Process Monitoring in Pharmaceutical Industry - Challenges and Recommended Solutions

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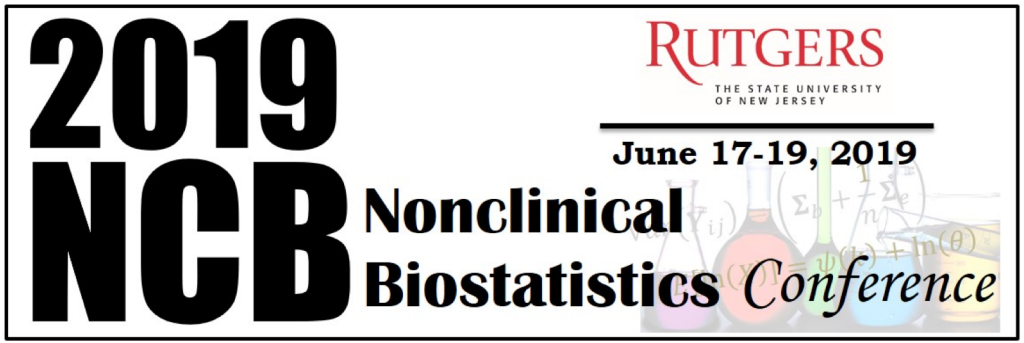


Outline

1. Introduction
   a. Sources of Variation
   b. “State of Control” vs. “Statistical Control”

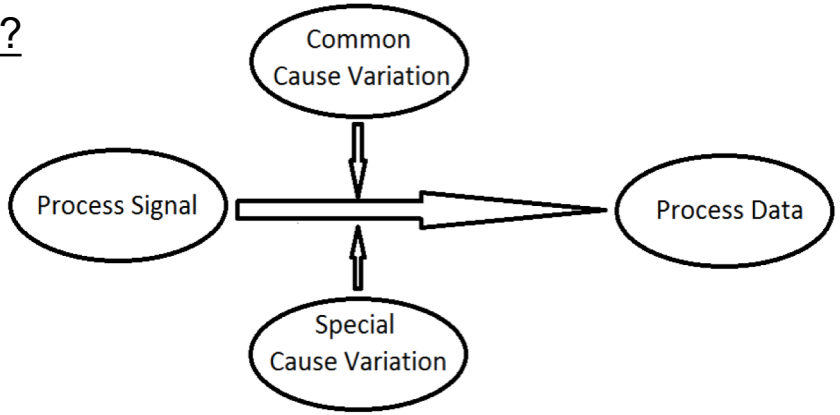
2. Process Monitoring
   a. Popular Control Charts and Monitoring Rules
   b. Challenges and Recommended Solutions

3. Connection with Process Capability

4. Summary

Process Data and Sources of Variation

What is process data?



Walter
Shewhart

- **Process signal:** process data with all sources of variability removed
- **Common cause variation**: variation inherent to the process
- **Special cause variation**: unusual variation, a result of some special cause
- **Process Data:** process signal plus common and special cause variation

Common and Special Cause Variations in Pharma

Process Data:

- Quality Attributes (QAs), e.g. potency, impurities
- Key Process Indicators (KPIs) e.g., yield, growth rate

Common cause variation:

- Raw material lots
- Assay reagent lots
- Inoculation train
- Calibration of measurement instruments

Special cause variation:

- Operator error in manufacturing or assaying
- Machine failure

The goal of understanding process data is to assess if the process is in a **state of control**

ICH Q9 and Q10 Define State of Control

State of control

- A condition in which the **set of controls** consistently provides assurance of continued **process performance** and **product quality**

Establish and maintain a state of control

- To develop and use effective **monitoring and control systems** for **process performance** and **product quality**, thereby providing assurance of continued suitability and capability of processes
- **Quality risk management** can be useful in identifying the **monitoring and control systems**

Statistical tools can support and facilitate **quality risk management**, including:

- **Process Monitoring (Control Charts)**
- **Process Capability Analysis (Capability Indices)**

Statistical Control & State of Control are Completely Different

Effective use of statistical tools requires understanding of Statistical Control and State of Control

Statistical Control ≠ State of Control

- **Statistical Control** – independent and identically distributed (i.i.d.)
  - Independence: one batch conveys no information about another
  - Identically distributed: the chance of any given result for a batch is the same
- **State of Control** – defined per ICH guidance. It does **NOT** require
  - Independence: biologics manufacturing has many sources of correlation e.g., raw materials, thaw, assay reagents, periodic calibration, all are inherent to the process and are due to common cause.
  - Identically distributed: shifts in means by campaign are expected and are common cause variation

Why many manufacturing processes are in a state of control but not in statistical control?

