involves milling an active pharmaceutical ingredient (API) into a powder of uniform particle size. The milled material is then blended with other ingredients to bulk up and evenly distribute the API. This blended material is then compressed into tablets, which are finally coated to aid shelf life, taste, and other properties. At the end of the process, various quality parameters, including critical to quality (CTQ) metrics, are populated, which further drive batch acceptance.

The process starts with a raw material that is a concentrated emulsion containing two organic compounds. The raw material is supplied by two vendors, and the incoming quality is monitored by measuring the concentration of the compounds in milligram per liter (mg/l). Each day, a quality lab operator takes raw input material in two batches from each supplier into the process.

The process of chromatography is a laboratory technique for the separation of a mixture. The company is currently leveraging gas chromatography (GC), a common type of chromatography used in analytical chemistry for separating and analyzing compounds that can be vaporized without decomposition.

The task

Recently, the Total Quality Management (TQM) team observed a significant variability in the quality of the drug delivered. To address this issue, a cross-functional team was formed to identify the root cause of the problem and then solve it. Lawrence, head of the team and a quality engineer, is a firm believer of data-enabled decision making. He also knows that building a strong quality culture into the process demands the application of statistical techniques to discover actionable insights. He is aware that bringing operational excellence into a manufacturing process is a sequential and multistage process starting from raw material to final inspection. Fortunately, methodologies like Quality by Design (QbD) ensure high quality throughout the production process (starting from raw material to finished product) while leaving enough flexibility in the manufacturing system.

The challenge for Lawrence's team is to resist just doing firefighting. To find a more sustainable solution, their strategy is to identify the key drivers for process variation and to improve stability, and finally, to optimize the process settings to better meet the customer requirements.

In this first stage of the project, we help Lawrence with the investigation of the raw material:

- Can we assume normality for our data?
- What is driving the variability in Compound 1 and Compound 2: Day, Batch or Vendor?
- Can the process be considered as stable and under control?
- Can the process be considered as capable (with a C_{pk} of 1.33 or higher)?
- Which vendor is supplying the compounds that better meet the specifications?
- Is the process stable from a multivariate perspective?
- Which actions should be taken by Vendor A and Vendor B to improve the stability and/or capability of the two compounds?
- What should be recommended as a follow-up study?

The data rm.jmp

The quality team collected samples of raw material quality for both compounds coming from both vendors for eight days for all the batches:

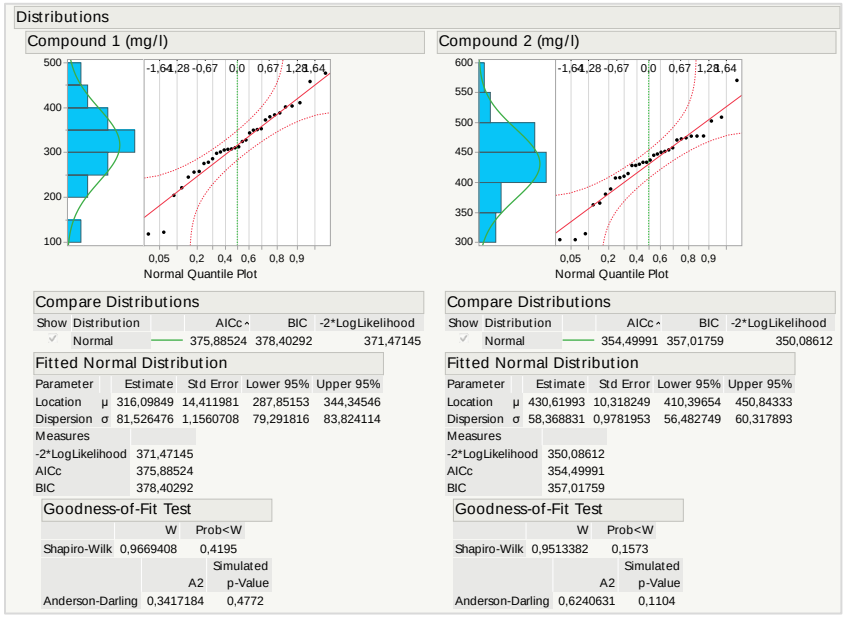
Day	Day on which sample was taken (eight days)
Batch	The serial number of the batch (two batches per day, so a total of 16 batches)
Vendor	Denotes the vendor (A and B) that supplied the compound
Compound1	Quality of Compound 1 measured in mg/l
Compound2	Quality of Compound 2 measured in mg/l

Compound 1, Compound 2, and Day contain continuous data. Batch is an ordinal variable, while Vendor is a nominal variable.

