

SPC

Background and Application

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Statistical Process Control

Contact Jeff, Ed, or Dave if you are interested in learning more about Statistical Process Control (SPC) or if you are interested in our full training presentation from which the following was taken

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SPC History

- Origins date back almost 100 years to use at Western Electric.
- Walter Shewhart pioneered use of statistical methods to manage/control production.
- Application in Japan pioneered by Deming in 50s/60s
- More widespread application in U.S. started in 1980s.
- SPC has demonstrated effectiveness in almost all industries including biopharmaceutical and diagnostic industries
- Paradigm shift – look at process rather than just test product.
 - **There is widespread acceptance that *appropriate* application of monitoring and/or SPC improves quality and decreases costs across industries.**

Before Applying SPC:

- What Question do you need to ask?
- What are the inputs into SPC process?
- Why is it important to consider alpha and beta error before initiating SPC?

Specifications and Statistical Control Limits

Specifications are the requirements/tolerance limits (Voice of the Customer). What is necessary to assure safety and efficacy.

Control Limits are process limits (Voice of the Process). What the process will produce for extended periods of time under normal conditions. Control limits may include alert and action limits

- If Specifications are set based on process data/process capability then there really are no specifications under this definition and SPC can't be effectively applied

Establishing Control Limits

- Based on prior knowledge applied in a disciplined and coherent manner:
 - Manufacturing process (QbD, Cpk)
 - Method (QbD, CpK, from control strategy)
- Statistical basis:
 - 3 sd for action limit and 2 sd for alert limit are common
 - A blind application of this statistical tends to create many alerts and may maximize alpha error and the associated noise

