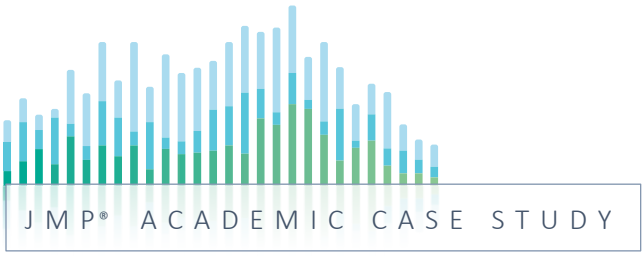

JMP048: Manufacturing Excellence in Pharma – Part 2

Measurement System Analysis (MSA), Analysis of Variance (ANOVA)

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Manufacturing Excellence in Pharma – Part 2

Measurement Systems Analysis (MSA), Analysis of Variance (ANOVA)

Key ideas

This case study requires the use of measurement systems analysis (MSA) to assess the precision, consistency, and bias of a measurement system. Within the Six Sigma DMAIC methodology, MSA addresses the Measure phase, while process behavior charts (or control charts) used in Part 1, address the Control phase. MSA helps to predict and characterize future outcomes. One can use the information gleaned from MSA to interpret and configure process behavior charts. This case also involves variability gauge charts to analyze continuous measurements that can reveal how a measurement system is performing. One can also perform a gauge study to see measures of variation in the data.

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 Quality Control Team observed a significant variability in one of the critical product properties of the drug delivered. To address this issue, a cross-functional improvement team was formed to identify the root cause of the problem and then solve it. The head of the Cross Functional Team is Lawrence, a quality engineer who is a firm believer of data-enabled decision making. He knows that building a strong quality culture into the process demands application of statistical techniques to the data to discover the actionable insights. He also knows from his experience that bringing operational excellence into the manufacturing process is a sequential and multistage process starting from raw material to final inspection. At the same time, Quality by Design (QbD) involves ensuring quality throughout the production process (starting from raw material to finished product), while giving flexibility to the manufacturing system.

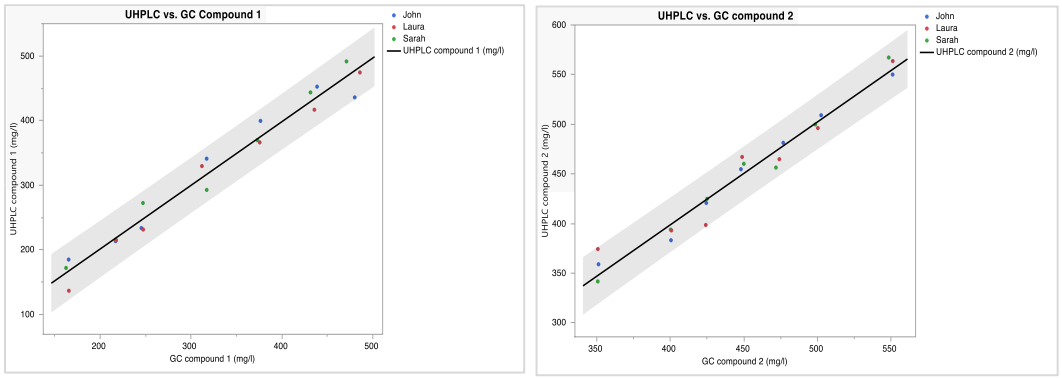
Lawrence and his team have a huge challenge ahead of them to identify the reasons for variation and find ways not only to minimize them, but also to identify the optimized process parameters to meet the quality standards.

In Part 1 of this case study, Lawrence decided to start the investigation with the raw materials, where he found that Vendor A's processes for Compound 1 and Compound 2 are stable but incapable. However, for Vendor B, Compound 2 is stable but incapable and Compound 2 is both incapable and unstable.

Based on their initial findings from raw material investigation, Lawrence and his team started exploring a UHPLC measurement system to enable faster and closer raw material monitoring. While raw material monitoring is still offline, it should be possible with UHPLC to measure all batches. They set faster inline analysis as a stretch goal for the future.

The dataset UHPLC_GC.jmp shows the measurements of GC and UHPLC for both Compound 1 and Compound 2 for each of the operators: John, Laura, and Sarah. A simple data visualization using Graph Builder help explain the precision.

Exhibit 1 UHPLC vs. Standard GC Analysis Results for Compound 1 and Compound 2



To create, Graph>Graph Builder>Drag GC compound 1 to X axis, UHPLC compound 1 to Y axis. Drop the Operator column to the Color zone on the right side of the panel. Select Line of Fit from the top chart list. Select Prediction instead of Fit from the Line of Fit option from the left panel. Repeat the same steps to create the chart for Compound 2.

