

Quality by Design Scenario Quality Control and Improvement Charts

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Scenario and Technical Approach

Scenario: A pharmaceutical manufacturing facility has been producing a single-dose tablet drug product for several years. Current measurement systems are based on storing finished material and performing offline quality tests to assure the finished product meets performance specifications. A manufacturing team has been assigned to investigate the manufacturing process and improve its consistency (sigma capability). In this step of the investigation, the team aims to use some Quality by Design tools from the Statistical Process Control arena to establish the current state of the process based on an analysis of the manufacturing data.

Technical Approach: The key tablet performance metric is the extent to which the tablet dissolves after one hour (60-minute mean dissolution time). Manufacturing processes, like the tablet production outlined above, can be analyzed with process control charts, which determine whether a manufacturing process is in a state of statistical control. If under statistical control, the future performance of the process can be predicted with certainty. If not under statistical control, the performance can be analyzed to determine the sources of variation to be eliminated and bring the process back under statistical control.

Quality control and improvement charts are central tools for Quality by Design. Control charts were invented by Walter A. Shewhart in the 1920's while working at Bell Labs trying to reduce the frequency of failures and repairs of telephone transmission lines. Shewhart created control and improvement charts on the basis of mathematical theory (common cause variation) in conjunction with the observation that observer variation in manufacturing data did not always behave just randomly (special cause variation). A control chart is comprised of the following:

- A collection of points representing measurements of product performance (quality) in samples taken from the manufacturing process at different times or events (batches).
- A center line corresponding to the process characteristic mean calculated from the data.

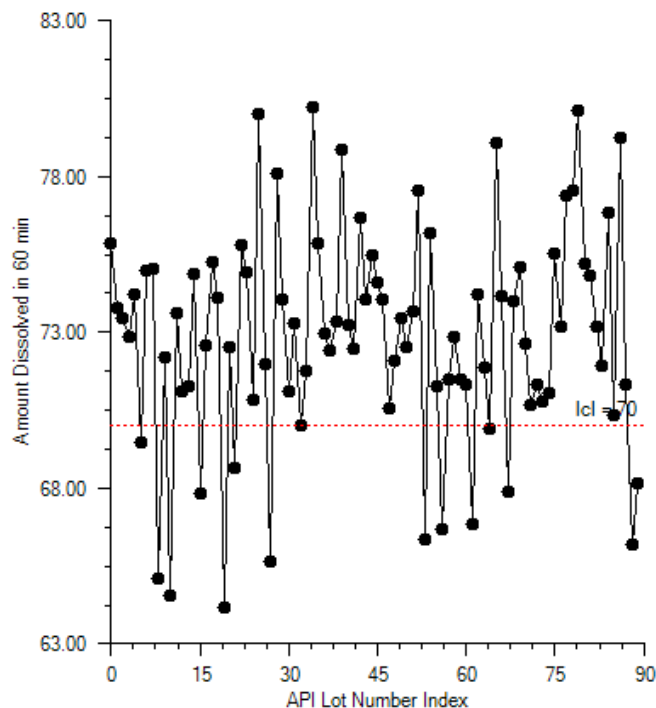
- Upper and lower control limits that indicate the threshold at which the process output is deemed statistically “unlikely.”

Application of quality control and improvements charts to manufacturing data is critical to process investigation and improvement. Unfortunately, desktop productivity software like Microsoft Office Word and Excel lack built-in facilities for quality control and improvement charts. In response to this shortcoming, manufacturing workers take one of the following routes. One, they purchase, learn and deploy specialized software directed at statistical process control. This is time consuming, expensive and ultimately requires multiple import and cut-and-paste operations to produce a results document. Or two, they acquire custom add-ins for Excel that provide support for quality control and improvement charts. This is both expensive and inflexible as the add-ins cannot be modified or extended to include additional features necessary for analysis.

But there is a better way. Using Inference for .NET in conjunction with Visual Numerics’ IMSL C# Numerical Library provides a quick, cost effective and reliable means to add quality control and improvement chart capability to desktop productivity software like Microsoft Word and Excel. Further, you can choose from your preferred, easy-to-learn scripting language like IronPython, IronRuby, managed Jscript or Dynamic VB. The use of IronPython in the analysis scenario is illustrated in the following examples.