Examples of Cpk/Cp

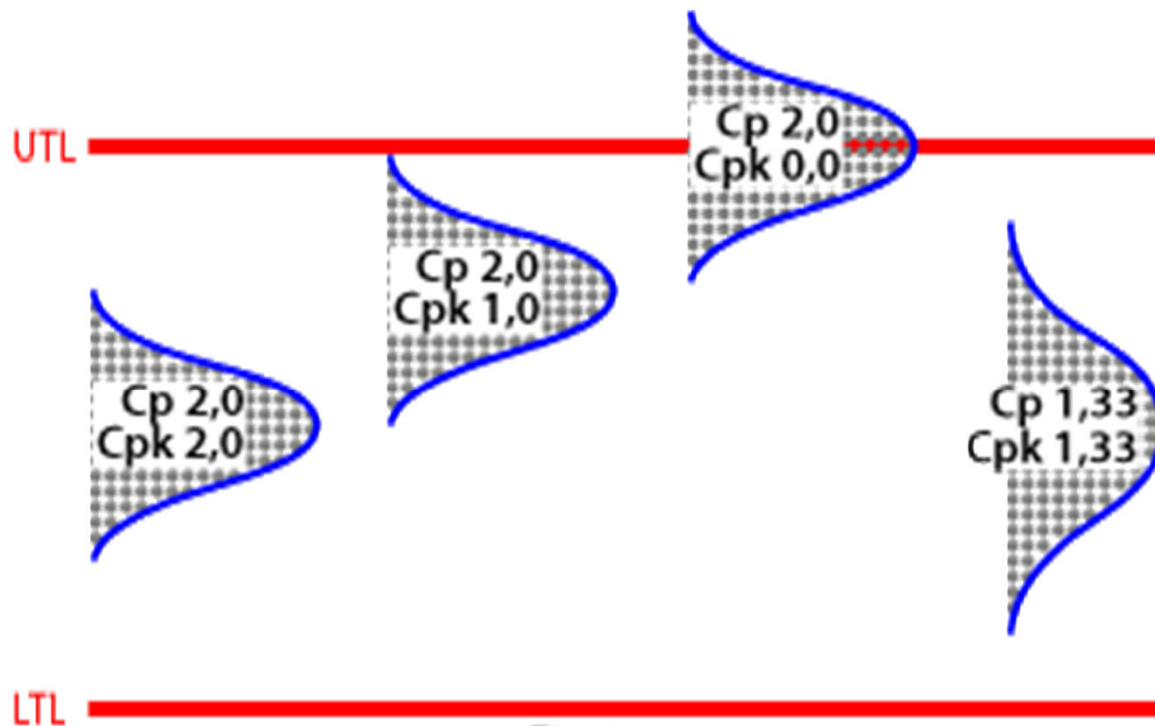
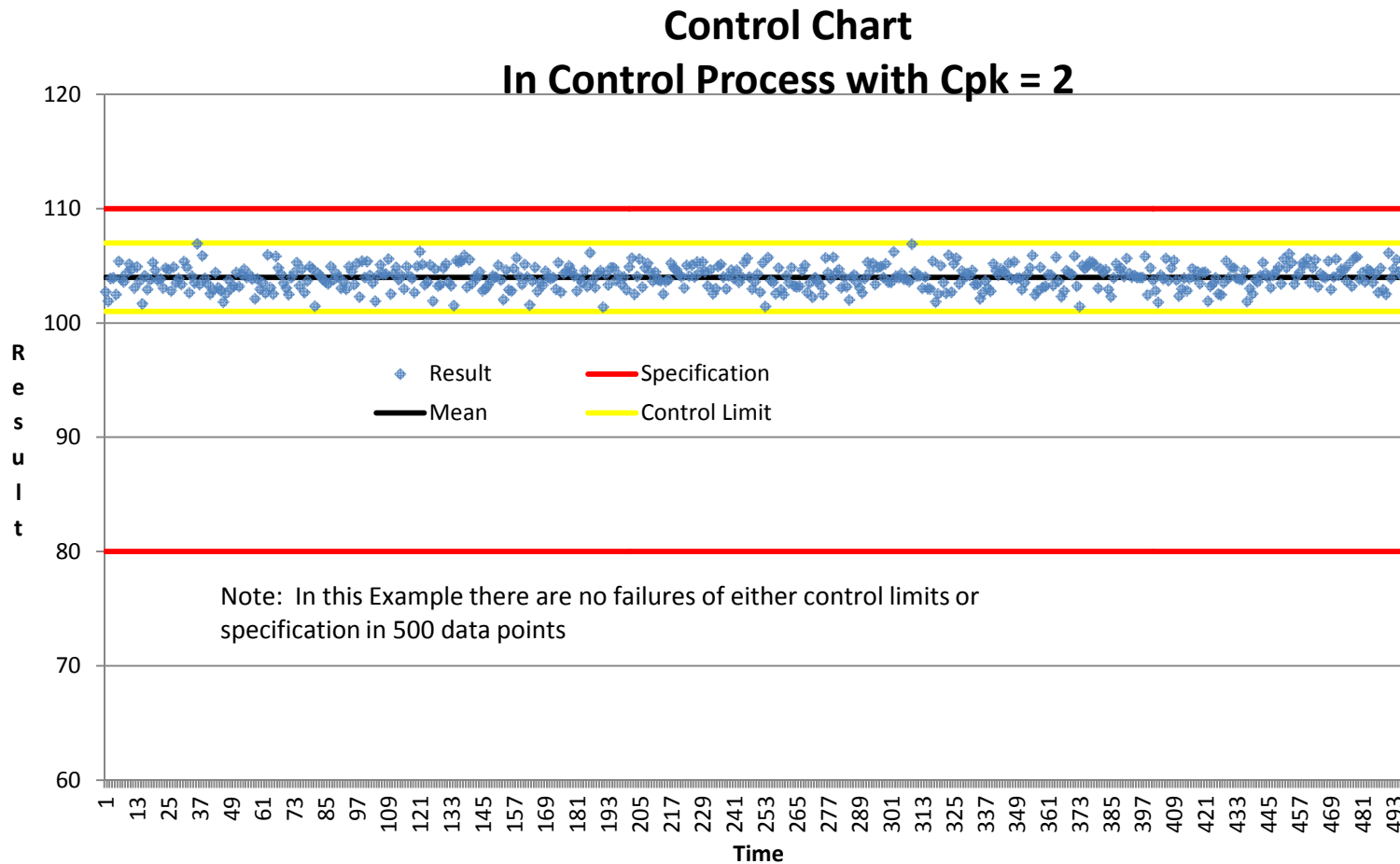


Fig 4

Cpk is the Link between Specifications and Control Limits



Some Differences Between Biopharm and Traditional Applications of SPC?