As shown in Exhibit 1, UHPLC is still in the preliminary exploration phase; it shows poor precision compared to the actual standard GC method.

Since the process involved three operators, the team wanted to examine how much of the variability is due to operator variation (reproducibility) and measurement variation (repeatability) when different raw material batches are analyzed, so they launched a Gauge R&R study. The main goal of the study is checking the extent to which the actual UHPLC method can discriminate between batches so that quality deviations can be detected. Poor Gauge repeatability and/or poor reproducibility are signs that the discrimination power is too low.

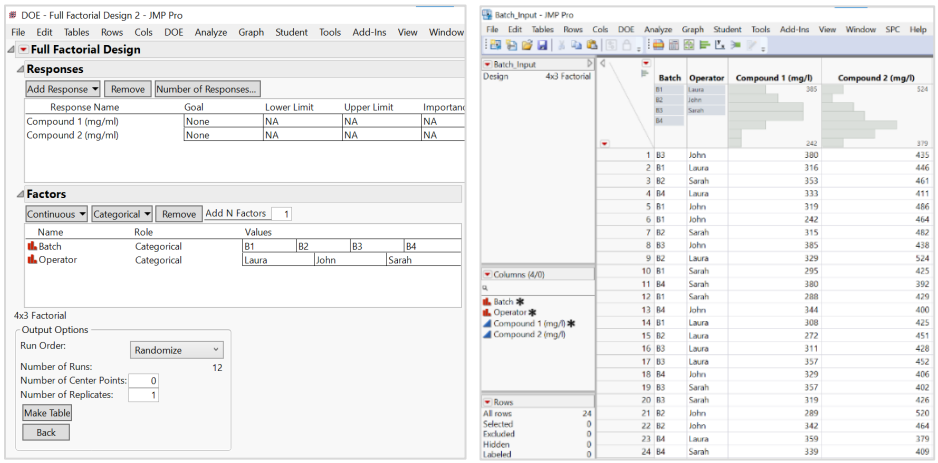
The data Batch_Input.jmp

After applying a full factorial experimental design, as shown in Exhibit 2, the quality team collected the UHPLC measurement data for both compounds (1 and 2) coming from three operators (John, Laura, and Sarah) for four batches (B1, B2, B3 and B4) with additional repeated measurement for the batches. The description of the variables is below.

Batch	The serial number of the batch (B1, B2, B3, B4)
Operator	The name of the operator
Compound 1	Quality of Compound 1 measured in mg/l
Compound 2	Quality of Compound 2 measured in mg/l

The Compound 1 and Compound 2 variables contain continuous data. The Batch and Operator variables contain nominal data.

Exhibit 2 Full Factorial Design for UHPLC Gauge R&R Study with Measured Responses



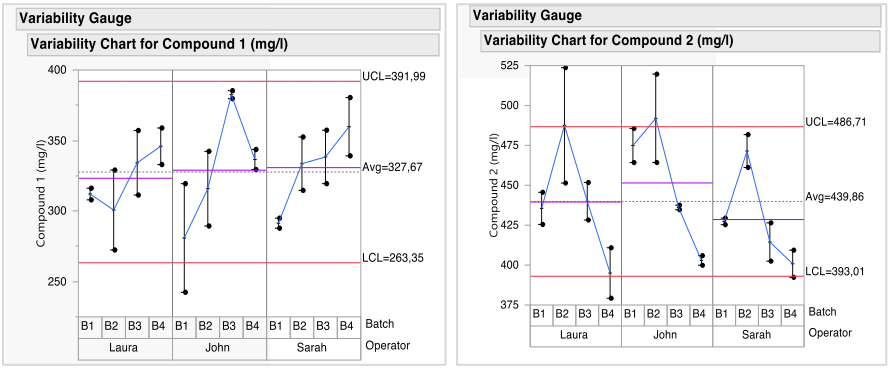
To create, DOE>Classical>Full Factorial>Add two responses: Compound 1 and Compound 2. Add Batch as a categorical factor with four levels and Operator with three levels. Update as shown in Exhibit 2. Set number of replicates to 1 and click Make Table. This will create a table with different factor settings to collect the data on the responses.

Analysis

Lawrence and his team began identifying the variation between the operators using a variability chart. Just as a control chart shows process variation across time, a variability chart shows the same type of variation across categories, such as parts, operators, repetitions, and instruments. A variability chart plots the data and means for each level of grouping factors, with all plots side by side. Along with the data, one can view the mean and range of the data in each category to see how measurements change across the categories.