Development for Statistical Control is Not Attainable

”Statistical Control is not an accident – must be an objective of development” – Donald Wheeler

Evaluation of statistical control (i.i.d.) requires tens or hundreds of individual batches

- not enough batches in development to evaluate statistical control
- much less to optimize the process for statistical control

Determining a process not explicitly developed for statistical control to be in statistical control based on lack of evidence to the contrary is dubious when we know that many sources of common cause variation, e.g., lots of raw materials, seed train, induce correlation between runs. These common cause variation are violations of statistical control

Development for State of Control is Attainable

Product Quality and Process Performance

- Process Monitoring (Control Charts)
  - Objective: quickly detect and understand changes in manufacturing process; ensure consistent process performance
  - How: - Near real time detection of changes: compare QAs and KPIs to control limits determined by historical data
    - Understand changes: investigations and root cause analysis
- Process Capability Analysis (Capability Indices and OOS)
  - Objective: measure and compare the process capabilities; ensure long term supply of drug with intended quality
  - How: periodically compare QAs to specification limits (theoretically) related to patient efficacy and safety

The state of control is attainable

- In development, obtain Process Knowledge: Experimentation at Small Scale (process characterization - scale down model verification), Manufacturing Scale Runs (clinical runs, qualification runs), Controls System Development (method development, validation, & transfers)

Challenges and Strategic Solutions

Challenges

- Applicability and interpretation of standard statistical tools assume that the process is in statistical control – often not true
- How to use the statistical tools to support the state of control of a manufacturing process?
- Efficient application to large manufacturing networks requires automation – minimizing the number of special cases

Strategic Solutions

- Use of statistical procedures that are robust to assumptions and amenable to automation

Process Monitoring in Pharma

Popular Control Chart

- Individual and Moving Range (I-MR) Chart
- Process signal is estimated by sample mean
- Common cause variation is estimated by the moving range approach
  - Average over all the differences between consecutive data points and divide by a constant

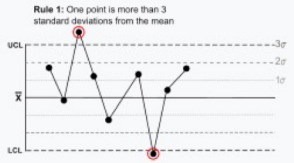
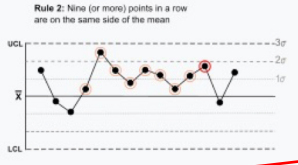
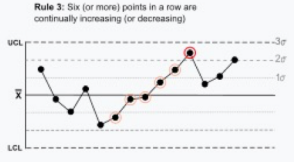
$$MRSD = \frac{\overline{MR}}{1.128} = \frac{1}{1.128} \times \frac{\sum_{j=2}^{N} |X_j - X_{j-1}|}{N-1}$$

- Control limits are computed as

$$\text{Process Signal} \pm \text{Common Cause Variation} = \bar{X} \pm 3 \times MRSD$$

Popular Monitoring Rules

- Nelson Rules ➔
- Westgard Rules
- Western Electric Rules
- Etc.

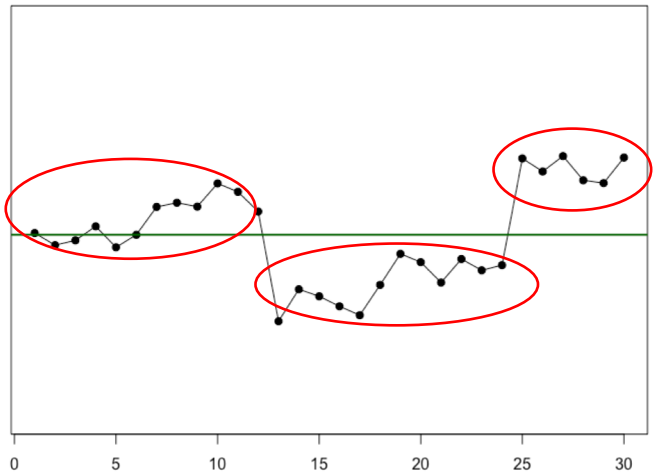
Rule	Description	Chart Example
Rule 1	One point is more than 3 standard deviations from the mean.	
Rule 2	Nine (or more) points in a row are on the same side of the mean.	
Rule 3	Six (or more) points in a row are continually increasing (or decreasing).	

- Atypical Value
- Shift
- Drift

Challenges with I-MR chart and Nelson Rule 2

- I-MR chart estimates the short term variation; However, not all the common cause variation are presented in short term in pharmaceutical industry
- Nelson Rule 2 generate signals for small shift away from the mean; However, such signals may not be practically meaningful or actionable

How to maximize the detection of special cause variation (true positive) while minimize the rule violations due to common cause variation (false positive) ?