- Knowledge of biological process involved in production and end use (patients) is limited compared to other industries due to inherent complexity of biological processes
- Amount of data available is often more limited
- Potentially larger portion of observed process variability is due to measurement process variability (sometimes called measurement error)
 - Translation of Motorola 6 Sigma to Diagnostics was greatly impacted by measurement variability.

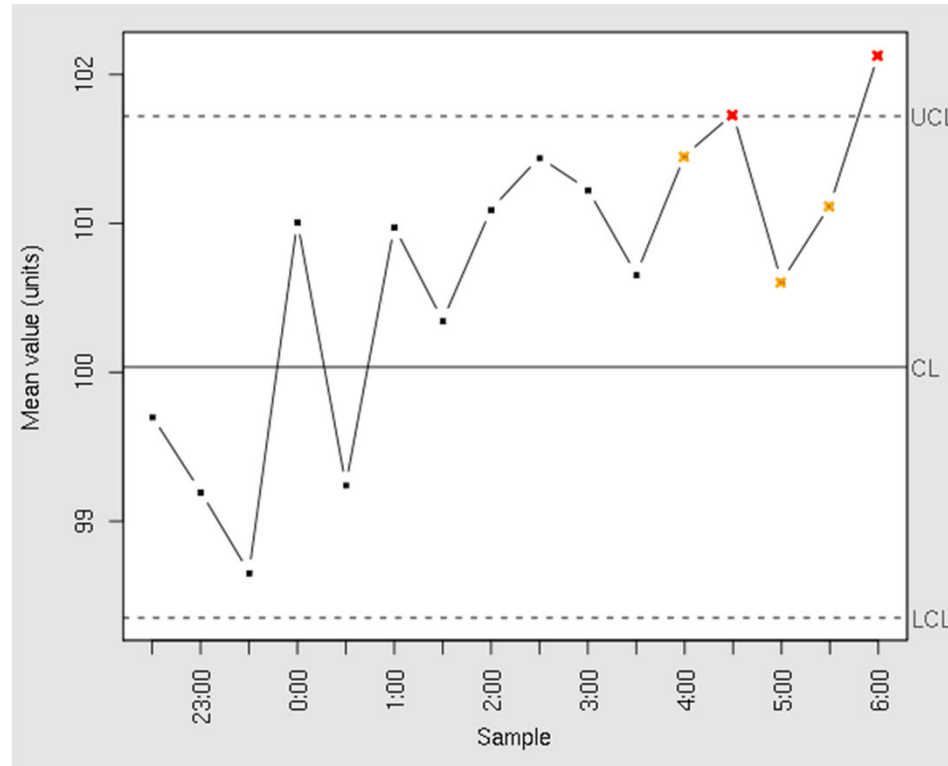
What is SPC: Some Different Definitions

- Application of Statistical methods and procedures (such as control charts) to analyze the inherent variability of a process or its outputs to achieve and maintain a state of statistical control.
- Definition—the use of valid analytical statistical methods to identify the existence of special causes of variation in a process. The basic rule of statistical process control is:
 - *Variation from common-cause systems should be left to chance, but special causes of variation should be identified and eliminated.*
 - This is the Shewhart original rule. However, the rule should not be misinterpreted as meaning that variation from common causes should be ignored. Rather, common-cause variation is explored "off-line." That is, we look for long-term process improvements to address common-cause variation.
- Statistical Process Control is a scientific visual method used to monitor, control and improve processes by eliminating special cause variation from manufacturing, service and financial processes. SPC is a key continuous improvement tool.
- Statistical process control (SPC) is a method of quality control which uses statistical methods. SPC is applied in order to monitor and control a process. Monitoring and controlling the process ensures that it operates at its full potential. At its full potential, the process can make as much conforming product as possible with a minimum (if not an elimination) of waste (rework or trash). SPC can be applied to any process where the "conforming product" (product meeting specifications) output can be measured.
- .. Statistical Process Control (SPC) is an approach that helps to monitor and control the output of a process by assessing the stability of the process and the type of variation that is present. SPC charts can aid decisions about whether a process is 'in-control' and whether or not an adjustment is necessary.
- the use of statistics to study a process in order to find out if it is working well or if it needs to be changed.

