

How JMP 14 can predict performance of future batches.

A game changer in validation of pharmaceutical processes

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Conclusion

In JMP 14 from SAS future pooled batch performance concerning C_p and C_{pk} can be predicted using historical batches, like validation batches. This is now a built-in feature in the Between-and-Within Six Sigma Capability calculation in the 3-Way-Chart in the Control Chart Builder. Specifically, for the pharmaceutical industry, it is a ready to go method for evaluating stage 2 validation, which is highly needed.

To a large extent, this is like doing a variance component analysis as recommended by International Society for Pharmaceutical Engineering¹. From confidence intervals on variance components the prediction can be enforced with confidence, which is needed in validation stage 3A. For processes with large variance between batches compared to variance within a batch many batches are needed in stage 3A. For processes with small variance between batches, the usual 3 batches are typically enough, and validation might be finalized already in stage 2.

Due to the way JMP converts ranges to standard deviation, it is our recommendation to use the within batch standard deviation chart in the 3-Way-Chart (Range by default) for more than 25 measurements in a batch. For few batches, which is typical in validation, the moving range method in the 3-Way-Chart of estimation of between batch variance is very sensitive to the order of data. A 3-Way-Chart where both between and within variance is estimated from variance components would be preferred.

Background

Most companies in the pharmaceutical industry still pass a validation simply on the fact that three consecutive batches individually pass an acceptance criterion based on estimated performance. Typical performance indices are:

- mean value
- standard deviation or $P_p = \frac{USL-LSL}{6s}$
- mean and standard deviation combined into $P_{pk} = \frac{\text{Min}\{USL-\bar{X}, \bar{X}-LSL\}}{3s}$

Challenges

There are two serious problems with that:

The estimated performance is the performance of the sample, not of the population

The consumer does not receive products from the sample, but from the non-tested part of the batch, which is often referred to as “the full population” or “the real world”. Hence, the consumer is interested in the performance of the population – not just the sample.

Validation is about predicting the future, NOT the past.

Even though the three batches had a good performance, it is insufficient for a validation.

Additionally, the prediction of future performance must meet pre-determined acceptance criteria. For this, between batch variance needs to be taken in to consideration.

Questions

This leads to two obvious questions:

1. How are acceptance criteria in validation based on population performance defined?
2. How is future performance predicted?

Answer Question 1: Enforce with confidence

The answer to the first question is straightforward: Place a X% (typically 95%) confidence interval around the estimated summary statistic. X% of these confidence intervals will contain the population/true value, so if the whole interval is in the acceptable region we can with X degree of confidence state that the population/true value is OK.

Answer Question 2 Predict the future

The validation batches should be considered as a random sample of on infinite population of all future batches. By doing either a Between-and-Within Sigma Capability calculation or a Variance Component Analysis in JMP the performance of future batches pooled together as in an Annual Product Review can be predicted. The advantage of the Between-and-Within Sigma Capability calculation is that it is a build in feature in JMP that directly gives C_p and C_{pk} values for future batches pooled together. In the Variance Component Analysis, variance components and mean (intercept) must be manually combined in to a P_{pk} value. The advantage of the variance component analysis is that it comes with confidence intervals. In the following, both methods will be applied on two data sets. A data set with low variance ratio of between batch and within batch variance and a data set with a high variance ratio.

Low Variance Ratio example

In Figure 1 the results from 3 batches with 20 measurements in each batch is shown. It is clearly seen that there is low variance between batches compared to within batches