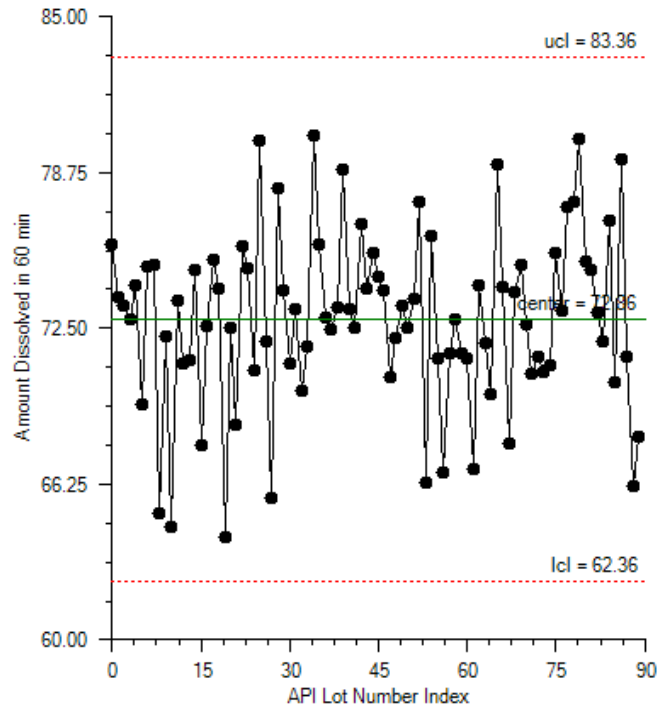
Drug Product Manufacturing Status

What is the Problem with the Manufacturing Process?



The analysis shows that 14 out of 90 batches failed to meet the 60-minute dissolution requirement.

Is Manufacturing Process Unders Statistical Control?

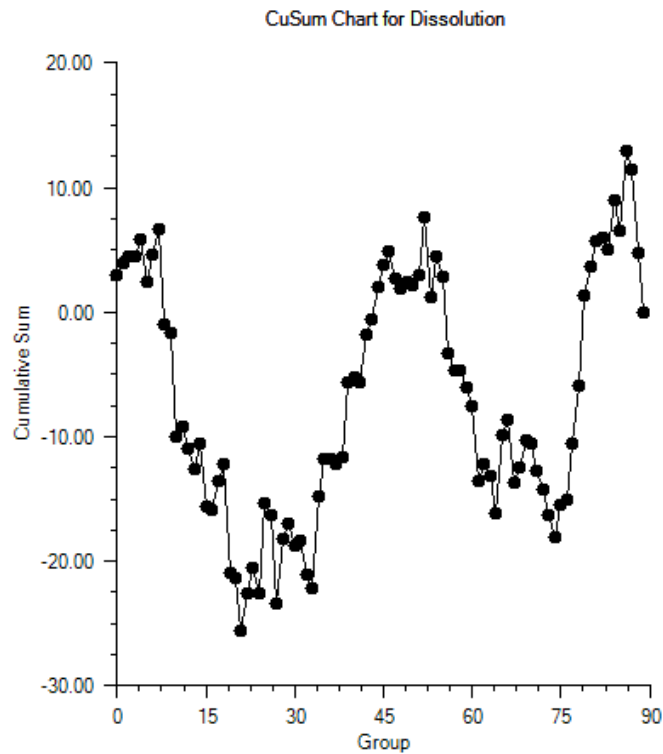


The analysis shows that the manufacturing process is under statistical control because the 60-minute percent dissolution for all historical batches falls within 3 sigmas of the long-term process center for all batches.

