Novel Statistical Tools for Robust Product Process Monitoring for Biopharmaceutical Drug Products

Nitin J. Champaneria
Senior Quality Engineer
Genentech, A member of the Roche Group
South San Francisco, CA
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Agenda & Outline

Purpose

- Share approaches and novel statistical metric tools that enhance robustness of product monitoring and process capability assessment

Topic Outline

- Challenges - Health Authority (HA) Expectations
- Product Process Monitoring (PPM) - Practice and Issues
- Remedies and New Tools
  - Stability Metrics
- Performance Analysis (PA) and Capability Metrics
  - Quantile-based Risk Indices

Desired Outcome

- Feedback from FTC/ASQ Statistics Community on new tools and ideas to enhance PPM/PA robustness

HA Regulators Expectations

- "Manufacturers should use ongoing programs to collect and analyze product and process data to evaluate the state of control of the process"
- Scrutiny of intra-batch as well as inter-batch variation is part of a comprehensive continued process verification program under § 211.180(e)
- Process capability assessment is critical to ensure quality supply to patients and is one of the proposed optional Quality Metrics

Process Product Monitoring Practice

What is Process & Product Monitoring?

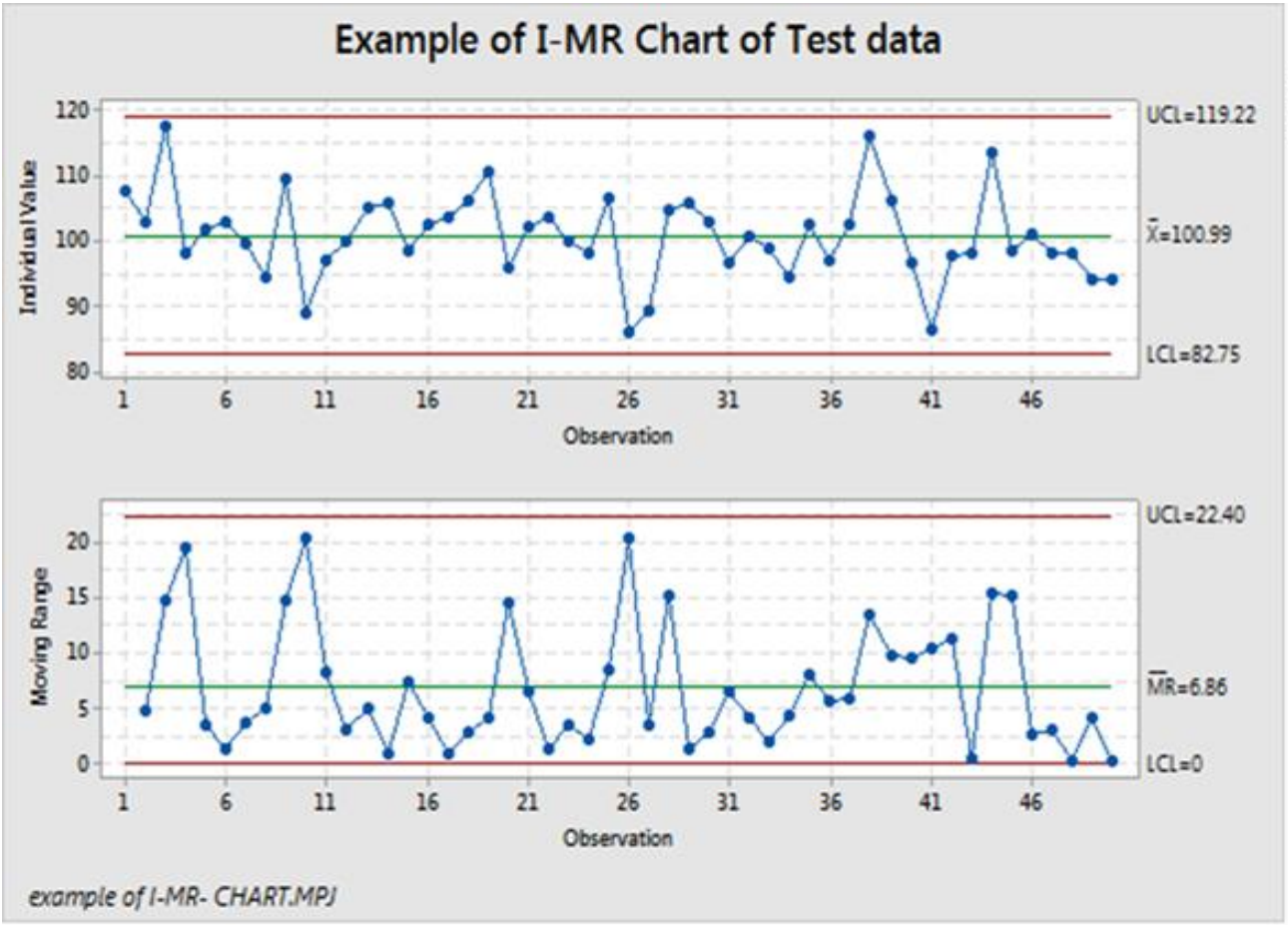
- Established data collection and control charting of Process and Critical Quality Attributes
- Online monitoring in Laboratory Information System
- Trends identified with Nelson rules, Escalation process for rule violation