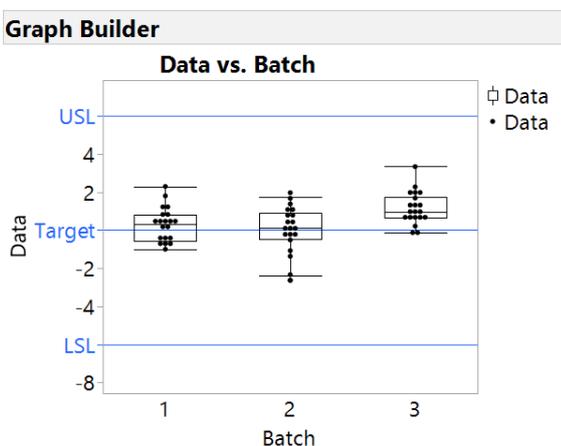


Figure 1: Data set with low variance ratio

Figure 2 shows the result of a Between-and-Within Sigma Capability calculation in JMP 14. Notice that a standard deviation chart for within is chosen, whereas a range chart is default. This is a

deliberate choice as JMP converts range to standard deviation by dividing with $d_2(n)$, using $d_2(25)$ when $n > 25$, thereby being too conservative for large subgroups sizes, which are typical in validation.

Due to the low variance ratio, even pooled batches have a nice bell-shaped distribution. As expected with the low variance ratio the estimated capability is fine. However, there is no confidence limit on it. To get it with confidence, a variance component analysis can be performed. P_p with confidence can be calculated from the total between and within variance component with confidence. P_k (centering index) with confidence can be calculated from the parameter estimate on the intercept (mean of batch means) with confidence.

$$\text{The formula for the centering index is } P_k = \text{Max} \left\{ \frac{T - \bar{X}}{T - LSL}, \frac{\bar{X} - T}{USL - T} \right\}.$$