Analysis prerequisites

Judith, a quality engineer and Green Belt on Lawrence's team, is aware that many quality tools assume that the data come from a normal distribution. Otherwise, reporting results based on a mean and standard deviation would not be meaningful. After quickly adding some analyses to a distribution analysis, as shown in Exhibit 1, she is able, with some relief, to confirm that there is no concern about normality of the two continuous variables.

Exhibit 1 Checking the Normality Assumption in Distribution

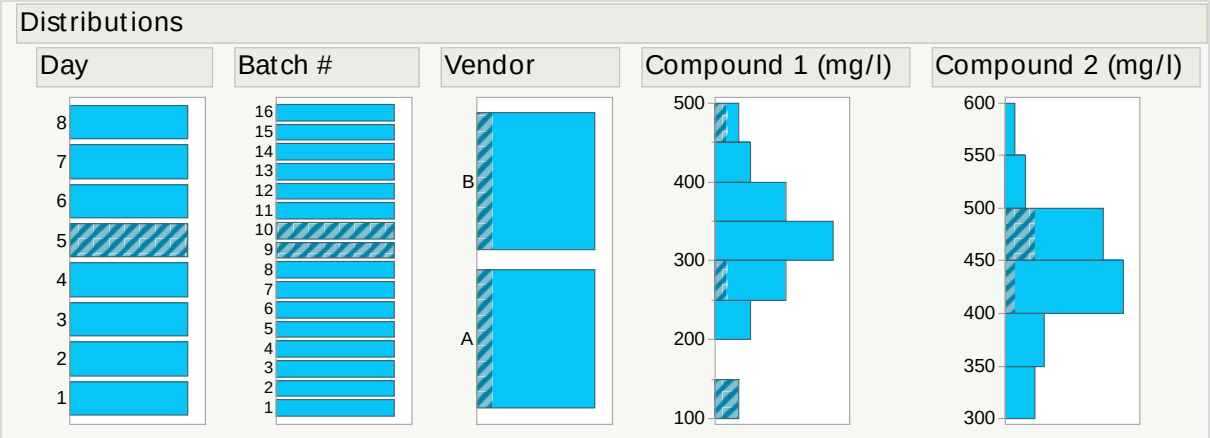


*To create, Analyze>Distribution. Drag **Compound 1** and **Compound 2** into Y,Column; check Histograms only. Click OK.*

For both variables, top drop-down>Normal Quantile Plot. Top drop-down>Continuous Fit>Fit Normal. Fitted Normal drop-down>Goodness of Fit.

Another good question was asked by Marc, a process engineer and long-time JMP user: What is driving the variation we observed in the two compounds?

Exhibit 2 Checking Day, Batch and Vendor as Potential Drivers of Variability



To create, Analyze>Distribution. Drag all variables into Y,Column; check Histograms only. Click OK. Select data by clicking to explore relationships.

By clicking on the Distribution report as shown in Exhibit 2, he shared some interesting findings:

- First, he confirmed that both vendors equally contributed to all batches and that two batches were used each day.
- By looking at the histograms of Compound 1 and Compound 2, he showed a huge variability after selecting individual batches, even comparing batches from the same day.

The team agreed that having a more systematic look into the variability components at a later stage of the project would be a good idea.