The report options assume that the primary interest is how the mean and variance change across the categories. Variability charts are commonly used for measurement systems analysis such as Gauge R&R. This analysis examines how much of the variability is due to operator variation (reproducibility) and measurement variation (repeatability).

Exhibit 3 Variability Chart of Compound 1 and Compound 2



To create, Analyze>Quality and Process>Variability/Attribute Gauge Chart. Drag Compound 1 to the Y zone. Drag Operator to the X zone and then drag Batch to the X zone. Click OK. Under the red triangle menu, choose Connect Cell Means, Show Grand Mean, Show Group Means, Points Jittered, Xbar Control Limits. Repeat the same steps to create a variability chart for Compound 2.

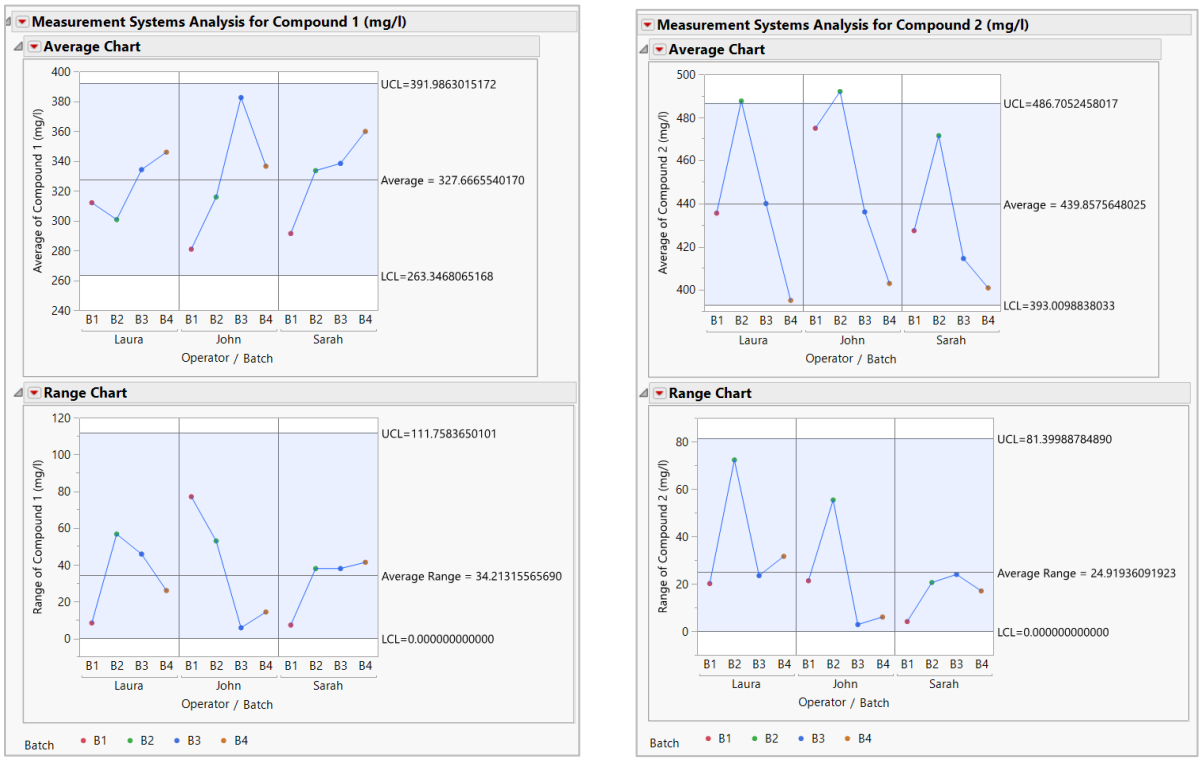
The variability charts in Exhibit 3 show patterns of variation that can be used to identify possible sources of variation (e.g., within operator, between operator, over time), also called variance components. If you notice that any of these sources of variation are large, you can then work to reduce the variation from that source.

The charts show the measured response on the y-axis and a multilevel, categorized x-axis. The chart shows the range of measurements for each operator by batch. Each measurement appears on the chart. Maximum and minimum bars indicate the range of values for each cell, and a cell means bar indicates the average value for each combination of values.

You can see for Compound 1 that John has more variation in his measurements than Laura and Sarah. However, for Compound 2, Laura has more variation in her measurements than the other two.

Based on these findings, the team wanted to understand how much variation in the response data can be assigned to the measurement setup. Thus, they performed a measurement system analysis, a systematic approach to reduce the noise to better see the signal in measured data.