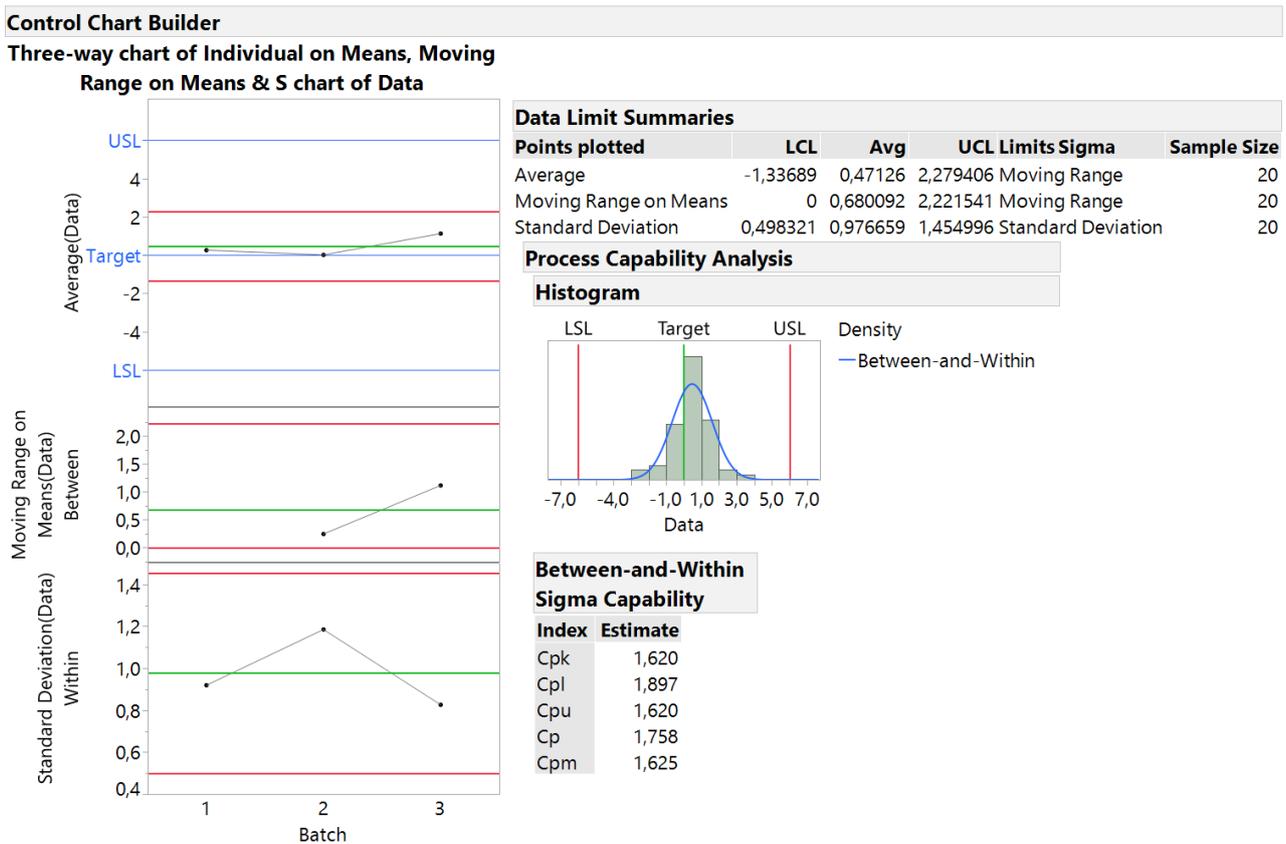


Figure 2 Between-and-Within Sigma Capability low variance ratio

Using the relation $P_{pk} = P_p(1 - P_k)$ the confidence intervals on pooled P_{pk} can be calculated adding the relative confidence uncertainty on P_p and $1 - P_k$ as a root sum square. As this is not standard JMP functionality, we have made a script that performs this calculation. The output from the variance component calculation is shown in Figure 3. It is seen that the major variance contributor (77%) is within batch.

Parameter Estimates								
Term	Estimate	Std Error	DF	t Ratio	Prob> t	Lower 90%	Upper 90%	VIF
Intercept	0,4712601	0,33793	2	1,39	0,2979	-0,515492	1,4580121	.

REML Variance Component Estimates							
Random Effect	Var Ratio	Var Component	Std Error	90% Lower	90% Upper	Sqrt Variance Component	Pct of Total
Batch	0,3006686	0,2937427	0,3427131	0,087816	14,233883	0,5419803	23,116
Residual		0,9769649	0,1830023	0,7363692	1,3700509	0,9884153	76,884
Total		1,2707075	0,3841785	0,8232053	2,2699784	1,1272566	100,000

Figure 3: Variance Component Analysis low variance ratio

These results are automatically generated by our script and converted to a capability calculation for pooled future batches. The result of this is shown in Figure 4. A requirement for P_{pk} of 1, is already proven with confidence after 3 batches in validation. Note: the slightly different estimated capability results in Figure 2 and Figure 4, is a result of differences in evaluation batch-to-batch variability using moving range on batch means (Figure 2) and variance on batch means (Figure 4). It only makes a small difference here because the major source of variation is within batch and this is calculated the same way in the 2 methods.