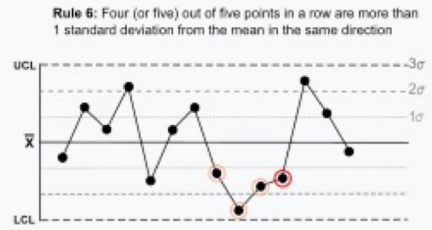


Recommended Solutions in Pharma

- Change from I-MR chart to Levey Jennings (LJ) chart
  - LJ chart: $\text{Process Signal} \pm \text{Common Cause Variation} = \bar{X} \pm 3 \times SSD$
  - Common cause variation is estimated using long term standard deviation (sample standard deviation)

$$SSD = \sqrt{\frac{\sum_{i=1}^{N}(X_i - \bar{X})^2}{N-1}}$$

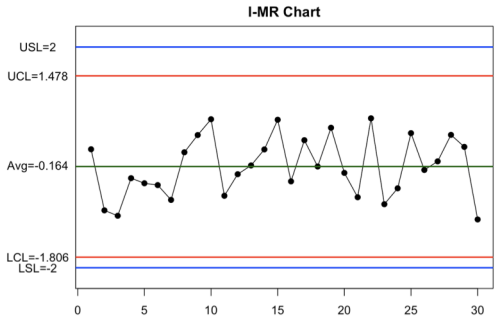
- Change from Nelson Rule 2 to Nelson Rule 6

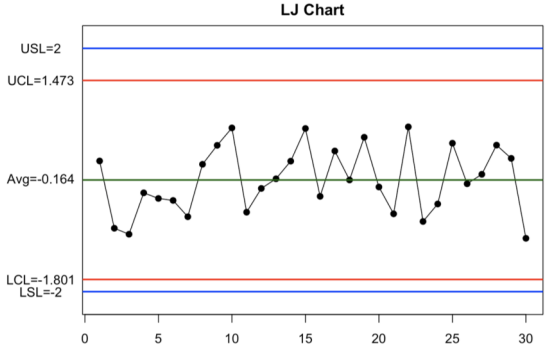
Rule 6	Four (or five) out of five points in a row are more than 1 standard deviation from the mean in the same direction.	

Detect large shifts quicker, which is more likely associated with special cause variation

I-MR Chart vs LJ Chart
Case 1: data are randomly distributed no special cause variation

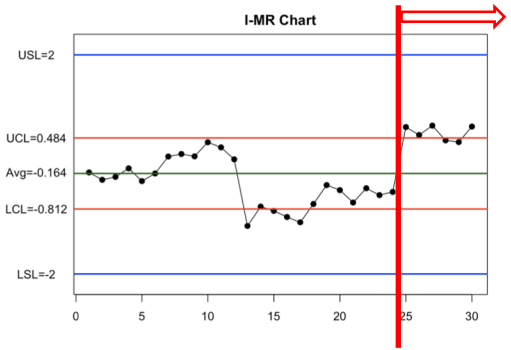
- Both I-MR and LJ charts provide appropriate limits. In fact, they are expected to be very similar

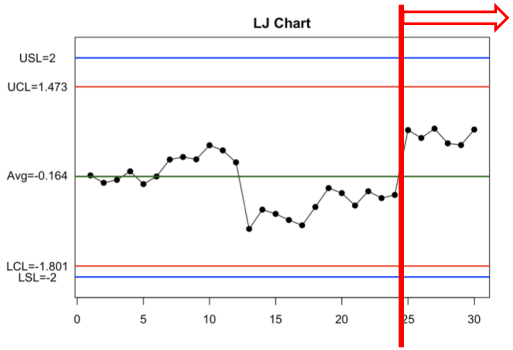




- These control limits are used for ongoing process monitoring

I-MR Chart vs LJ Chart
Case 2: data are not randomly distributed due to special cause variation



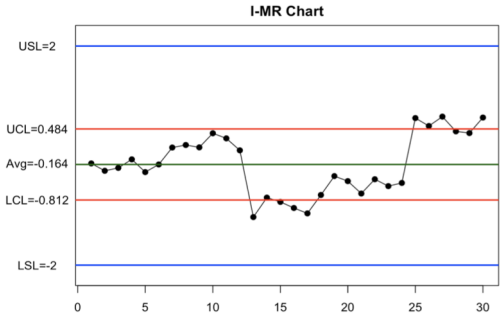


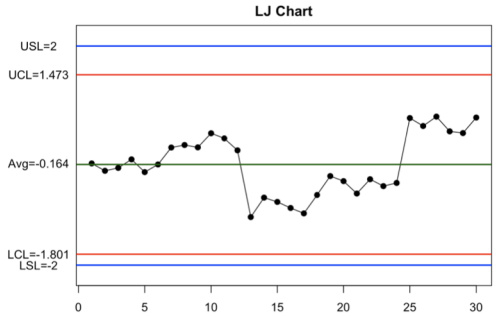
This is not the control limits

- After collecting new 30 data points from the fixed process, suppose we have randomly distributed data. Then we are facing Case 1 again – both charts are appropriate
- Note: data used for establishing control limits must not contain any special cause variation