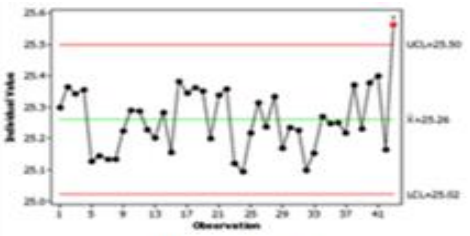
Expectations

- Identify relevant **process trends**.
- Data **statistically trended** and reviewed by trained personnel.
- Continual assurance that the process **remains in a state of control** (the validated state).
- Meet FDA's CPV "Continued Process Verification" guidance

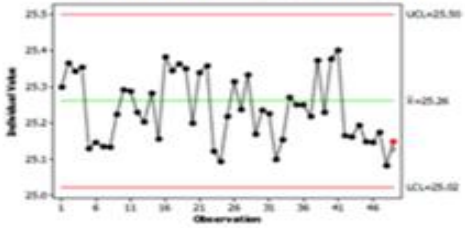
Control charts are established to determine if process is a state of statistical control.

Determination of State of Control

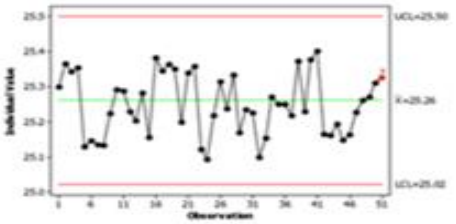




Rule 1 violation:
Control limit excursion



Rule 2 violation:
Trend shift



Rule 3 violation:
Trend drift

We monitor processes with first three modified Nelson rules. Process is considered in a state of control i. e. “stable” when NO rule violations occur.

Statistical Challenges in PPM

- Biopharmaceutical industry faces a significant challenge in application of conventional SPC techniques:
  - Often data do not follow SPC assumptions
  - Sampling from “Bulk” Sampling does not permit intra-batch assessment
  - Processes not continuous , Short run lengths
  - Auto correlated data
  - Conformance to rule violation often questioned for practical reality
  - Increased occurrence of false alarms

False Alarm Rate		
Rule	**Occurrence Prob. (%) [5] (normal**	**Symptom in Control Chart**
One point outside Control Limit (OOC)	0.00135	Sudden and high change
Eight points on either side of centerline- SHIFT	0.00781	Quality shift, Process /Material change
Six points in a row all increasing or decreasing	0.00278	Trend – Drift e.g. wear, reaction

- Consequence: Wasted effort in Process Stability evaluation
- Novel tools are needed to assess process stability