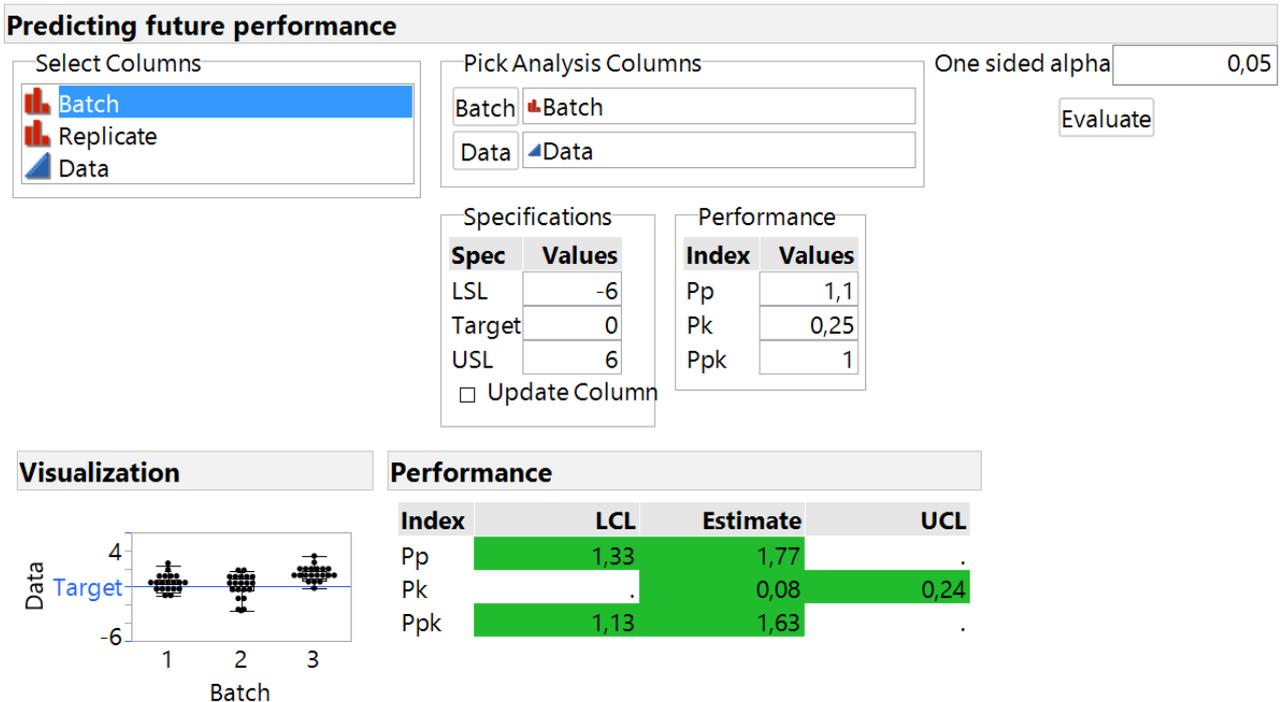


Figure 4. Capability calculation with confidence low variance ratio.

High Variance Ratio example

Figure 5Figure 1 shows the results from 3 batches with 20 measurements in each batch. It is clearly seen that there is a high variance between batches compared to within batches. In addition, the overall performance seems at least as good as on Figure 1.

Graph Builder

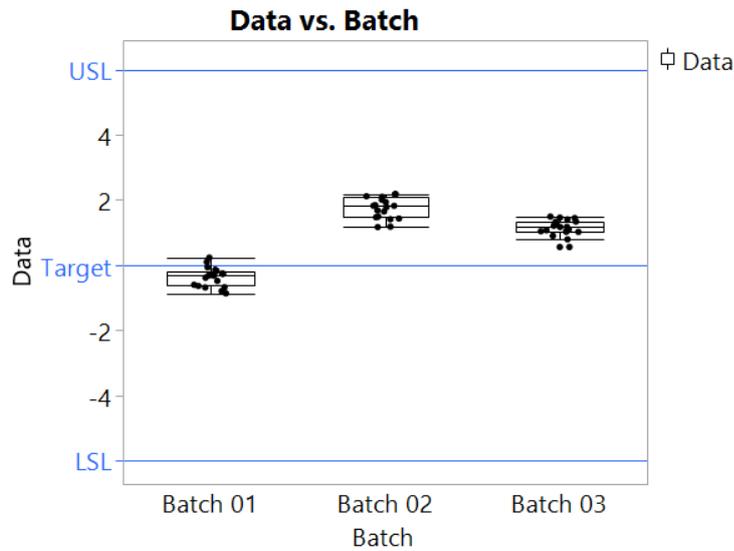


Figure 5.: Data set with high variance ratio

Figure 6 shows the result of a Between-and-Within Sigma Capability calculation. Due to the large variance ratio, the pooled distribution is multimodal. Even though the range on Figure 6 is narrower than on Figure 2, the pooled C_p is lower due to the large batch-to-batch variation illustrated by the blue curve. In Figure 6 the blue curve is much wider than the data in the histogram, while in Figure 2 the width of the blue curve and the histogram is similar. Thus, the overall performance is punished, as it should be, due to the large batch-to-batch variation on the estimate. As there's only 3 batches, the overall performance with confidence will be even worse.

Figure 7 shows the variance component calculation on the high variance ratio data set, and it is seen that the major contribution is batch to batch variation (94%). Notice the wide confidence interval on total variance, due to few batches with the majority of variance.