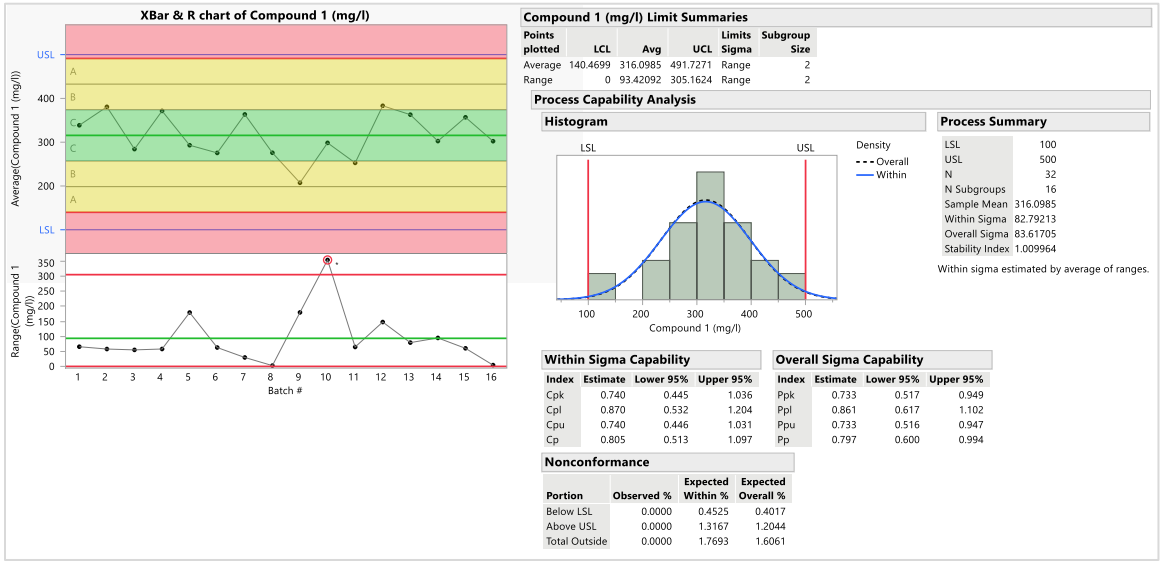
Control limits and process stability

After checking for normality and analyzing the histogram, Lawrence and his team started to explore the quality aspects using the Control Chart Builder platform in JMP. A control chart is a graphical tool for monitoring process variation. Control limits help distinguish *common-cause variation* from *special-cause variation*. Typically, action is taken to identify and eliminate special-cause variation. It is also important to quantify the common-cause variation in a process, as this determines the capability of a process.

Control limits are based on the performance of the process and help in describing the variability in the process. Upper control limits (UCLs), center lines, and lower control limits (LCLs) are automatically calculated when a control chart is created based on the process data. These control limits will help in identifying process changes.

It is important to note that control limits are different from specification limits, which are often used in capability analysis. Specification limits are set by external system or process requirements, which are often demanded by the customer. In this case, the lower and upper specification limits for Compound 1 are 100 mg/l (LSL) and 500 mg/l (USL).

Exhibit 3 Control Chart of Compound 1



To create, Analyze>Quality and Process>Control Chart Builder. Drag Compound 1 to the Y zone. Drag Batch to the Subgroup zone at the bottom.

Once the XBar & R chart appears, right-click on the graph. Select Limits. Under limits, select Zones and Shaded Zones. Under the same drop-down, select Spec Limits and populate 100 as LSL and 500 as USL.

The control chart output consists of an XBar & R chart, along with the Process Capability Analysis, as shown in Exhibit 3.

The XBar chart displays subgroup means (here, the averages of multiple batches). A close examination shows that all the points are falling within the control limits (green and yellow zones) and that the points are randomly placed within these limits.

In the XBar chart, right-click and select Warnings > Tests > All Tests. Notice that no points were circled or flagged, which means that the process is “in control” or stable (only showing common-cause variation).

The R chart is a type of control chart used to monitor the process spread (as the range). Each point on the chart represents the value of batch range. In the R chart, right-click and select Warnings > Test beyond limits.

Looking at the graph, we see that Batch 10 falls outside of the control limits, showing some special-cause variability in addition to the standard variation of the process.

Process capability indices, in partnership with control charts on critical process variables, help to identify processes that are performing poorly. Stability is evaluated using control charts. For a stable process, the capability is evaluated based on the ability to meet customer specifications. A capable process must be stable, but a stable process might not be capable. The best processes are both stable and capable.

Process capability indices

The process capability index C_p is the ratio of the width of the spec limits to the width of the distribution of the process characteristic. C_p does not include information about the center of the process, estimated by XBar, relative to the spec limits. Because the C_p index assumes that the process is centered, this index is also called the potential process capability. It is a measure of what the capability could be if the process were on target.