Exhibit 4 MSA Initial Report: Average and Range Charts of Compound 1 and Compound 2

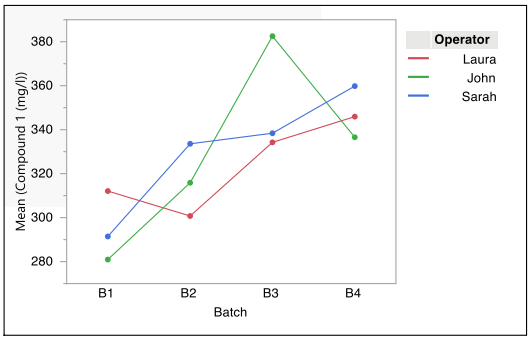


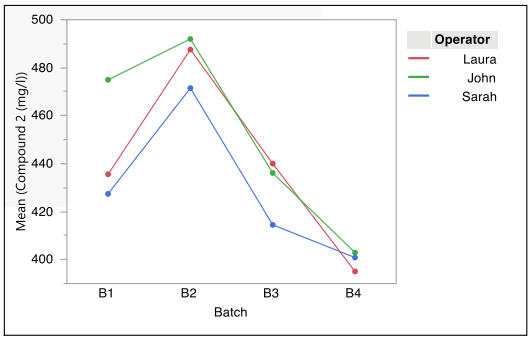
To create, Analyze>Quality and Process>Measurement System Analysis. Drag Compound 1 and Compound 2 to the Y zone. Drag Operator to X Grouping and Batch to Part zone. Click OK. Under the red triangle menu, choose Parallelism Plots, Test-Retest Error Comparison and EMP Gauge R&R Results.

The average chart in Exhibit 4 shows the average measurements for each operator. The means of the measurements are generally within the control limits for both the compounds, with the exception of John for Compound 2. The range chart shows the variability for each operator. Since the ranges are within the control limits for both Compound 1 and Compound 2, it indicates that the operators are measuring parts in the same way and with similar variation.

The control limits of the average charts in Exhibits 3 and 4 are computed from the random test-retest measurement error (natural within-batch variation). One can clearly see that the large measurement error causes wide limits that obscure any potential systematic batch variation and instability effect!

Exhibit 5 Parallelism Plots for Operator and Batch for Compound 1 and Compound 2





The parallelism plots in Exhibit 5 show the average measurements for each batch by operator. Because the lines are not parallel and there is a major crossing, one can conclude that there may be interaction between operators and batches for both Compound 1 and Compound 2. Interactions indicate a serious issue that requires further investigation.

Evaluating the measurement process (EMP) is a modern and visual assessment of the measurement setup, and the EMP Gauge R&R Results (Exhibit 6) partition the variability in the measurements into product (or part) variation and Gauge R&R (measurement) variation. The calculations in this report are based on variances, not ranges. We get the same results as from the Gauge R&R report in the variability chart platform, except that the calculation for reproducibility does not include interactions and negative variance components are set to zero. Zero values could indicate the presence of outliers in the results.

Exhibit 6 EMP Gauge R&R Results for Compound 1 and Compound 2

EMP Gauge R&R Results

Component	Std Dev	Variance Component	% of Total	20 40 60 80
Gauge R&R	27.670253	765.6429	56.3	
Repeatability	27.670253	765.6429	56.3	
Reproducibility	0.000000	0.0000	0.0	
Product Variation	24.391369	594.9389	43.7	
Interaction Variation	0.000000	0.0000	0.0	
Total Variation	36.886065	1360.5818	100.0	

EMP Gauge R&R Results

Component	Std Dev	Variance Component	% of Total	20 40 60 80
Gauge R&R	22.598991	510.7144	30.7	
Repeatability	20.817847	433.3827	26.1	
Reproducibility	8.793841	77.3316	4.7	
Product Variation	33.928918	1151.1715	69.3	
Interaction Variation	0.000000	0.0000	0.0	
Total Variation	40.766234	1661.8858	100.0	

Performing a Gauge R&R study helps to attribute the total variation to the following sources:

- The process variation from one batch to another, which is the ultimate variation that you want to study if measurements are reliable.
- Repeatability, the variability inherent in making multiple measurements, which is also called the within variation.
- Reproducibility, the variability resulting from different operators measuring batches.