I-MR Chart vs LJ Chart

Case 3: data are not randomly distributed due to common cause variation





This is the control limits

- Because they are due to common cause variation, we should include them in computing the control limits
- LJ chart successfully captures the long term common cause variation
- I-MR chart fails to do so as it keeps triggering rule violations due to these common cause variation (false positives)

I-MR Chart vs LJ Chart
Summary of Cases 1, 2, and 3

- While both I-MR chart and LJ chart can handle cases 1 and 2, I-MR chart fails case 3 but LJ chart succeeds.
- Root cause of I-MR chart failure:
  - the short term SD fails to estimate all the common cause variations that appearing over time in the process
  - In Pharma, it is not unusual that the common cause variations can lead to non-random data. The I-MR chart is not appropriate to use when the non-random data are due to common cause variation
- Thus, LJ chart is more appropriate for Pharmaceutical industry than I-MR chart
- Alternative methods should be used when appropriate

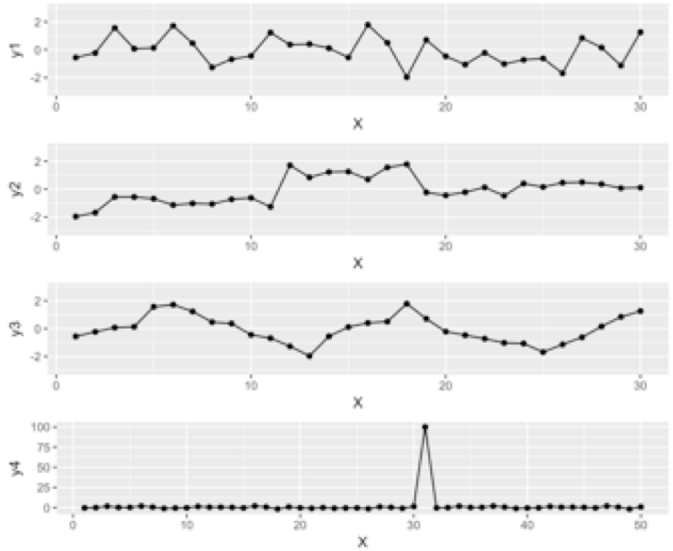
Connection with Process Capability

Process Capability (PC)

- A process is capable if it consistently produces material that meets specifications
- Process Capability indices are numerical values that measure the capability of a process
- Examples of PC indices includes Cpk, Ppk, Rpk
  - Cpk: a process capability index
  - Ppk: a process performance index
  - Rpk: a more robust process performance index proposed by Roche

Do Not Use PC Indices to Justify No Action for PM Rule Violations

Data ~ N(0,1), LSL = -3, USL = 3



Data	Cpk	Ppk	Rpk	OOS
Random	**0.97**	**1.00**	**0.59**	0
Shift	**2.22**	**1.00**	**0.59**	0
Drift	**2.00**	**1.00**	**0.59**	0
Atypical Value	0.07	0.02	0.62	1/50

- Cpk suggests that data with shift or drift are better than random. This is wrong!
  - In fact, more Nelson rule 2 or 6 (shift), or rule 3 (drift) violations, better Cpk.
- Ppk or Rpk simply do not suggest any difference between random, shift, drift data
- None of these PC indices are designed to justify no action for PM rule violations

Misunderstanding of OOS Prediction

- Accurate prediction of OOS requires statistical control – often not attainable
- Even when the process is under statistical control, the predicted OOS rate is the rate due to common cause variation
- Predicting the OOS rate due to special cause variation is akin to predicting a stock market crash
- Many OOS are due to special cause variation, thus determining the rate of OOS due to common cause variation is not useful in pharma
- One reason Cpk being misused is that its interpretation assumes statistical control and gives chance of OOS due to common cause variation

Summary: PM and PC are Orthogonal

	Process Monitoring	Process Capability
Methods in Roche	LJ chart with Nelson rules 1, 6, 3	Rpk
Primary Goal	Eliminate special cause variation in the manufacturing process through quick detection and root cause analysis	Enable comparison of the process risk due to common cause variation across the manufacturing network to inform resource planning and allocation
Primary Customer	Manufacturing Sites	Process owners / Network
Focus	Individual batches	Majority of process batches
Timeline	Near Real time	Periodic (e.g. annual) review
Limits	Control limits (Historical Manufacturing Data)	Spec limits (Related to clinical effect)
Predictability	Special cause is not predictable	Common cause is predictable, but most OOS is due to special cause
Ultimate Goal	Establish state of control	

Doing now what patients need next