Challenges and Remedies

Issue	Reason	Consequence	Remedy
1. No Intra-batch monitoring	Only one sample taken per lot	Inadequate assessment of within-lot variation	**Increase sampling within lot, Duplicate testing**
2. Auto correlated data	Sampling from same bulk supply	Inaccuracy in trend monitoring	**Skip lot plotting, ARIMA charts**
3. Run-to Run Differences	Variation between processes, raw material	Inaccurate monitoring with one Control chart	**Variable CL with Stages**
4. Difficulty in quantifying level of instability	False Alarms with multiple Trend rules	Wasted effort in review /investigation	**Stability Metrics [2,4. Ramirez] and Decision Rules [8, Tara Scherder]**

Novel Tools to assess Process Stability

1. Test of Practical Significance (Example 1)

2. “Minitab Assistant” Diagnostic report (Example 2)

3. Stability Metrics (Ramirez [2, 4] *)
   a) Standard Deviation Ratios (SR test)
   b) ANOVA
   c) Instability Ratio

* The number in [ ] refers to reference number at the end of presentation

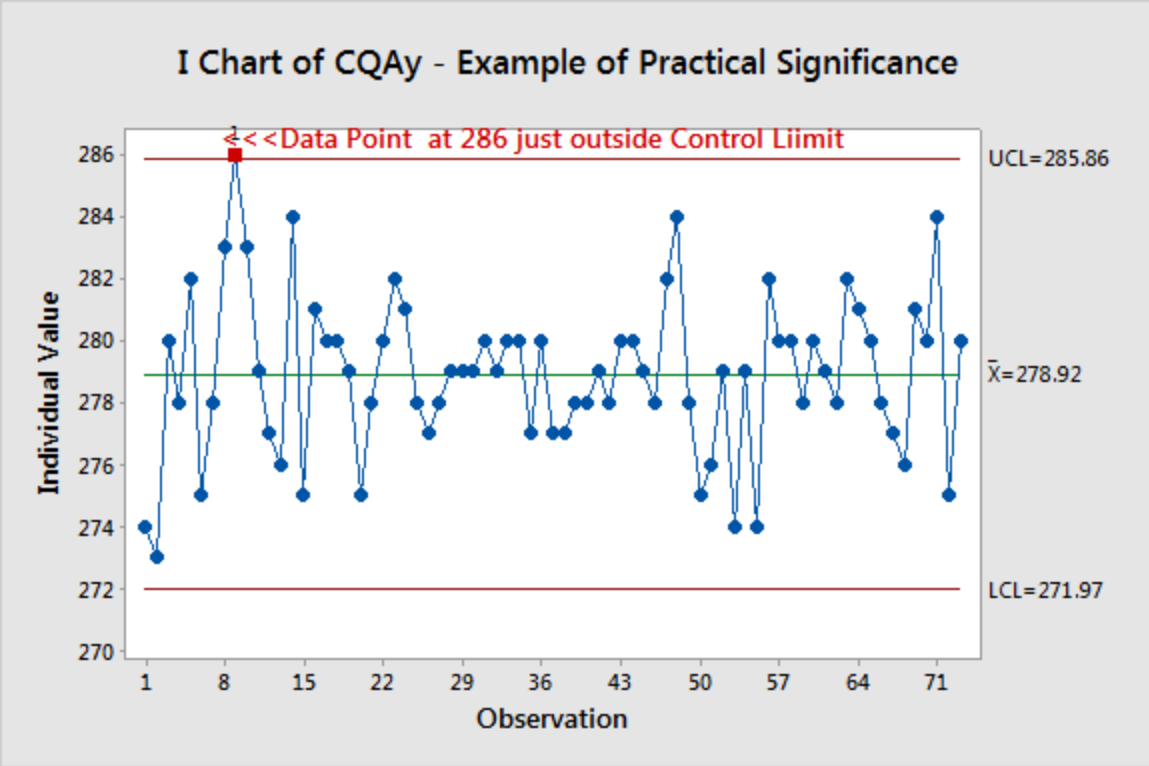
Technique 1 -Test of Practical Significance