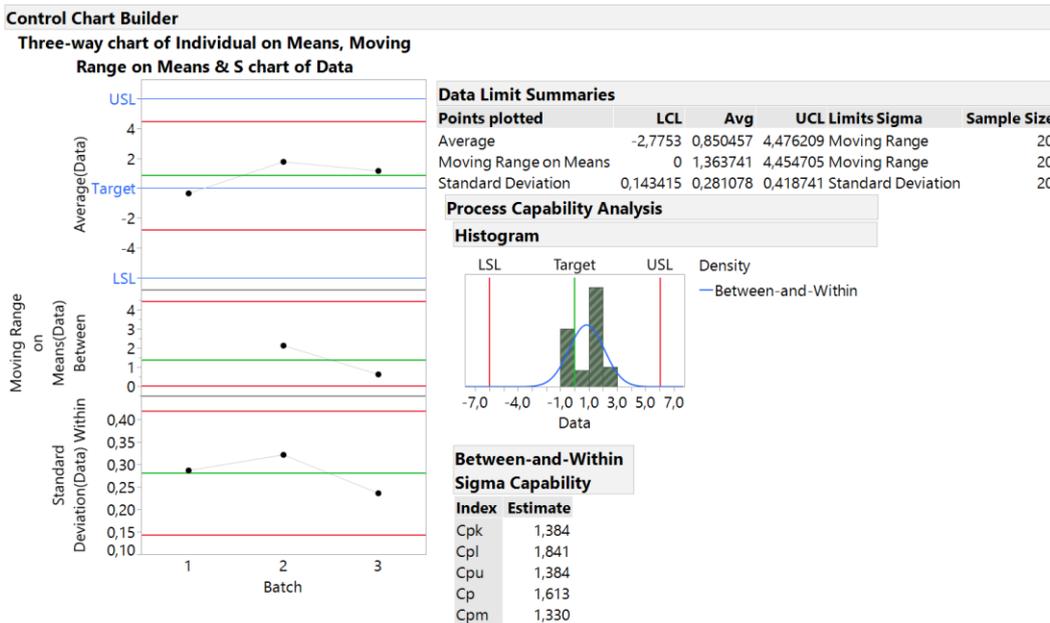


Figure 6: Between-and-Within Sigma Capability high variance ratio

Parameter Estimates									
Term	Estimate	Std Error	DF	Den	t Ratio	Prob> t	Lower 90%	Upper 90%	VIF
Intercept	0,8504565	0,629518	2		1,35	0,3092	-0,987727	2,6886403	.

REML Variance Component Estimates						
Random Effect	Var Ratio	Var Component	Std Error	90% Lower	90% Upper	Pct of Total
Batch	14,767345	1,1848674	1,1888794	0,3945741	23,494162	93,658
Residual		0,0802356	0,0150295	0,0604761	0,1125188	6,342
Total		1,265103	1,1889649	0,4411191	18,446687	100,000

Figure 7: Variance Components high variance ratio

Figure 8 shows the capability results with confidence. It is seen that the estimated values are fine, but the confidence limits are not. In cases with large variance ratio, more batches are required. Notice that in this example there is a larger difference between the estimated values for the two methods in Figure 6 and Figure 8. For the typically few validation batches, the moving range method is very sensitive to the order of data.

In the shown example, mean 1 is compared to mean 2 and mean 2 to mean 3, so batch 2 is the reference in both comparisons. Since batch 2 is the extreme batch of the 3 batches, this leads to too conservative results in Figure 6. For that reason, we recommend the variance method instead of moving range.