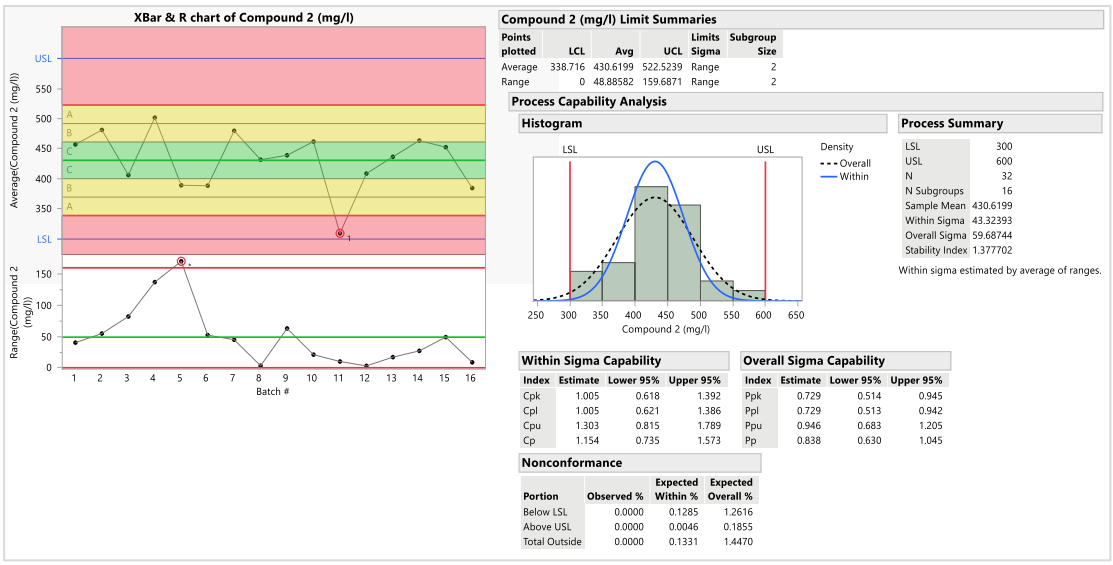
C_{pl} is used to examine the ability of a process to meet the lower spec limit, and C_{pu} is used to examine the ability to meet the upper spec limit. C_{pk} is the minimum of C_{pl} and C_{pu}. If the process is perfectly centered within the spec limits, C_p and C_{pk} will be the same. If the distribution is perfectly centered and the process spread equals the width of the spec, both C_p and C_{pk} will be 1.0. A barely capable process is considered to have a C_{pk} of 1.0 (higher values are better). Some guidelines require a minimum C_{pk} value of 1.33 or even higher.

Looking at the C_{pk} value (0.740) and C_p value (0.805), we can conclude that the Evolution (GC) raw material Compound 1 is unstable and not capable of meeting the specification.

Note that due to the subgrouping of the data by Batch, we have different options to calculate sigma: Within (or short-term) Sigma Capability C_p (which only considers the spread within a subgroup, here estimated by using the ranges per batch) or Overall (or long-term) Sigma Capability P_p, which is typically lower because it considers a larger spread calculated from all groups overall.

Following a similar approach, Exhibit 4 shows the XBar & R chart for Compound 2.

Exhibit 4 Control Chart of Compound 2



To create, Analyze>Quality and Process>Control Chart Builder. Drag Compound 2 to the Y zone. Drag Batch to the Subgroup zone at the bottom.

Once the XBar & R chart appears, right-click on the graph. Select Limits. Under limits, select Zones and Shaded Zones. Under the same drop-down select Spec Limits and populate 300 as LSL and 600 as USL.

In the XBar chart, right-click and select Warnings > Tests > All Tests. Notice that Batch 11 falls into a red zone and is circled or flagged, which indicates that the process is not in control or stable.

The R chart is a type of control chart used to monitor the process variability (as the range). Each point on the chart represents the value of batch range. In the R chart, right-click and select Warnings > Test beyond limits. Looking at the graph, we see that Batch 5 exceeds the control limits, showing some special-cause variability in the process.