Trend Rule	Chart	Out of Trend Evaluations	Recommended Action
1 -OOC	I-Chart	Plotted data beyond control limits	Investigation but verify how far is the point beyond CL
2 –Quality Shift	I-Chart	Plotted data results in eight consecutive plotted data on the same side of the centerline (CL)	Investigation if the observed difference between CL and average of eight points > X * AR Adjust the process or reset control limits
3 – Quality Drift	I-Chart	Plotted data results in six consecutive plotted data all increasing or decreasing	Investigation if the observed difference between the last and the latest plotted data points> X* AR
1 -OOC	Moving Range	Plotted data beyond upper control limits	Formal investigation if the observed difference between the last and the latest plotted data points> X* AR

- *SME Decision how much change is practically significant based on X fraction of Allowable Range (Maximum Allowable Specification Tolerance)*

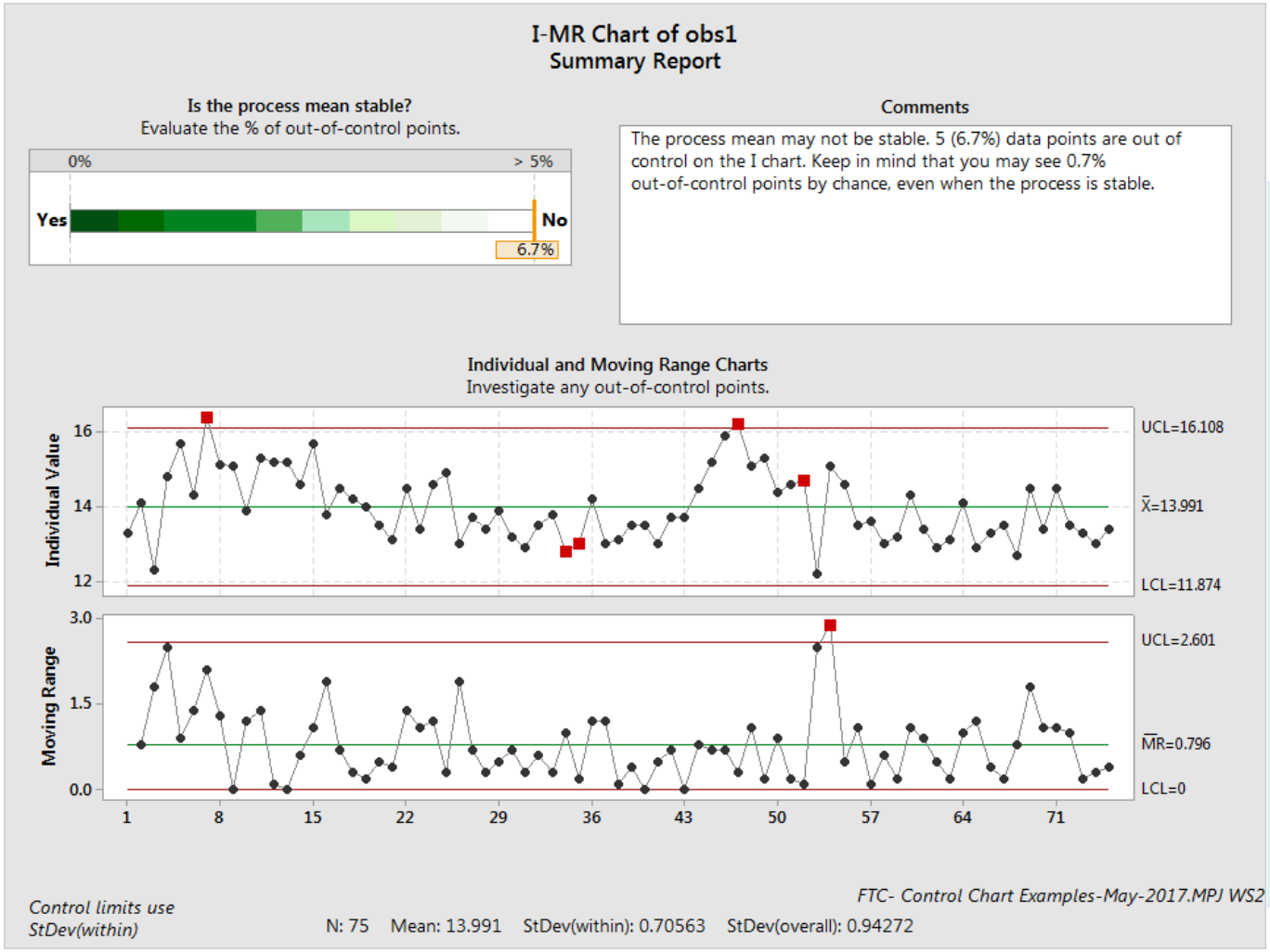
Example 1 -Test of Practical Significance