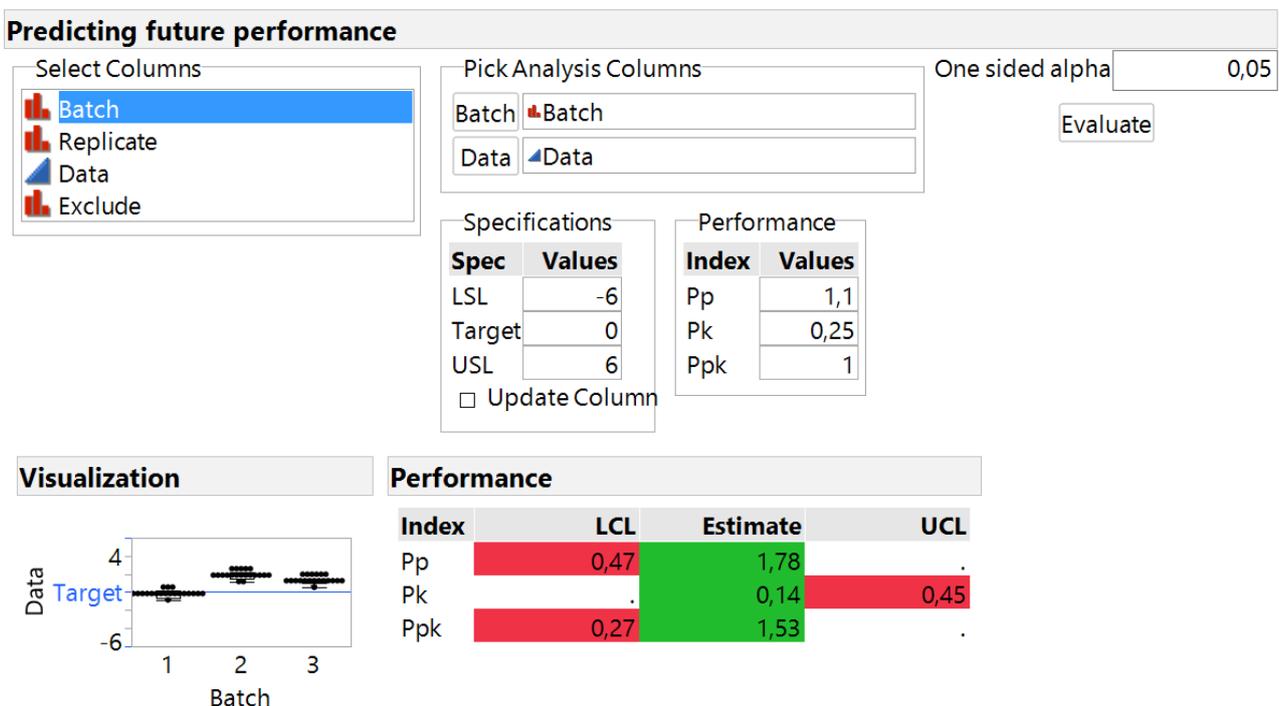


Figure 8: Capability results with confidence high variance ratio

After 6 batches, the calculation is performed again as shown in Figure 9 to Figure 11. It is seen that the acceptance criterion on P_{pk} is fulfilled after 6 batches.

Graph Builder

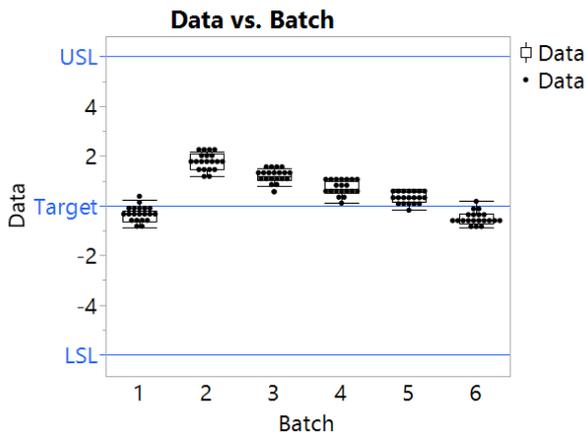
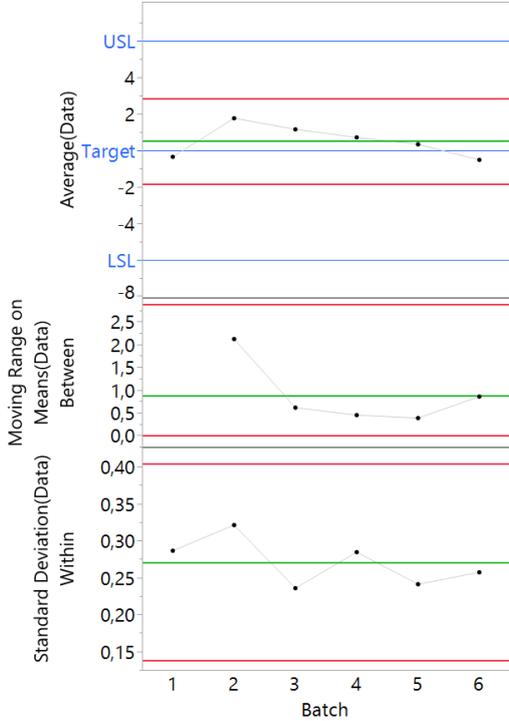