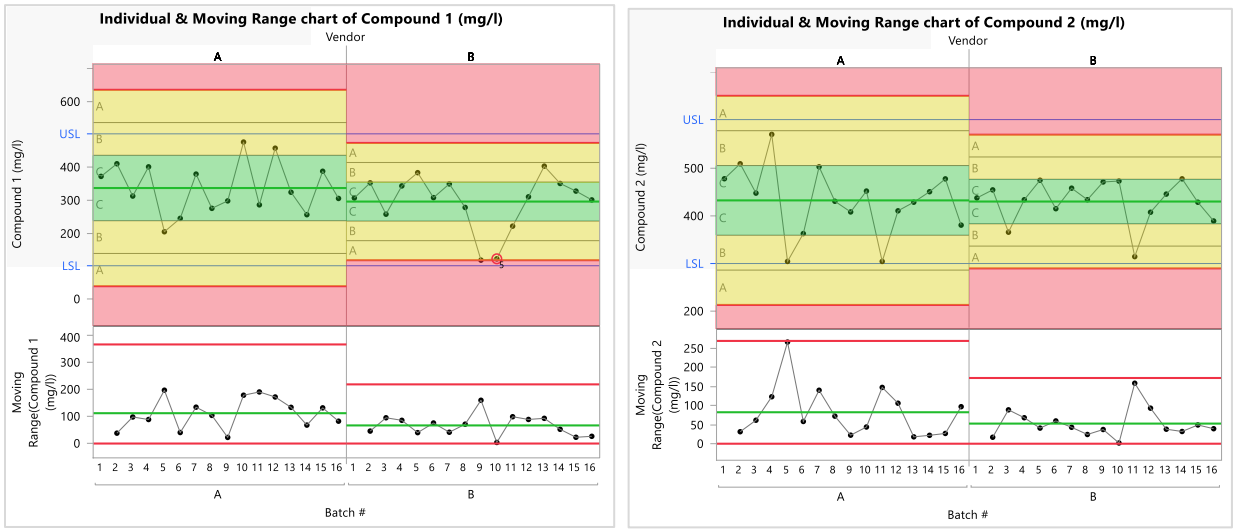
Looking at the C_{pk} value (1.005) and C_p value (1.154), we can conclude that the Evolution (GC) raw material Compound 2 is unstable and not capable of meeting the specification.

Process capability and vendor

Now that Lawrence and his team have discovered that there is a special process variability in both compounds, the next stage is to explore these variations from a vendor perspective. Having control charts for each vendor next to one another will help us understand this better.

Follow similar steps as described previously to create XBar & R charts. Drag and drop Vendor to the top of the chart (Phase zone) to split the control charts by Vendor, as shown in Exhibit 5.

Exhibit 5 Control Chart of Compound 1 and Compound 2 Split by Vendor



To create, Analyze>Quality and Process>Control Chart Builder. Drag Compound 1 to the Y zone. Drag Batch to the Subgroup zone at the bottom. Drag Vendor to the top of the chart in the Phase zone.

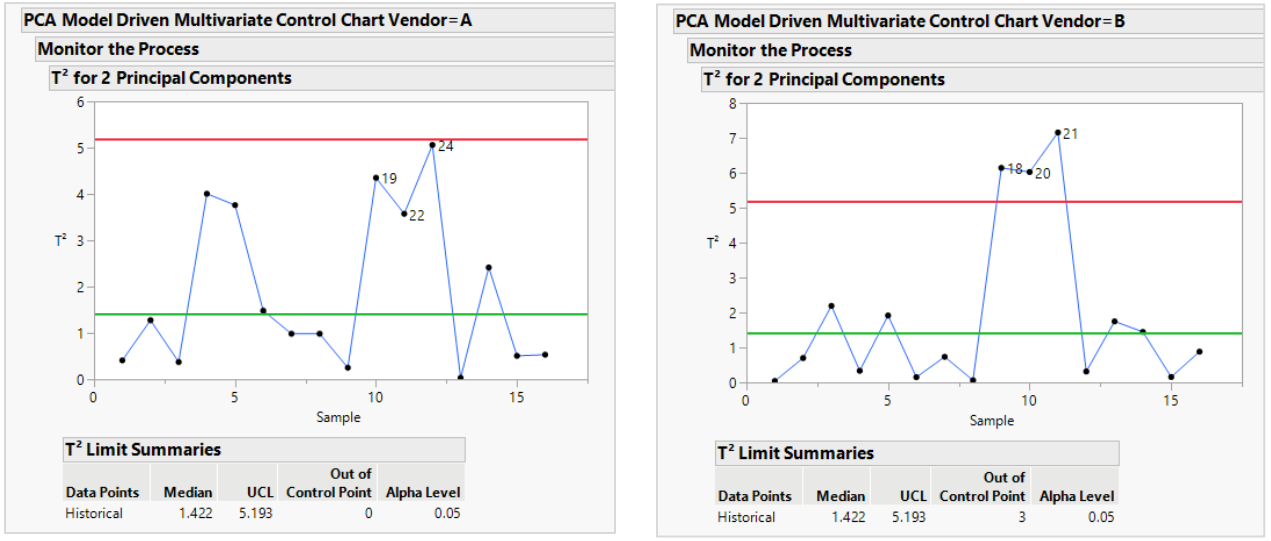
Once the XBar & R chart appears, right-click on the graph. Select Limits. Under limits, select Zones and Shaded Zones. Under the same drop-down select Spec Limits and populate 100 as LSL and 500 as USL. Repeat the same steps to create XBar & R chart for Compound 2 by Vendor by using 300 as LSL and 600 as USL.