Trend Rule	Chart	Out of Trend Evaluations	Recommended Action
2 –Quality Shift	I-Chart	Plotted data beyond control limits	Formal Investigation but verify how far is the point beyond CL



Is difference 286 vs. UCL 285.86 significant?
SMEs decide how much change is practically significant

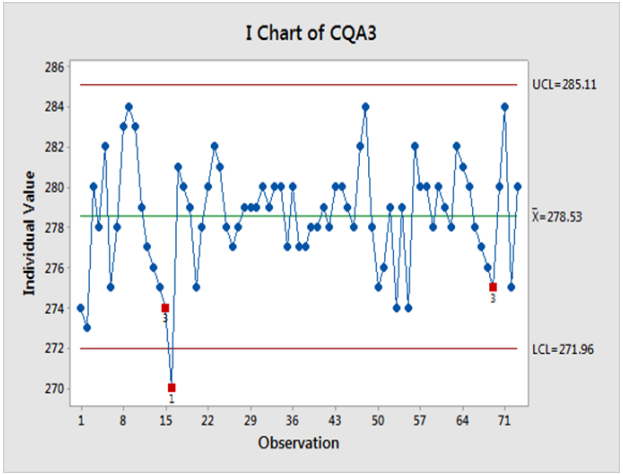
Technique 2 - Report from Minitab Assistant



- Process is not stable.
- Stability: The process mean and variation may not be stable.
- 5 (6.7%) points are out of control on the I chart. 1 (1.4%) point is out of control on the MR chart.

Technique 3 - Stability Assessment

- Stability Metrics
  1. Standard Deviation Ratios (SR test)
     - SR= $S^2_{\text{long term}} / S^2_{\text{short term}} =$ (2.739/2.192)**2=1.561 vs. Fcritical=
     - P value using variance test $F_{(73,45,0.05)} = 0.057$
     - ✓ P close to 0.05, Process on verge of being
  2. ANOVA
     - Factors: Between vs. Within subgroups
     - ✓ If P value <0.05 : Process unstable
     - Use ANOVA Table (below)