Manufacturing Trend Analysis

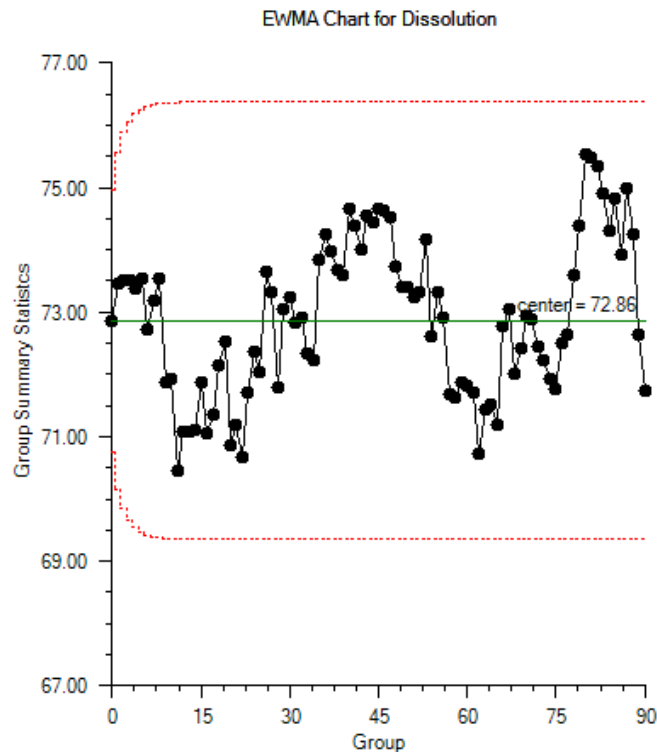
Cusum Chart of the Manufacturing Process

Cusum charts display how the group summary statistics deviate above or below the process center or target value, relative to the standard error of the summary statistics. They are useful to detect small and permanent variation of the mean of the process.



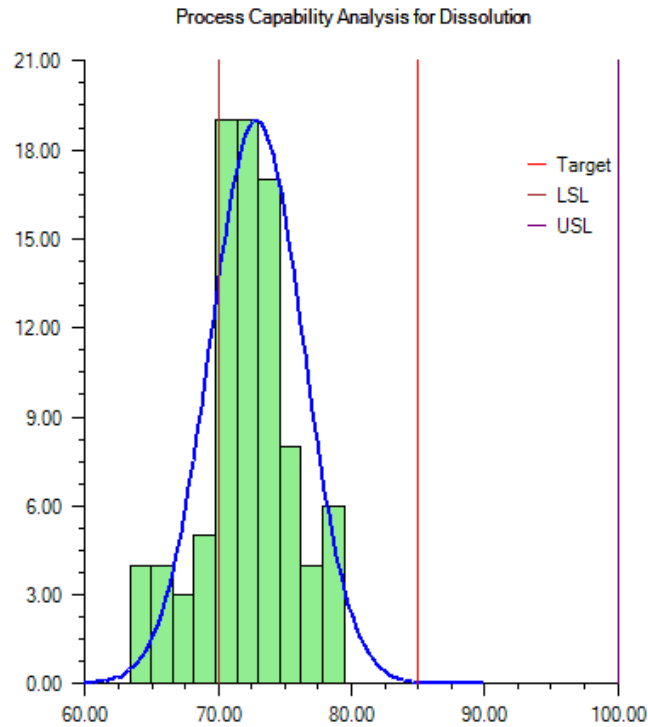
EWMA Chart of the Manufacturing Process

Exponentially weighted moving average (EWMA) charts smooth a series of data based on a moving average with weights that decay exponentially. As for the cusum chart, this plot can also be used to detect small and permanent variation on the mean of the process.



Process Capability Analysis

Once a process is under control the question arises, "to what extent does the long-term performance of the process comply with engineering requirements or managerial goals?" For example, how many of the manufactured tablet batches fall within the design specification limits? In more general terms, the question is, "how capable is our process (or supplier) in terms of producing items within the specification limits?" Process capability analysis allows us to summarize the process capability in terms of meaningful percentages and indices, and it provides the basis for assigning product specifications.



# of Obs	90
Center	72.86056
StdDev	3.5

Target	85
LSL	70
USL	100

Cp	1.43
Cp_l	0.27
Cp_u	2.58
Cp_k	0.27
Cpm	0.4

Obs<LSL	14.0%
Obs>USL	0.0%

It is important to note that the observed overall process capability is due to contributions of measurement system capability and manufacturing process capability, which in turn is due to contributions of supplier process capability and production process capability. Given this caveat, the results display fair process capability — that is, the distribution is off-center although the spread is narrow. The objective in development then becomes to move the distribution toward the center while maintaining the same spread.