From Exhibit 5, it can be observed for both compounds that Vendor A has more “natural” batch-to-batch variation than Vendor B. However, while Vendor A is stable (within the control limits) for both compounds, Vendor B also exhibits special cause variation for Compound 1.

Model-driven multivariate control charts (MDMVCC)

Model-driven multivariate control charts are used to monitor parameters for multiple processes in a single control chart. With the Model-Driven Multivariate Control Chart (MDMVCC) platform, a control chart can be built based on principal components or partial least squares models. For a set of continuous variables, the MDMVCC platform uses principal components to build the control chart. Use multivariate control charts to monitor a multivariate process. The added value is the ability to detect instability in a multidimensional space, which seems to be stable by just looking at the individual dimensions independently. As a special feature, one can interactively drill down to investigate the contributions of individual variables to the overall signal to diagnose the process.

Exhibit 6 Model-Driven Multivariate Control Chart for Vendor A and Vendor B



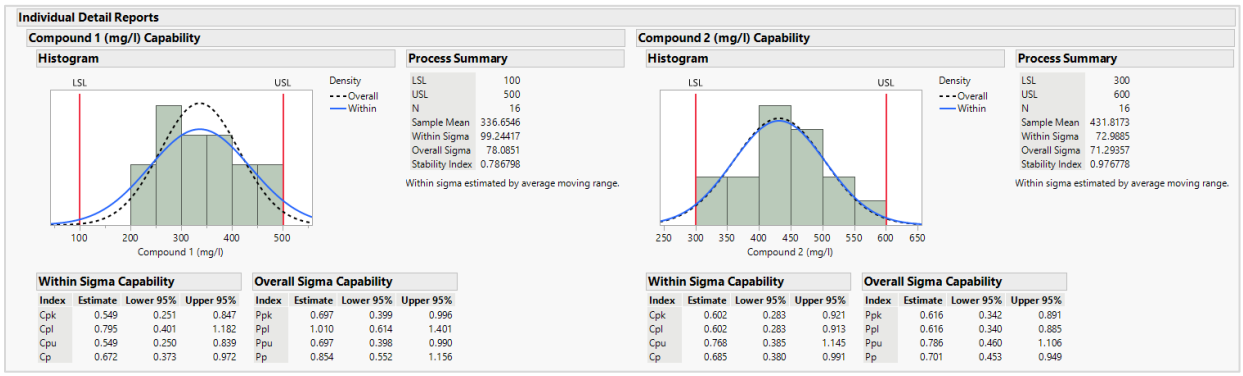
To create, Analyze>Quality and Process>Model Driven Multivariate Control Chart. Select both Compound 1 and Compound 2 and drag them to Process. Drag Batch # to Time ID; drag Vendor to By. Click OK.

The T^2 values for Vendor A are within limits. For Vendor B, it is clearly visible that there is a multivariate instability as evidenced by the steep increase in T^2 values for Batches 9, 10 and 11. The same is mentioned in the limit summaries where three batches are out-of-control points for Vendor B.

Process capability analysis

Process capability analysis measures how well a process is performing compared to given specification limits. A good process is one that is stable and consistently produces a product that is well within specification limits. A capability index is a measure that relates process performance, summarized by process center and spread, to specification limits.

Exhibit 7 Individual Detail Reports of Compound 1 and Compound 2 for Vendor A



To create, Analyze>Quality and Process>Process Capability. Select both Compound 1 and Compound 2 and drag them to Y, Process. Select both processes from the right panel, then select Distribution Options>Set Process Distribution. Under the Distribution drop-down, select Best Fit, drag Vendor to By and click OK.

A pop-up will appear asking for LSL and USL for Compound 1 and Compound 2. Enter 100 and 500 as LSL and USL for Compound 1; enter 300 and 600 as LSL and USL for Compound 2. Select All Show Limits. The output will give process capability by Vendor and by process. Click the red triangle next to Process Capability Vendor A and Vendor B, select Individual Detail Reports and Process Performance Plot. On the red triangle for each goal plot, select Shade Levels.