Figure 9: Data high variance ratio after 6 batches

Control Chart Builder

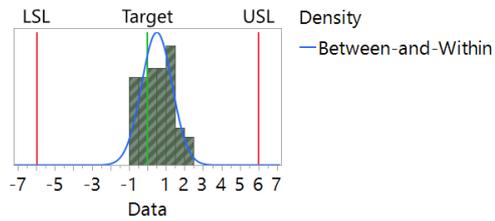
Three-way chart of Individual on Means, Moving Range on Means & S chart of Data



Data Limit Summaries					
Points plotted	LCL	Avg	UCL	Limits	Sample Size
Average	-1,83249	0,509348	2,851185	Moving Range	20
Moving Range on Means	0	0,880827	2,87725	Moving Range	20
Standard Deviation	0,138274	0,271002	0,403731	Standard Deviation	20

Process Capability Analysis

Histogram



Between-and-Within Sigma Capability

Index	Estimate
Cpk	2,218
Cpl	2,629
Cpu	2,218
Cp	2,424
Cpm	2,062

Figure 10: Between-and-Within Six Sigma Capability high variance ratio after 6 batches

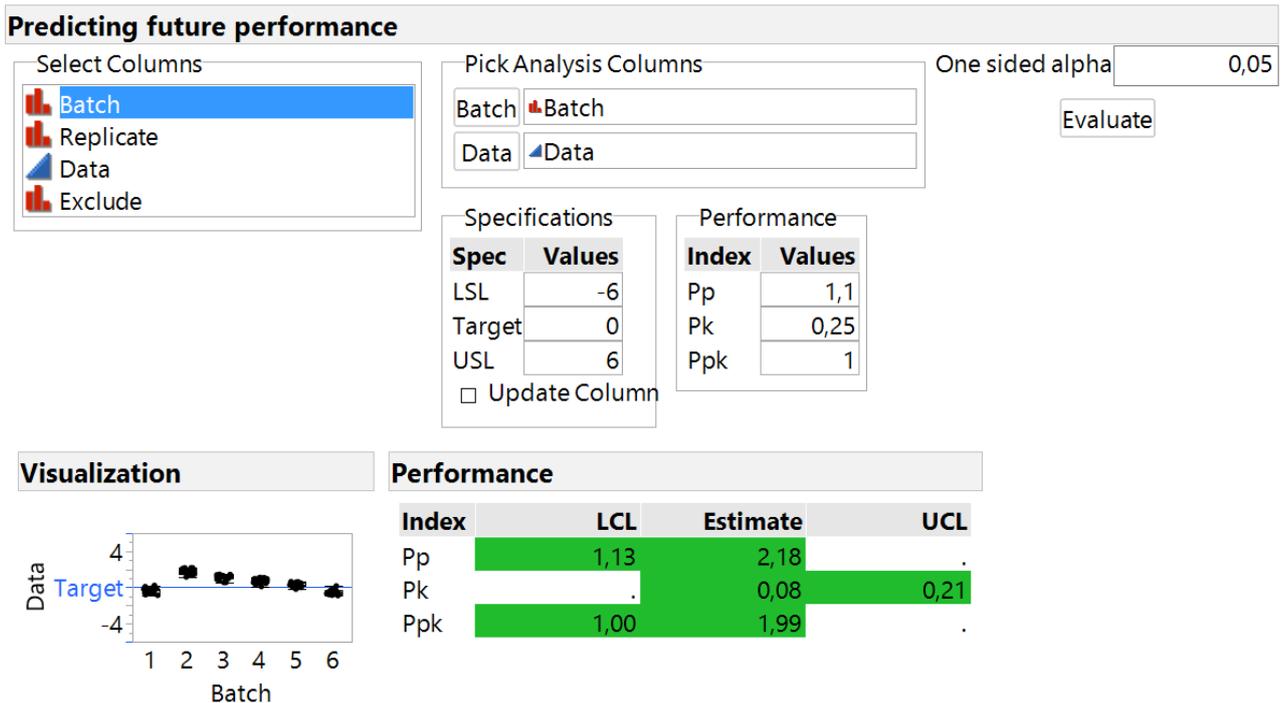


Figure 11 Capability results with confidence after 6 high variance ratio batches

How to do it in practice?

In case of a high variance ratio, much more than 3 batches might be needed before it is proven with confidence that the future pooled capability is good. For practical reasons, they cannot be made in stage 2 of the pharmaceutical validation flow, see Figure 12. In stage 2 batches are quarantined