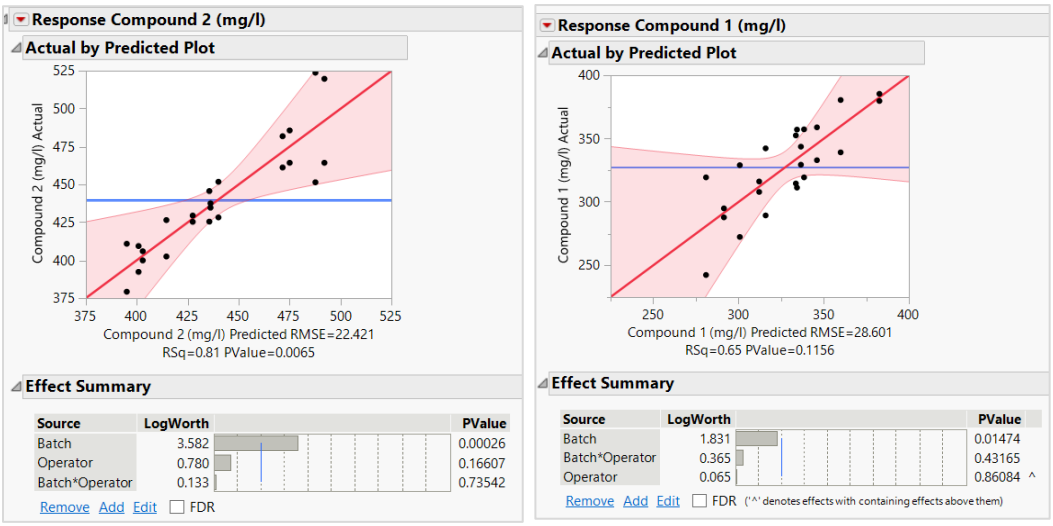
A Gauge R&R analysis then reports the variation in terms of repeatability and reproducibility.

The main component in the Gauge R&R is repeatability, which accounts for 56.3% of the total variation for Compound 1 and 26.1% for Compound 2. It can be concluded that the main task for improving the UHPLC measurement system is optimizing repeatability. As the reproducibility component only accounts for 0-4.7% of the gauge variation, operator bias doesn't appear to be an issue so far.

Analysis of variance (ANOVA)

Lawrence and his team also wanted to explore the differences between batches and between operators, including their interactions, to study their synergistic effect. They conducted a two-way analysis of variance (ANOVA), a statistical method to explore the variation among groups.

Exhibit 7 ANOVA Results for Compound 1 and Compound 2



To create, Analyze> Fit Model. Drag Compound 1 and Compound 2 to the Y zone. Drag Batch and Operator to the Model Effects, select both Batch and Operator from the columns list and click Cross. This will add the interaction between Batch and Operator to the model effects. Select the option Fit Separately and click Run.

According to the Effect Summary, there is a significant batch variation for both compounds. Statistically non-significant operator and batch interaction effects can be detected; however, this can be a consequence of high RMSA caused by the large measurement error. By improving repeatability operator and interaction, effects may show up again later.

A very important conclusion drawn from the charts above is that the actual UHPLC measurement method is unable to detect quality shifts caused by significant systematic batch-to-batch variation as is shown in the ANOVA analysis (Exhibit 7).

Summary

Statistical insights

This case introduced the concept of variance components, which can include process variables, as well as settings of the measurement procedure. Now that Lawrence and his team have found the sources of variation in the data using measurement system analysis, the next stage will be to ascertain the possible variables/factors and their effects (whether linear, nonlinear or interaction) on the measured variation. Finally, it will be important to find the optimal settings for those factors and to make the process more robust.

Managerial implications

Again, manufacturing excellence had to be applied before making any decisions or requesting process changes. As shown here, it is important to eliminate (or minimize) the variation introduced by the measurement itself. This variation would just add noise to our measurements, which makes it difficult to analyze the signal. For this reason, a measurement systems analysis should always kept in mind if the signal-to-noise ratio is poor.

JMP features and hints

This case used Graph Builder for data visualization and DOE to design a full factorial experiment. It also leveraged Quality and Process platforms and used variability charts measurement system analysis (MSA) to compare the variance components. Fit Model was used to create an ANOVA report to explore the effects of different batches and operators.

Exercise

FVM Pharmaceuticals has a liquid drug that has three compounds from three batches. The process involved four operators (Tina, Byron, Kelci and Mary). The team wanted to examine how much of the observed variability is due to operator variation and measurement variation. The data is presented in the data set, FVM_Exercise2.jmp.

A) Construct a variability chart for each of the three compounds and comment on the metrics.
B) Perform a measurement systems analysis to find the sources of variation.
C) Determine if there is any statistically significant impact of the interaction between Batch and Operator on the quality measurement of the compounds. (Hint: perform a two-way ANOVA.)