Exhibit 8 Individual Detail Reports of Compound 1 and Compound 2 for Vendor B

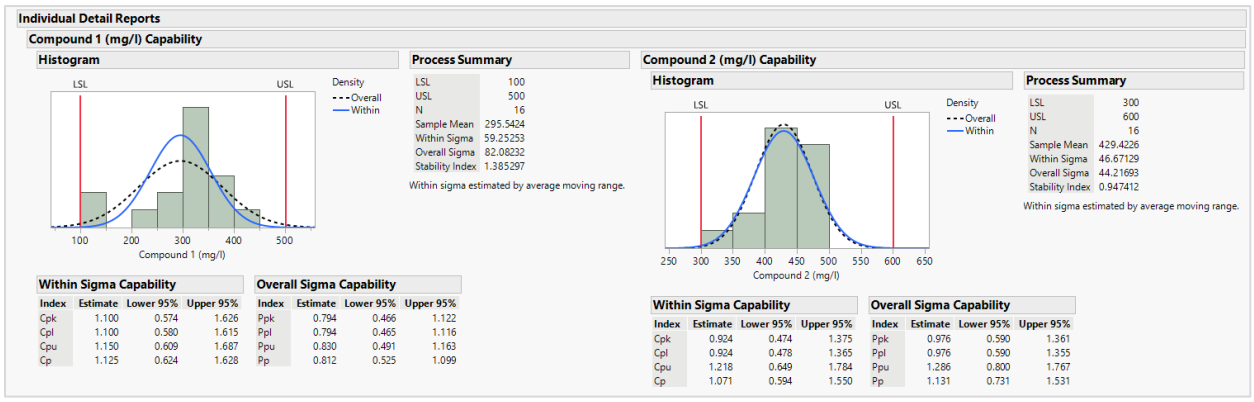


Exhibit 9 Goal Plot and Process Performance Plot for Compound 1 and Compound 2 for Vendor A

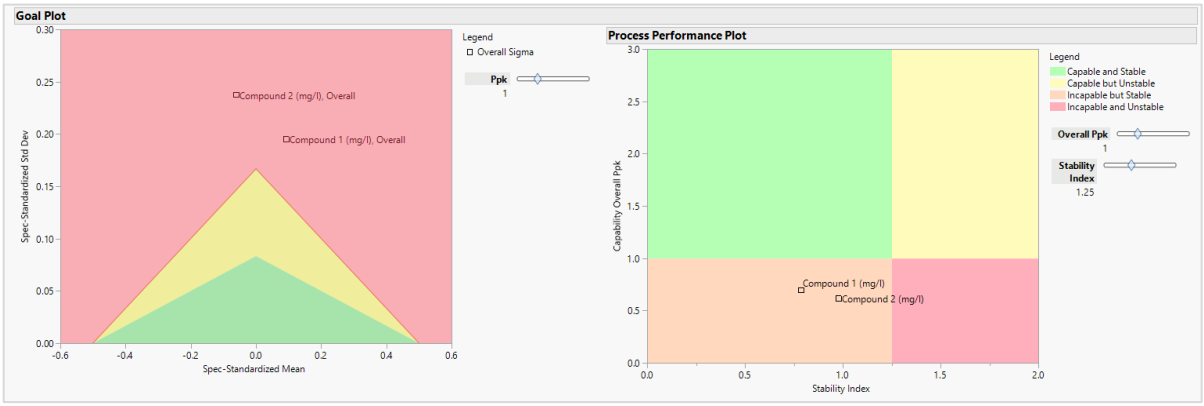
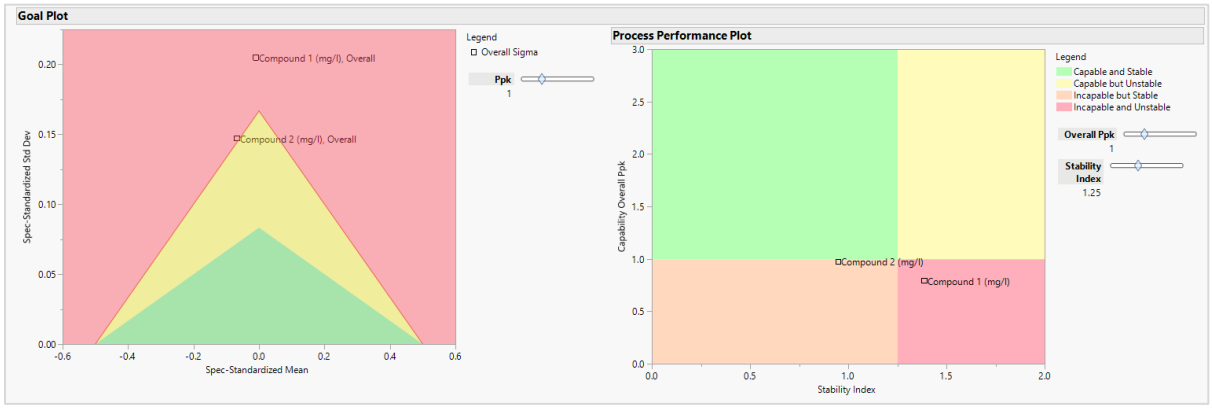