until the performance is proven. It is therefore recommended to perform batch release based on the capability of the individual batch with confidence. However, the validation cannot be completed until the pooled performance is proven with confidence. So, we recommend only evaluating the estimated pooled performance in stage 2 and make the final evidence in stage 3A, where batches can be continuously released. Since stage 2 does not rely on confidence intervals, the 3-way chart can be used here. This of course requires that there is a sufficient QC inspection that will catch ANY defect batches after Stage 2. However, this is typically the case in the pharmaceutical industry. When the performance is proven, sometime later in stage 3A, it can be considered to reduce inspection efforts. Instead of considering it as a threat to make stage 2 longer, see it as a possibility to reduce QC inspection somewhere in stage 3.

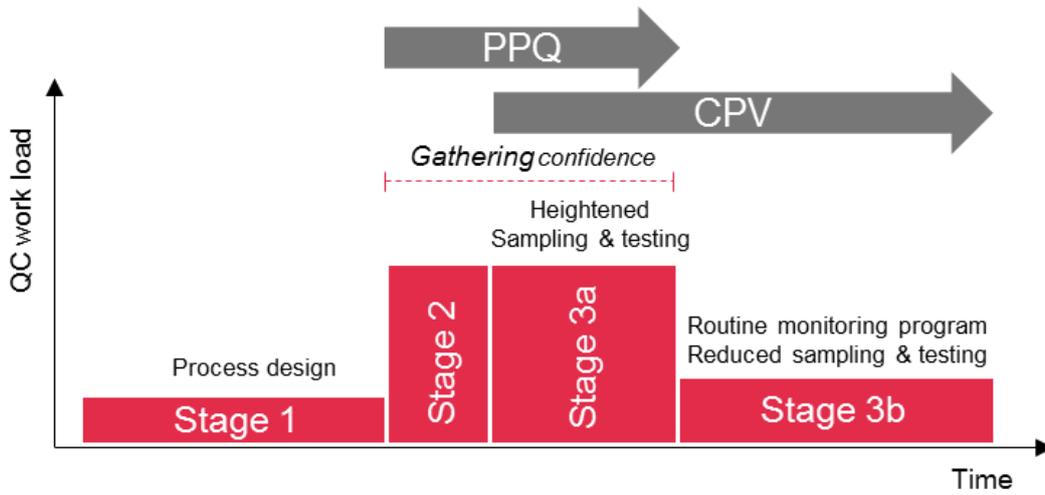


Figure 12: Validation stages

ⁱ <https://www.ispe.org/ispeak/evaluation-of-impact-of-statistical-tools-on-process-performance-qualification-ppq-outcomes>