SPC can be applied to:

- Manufacturing processes (e.g., CPV)
- Test methods (e.g., charting control values) that will reflect method and instrument performance
- Trending in stability studies (not classic SPC)
- Environmental monitoring (Alert limits and action limits vs specifications to use an area)
- Plus many more items!

Control Charts: Backbone of SPC

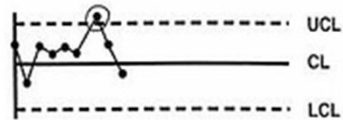


What does this figure suggest to you?

Run Rules for Evaluating SPC Include:

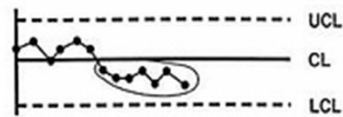
- Western Electric rules
- Nelson rules
- Wheeler rules
- Westgard or multi-run rules (common in diagnostic industry, more later)
 - It is beyond today's discussion to compare and contrast statistical advantages/disadvantages of different and **overlapping** rule systems. However, all run rules have an underlying statistical basis assuming a normal distribution.

Example of Run Rules



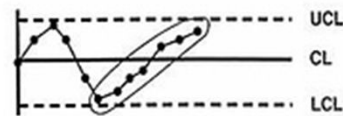
Point outside of the limit:

Control limits are calculated to measure the natural variability of a process. Any point on or outside the limit is considered abnormal and requires investigation.



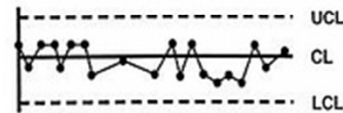
Shift (Run):

A shift is indicated when points lie continually on one side of the center line. A shift of seven consecutive points is considered abnormal. Also considered abnormal: 10 out of 11, 12 out of 14, or 16 out of 20 points on one side.



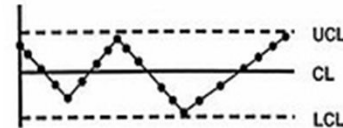
Trends:

Seven consecutive points in a continuous upward or downward direction.



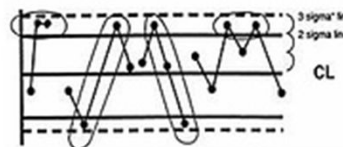
Hugging the center line:

When most points lie within the center line and 1.5 sigma, the process is not in a controlled state. This usually indicates the mixing of data from different populations, which makes the control limits too wide and stratification of data necessary.



Cycling (periodicity):

Any repeated, consistent up and down cycle is abnormal and requires investigation.



Approaching control limits:

2 of 3 points lying outside the 2 sigma line is considered abnormal.

What Happens When a Run Rule Violation is Flagged?

Alert and Action Limits are Frequently Used

- Alert limits:
 - Example: email when stability chamber set for 15 +/- 2 deg temporarily hits 17 deg.
 - Process trending outside of prescribed control limits brought to attention of supervisor or into a scheduled meeting.
- Action limits:
 - Receiving a phone call at 2:00 am because -70 deg freezer has been at -45 deg (or warmer) for 30 minutes.
 - Receiving a phone call at 1:00 am because process trending triggers response (e.g., related to oxygen or pH for culture)
 - Process trending is outside of prescribed limits is required to be discussed at a meeting.

Applying SPC/Control Charts

- When applied?
- How applied:
 - Different approaches probably only limited by imagination
 - Some method approaches
 - Some process approaches
- Responses to OOT
- Technical aspects

Critical Questions

- What should guide application of SPC/monitoring?
- What concerns should we have about over-application of SPC/monitoring (alpha/beta error)?



Interesting example.....

- How should “automation” be used to help with SPC?
 - Recent personal observation: A company indicated that GMP required trending of all data generated by QC.....