Exhibit 10 Goal Plot and Process Performance Plot for Compound 1 and Compound 2 for Vendor B



Exhibits 7 and 8 show the detailed capability results. The specification limits appear on the histogram in the process capability report so that the data can be visually compared to the limits. Exhibits 9 and 10 show the goal plots and process performance plots.

This process performance graph highlights the two dimensions of process health, namely Stability Index and Capability (P_{pk}). A stable process will have a Stability Index near 1. Note that higher values of the Stability Index indicate a less stable process. Capability Index is a measure that relates process

performance, summarized by process centering and variability. Six Sigma initiatives aim for much higher capability levels that correspond to extremely low rates of defective parts per million.

Using the parameters P_{pk} and the Stability Index, the parameters are distributed in four quadrants. The ideal settings (Capable and Stable) are shown in the green shaded region of the plot, where $P_{pk} > 1.0$ and Stability Index < 1.25. The Incapable and Unstable settings are in the red-shaded region, where $P_{pk} < 1.0$ and Stability Index > 1.25. Both thresholds can be changed by using the sliders on the side.

From Exhibits 9 and 10, it can be observed that for Vendor A, both processes for Compound 1 and Compound 2 are stable but incapable. However, for Vendor B, Compound 2 is stable but incapable and Compound 1 is both incapable and unstable.

Further actions

Now that Lawrence and his team have detected special cause variation in the raw material, the following has been decided:

1. Use I&MR charts and multivariate control charts to monitor the raw material quality of both vendors and key process parameters. The suppliers are also asked to use these control charts to reduce process variation.
2. Increase the frequency of the raw material analysis. If the incoming product is not stable, all supplied batches will be measured. Currently this is not possible, since the actual GC analysis method is too slow, creating a bottleneck. Ultra-high-pressure liquid chromatography (UHPLC), a rapid analysis method is under development in the quality lab. The new analysis method is not yet ready for validation because of too much high measurement variation. Also knowing that a few conditions during data collection influence the accuracy and precision, the measurement procedure should be analyzed and optimized as a next step.
3. A stretch goal is to use UHPLC for inline process control and to use goal and process performance plots to monitor overall process stability and capability.

Summary

Statistical insights

The key task in this case was to better understand and control process variation and process quality. Variation is inherent in any real-world system or process and must be considered before any process assessment or improvement. Toward this goal, we looked at both common and special causes for variation and tried to eliminate the latter by applying statistical process control. The key tools are control charts, either univariate or multivariate. By eliminating special causes, it is possible to also assess the process outcome compared to external requirements, which was done by a capability analysis.

Managerial implications

Achieving manufacturing excellence is the goal of every quality engineer. To reach that goal, it is important that the quality department continuously works to identify the sources of process variation and then takes appropriate measures to control them. Quality should be built into the process, which not only adds flexibility but also ensures that the requirements of the product and services are met.

JMP features and hints

This case used the Distribution platform to visualize the data in the form of a histogram and check for the normality of the distribution. It also leveraged several Quality and Process platforms, starting with Control Chart Builder to produce control charts easily, up to more advanced model-driven control charts. Process Capability was used to analyze the capability and stability with respect to specification limits. Goal plots and process performance plots combine variation (spread) and capability (location) into one output, which is extremely useful if there is a large number of processes to be monitored.

Exercise

FVM Pharmaceuticals has another liquid drug that has three compounds supplied by three vendors. The quality team collected the samples of raw material quality data for all the three compounds (Compound Q, Compound R and Compound S) coming from three vendors (Vendor A, Vendor B and Vendor C) for 10 days for all the batches. The data is presented in the data set FVM_Exercise.jmp

The specification limits are listed in the table below:

Compound	LSL	USL
Q	300	600
R	150	450
S	400	900

A) Visualize the data using the control statistical process control charts.
B) Comment on the process performance.
C) Classify the processes based on the stability and performance. Present your conclusions.