Applications

- Analytical methods
- Manufacturing



General Applications

- Certain data violating a SPC rule can be “flagged” and considered an OOT (out of trend)
- OOT applies to SPC whereas OOS is applied to samples relative to product specifications
- Manual and software driven systems are used:
 - Connecting results to analysis and analysts can be a frequent point of failure
 - Getting analysis to person needing to take action can be a frequent point of failure

Examples Flags/OOTs.

- Alert limits:
 - Example: emails when stability chamber set for 15 +/- 2 deg temporarily hits 16.5 deg
 - Process trending outside of prescribed limits brought to attention of supervisor or into a scheduled meeting
- Action limits:
 - QC reference OOT requires an investigation for running high
 - Process trending is outside of prescribed limits must be addressed at daily meeting
 - Receiving a phone call at 2:00 am because -70 deg freezer has been at -45 deg (or warmer) for 30 minutes
 - Receiving a phone call at 1:00 am because process trending triggers response (e.g., related to oxygen or pH for culture)
- Bioprocess OOT of lactose levels requires an investigation that results in shut down with material being discarded

Some SPC Applications to Methods Observed Examples:

- Invalid run if reference/control is outside control limits - system suitability criteria
- Control is trending high (assays valid) – investigation determines issue with instrument
- Investigation required when X# of consecutive invalid results are observed for a method
 - Useful for contract labs or when data is limited
- Establishing limits for % invalids (FPA/RFT)
 - Limits can be “hard” or “soft”

Some Industry Discussion



- Recent discussion by LinkedIn Quality Group regarding OOT:
 - All flags need to go into deviation or investigation system
 - Need significant statistical foundation before using SPC
 - Need statistical justification to call something a trend
 - Can apply SPC/OOTs without extensive statistical foundation
 - OK for trends used in stability that don't have sufficient data for "statistical rigor".
 - **Can't include single data points in OOT system since 1 data point can't be a trend**
 - Everything should be trended
 - More focused trending should be applied
 - Mimics some of the discussions at CMC Summer Forum on Control Strategy.

Point in Time Versus a Control Strategy

- Point in time examples include:
 - Process transfers
 - Process changes
 - Method transfers
 - Method changes
- SPC can be part of a control challenge to manage change subsequent to a point in time evaluation



- Can we be more tolerant of differences and biases observed at a point in time when effective SPC is in place to control process over time?

Key Thoughts

- There are a lot of different approaches to SPC
- There are significant disagreements on proper application of SPC
- Application of SPC can (should?) be an integral part of different control strategies

Application of SPC

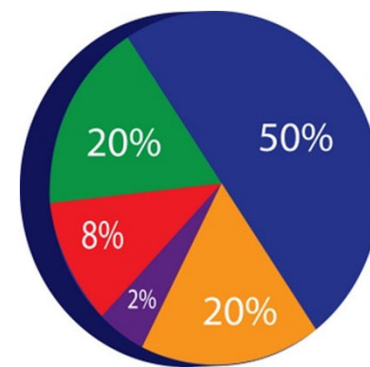
Challenges

Challenges To SPC Application in the Biopharmaceutical Industry

- Deriving customer-driven specifications
- Statistic foundation challenges extent SPC can be applied
- Multiple sites from same company
- CMOs and CTOs
- Over-use of SPC (alpha vs beta error)
- Changes in processes
- Evaluation of SPC application by QA and/or regulators

“Strong” Statistical Foundation

- Can SPC be applied sufficiently often if we demand a minimum of 20-30 normally distributed data points as a predecessor event?
- When can a moving mean of 20 data points be used?
 - How do we make compromises
Allowing maximum use of SPC?



Recap of Key Items

- SPC/monitoring is ~100 years old although application for biopharmaceuticals is in its infancy
- Effective application of SPC/monitoring leads to better products/cost savings
- It's important to [ask what and why](http://www.biopha.com/webmail) before instituting SPC and delving into statistical foundation
- Application of SPC can vary for level of application, where applied, how limits are established, response to limits, and how the QS/submissions manage SPC
- Whatever is the “standard” now is bound to change

For Further Information

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