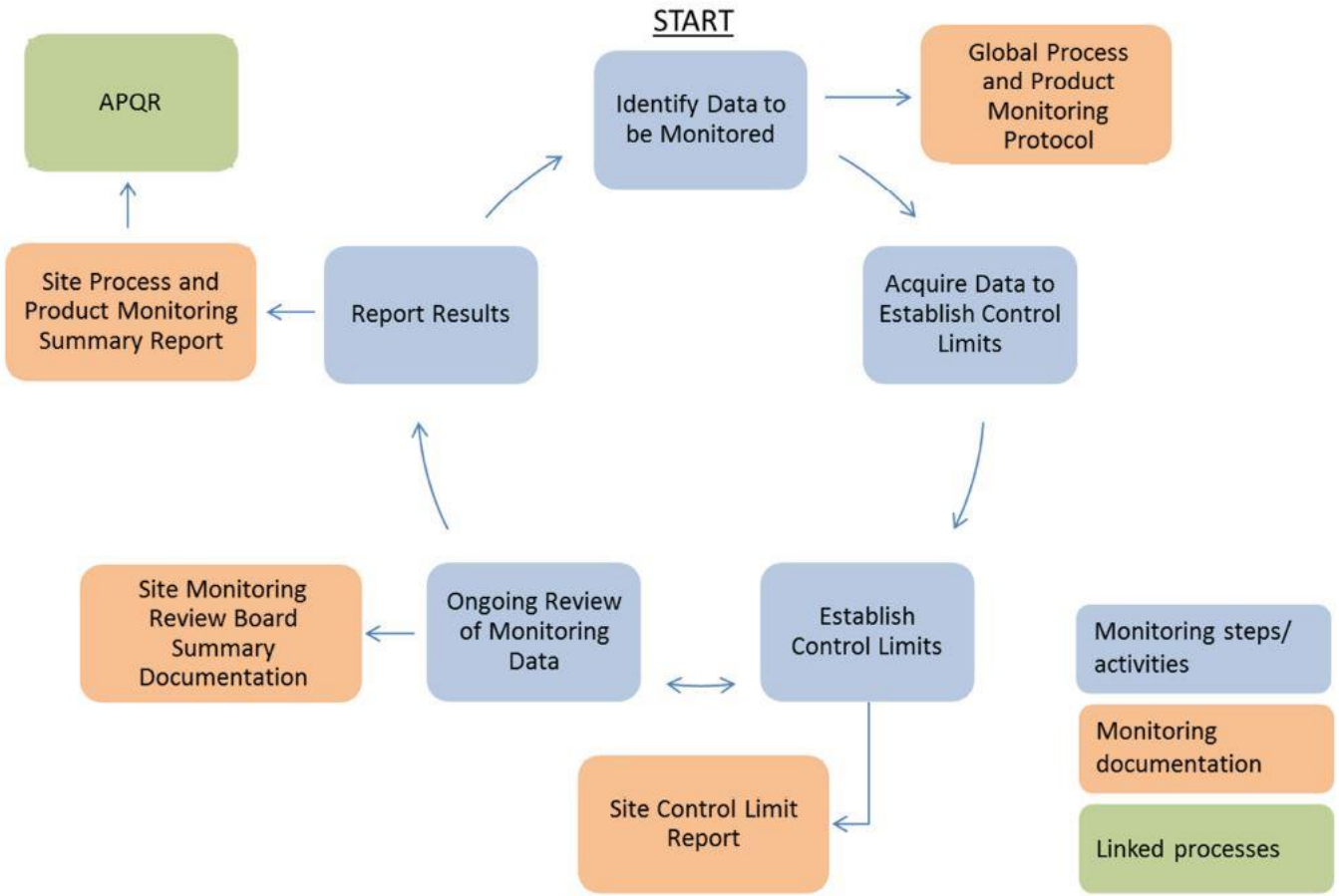
3. Instability Ratio (I_{NSR})
   - Percentage of subgroups with violation of the number of subgroups plotted (e.g. 3/73*100) =0.041 vs. Pfalse= (1- (1-0.00135)^73)+2*0.00278)=0.0994

   X Stable since I_{NSR} is less than false alarm probability

Source	DF	Adj SS	Adj MS	F-Value	P-Value
subgroup	35	355.5	10.157	2.00	0.021
Error	36	182.5	5.069		
Total	71	538.0			

PPM Implementation at Roche

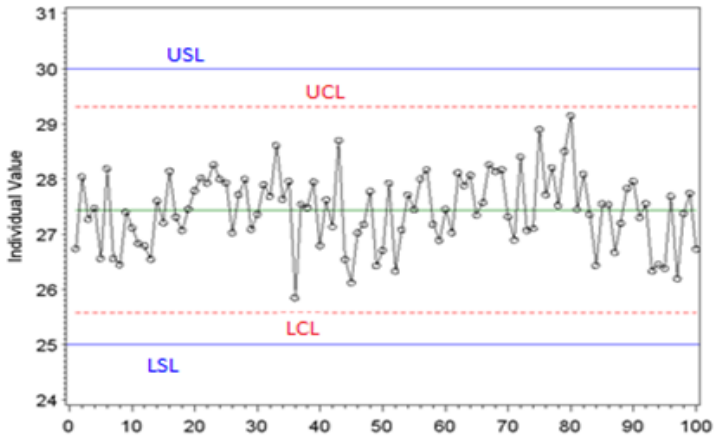
Figure 1: Overview of Process and Product Monitoring



Process Performance:

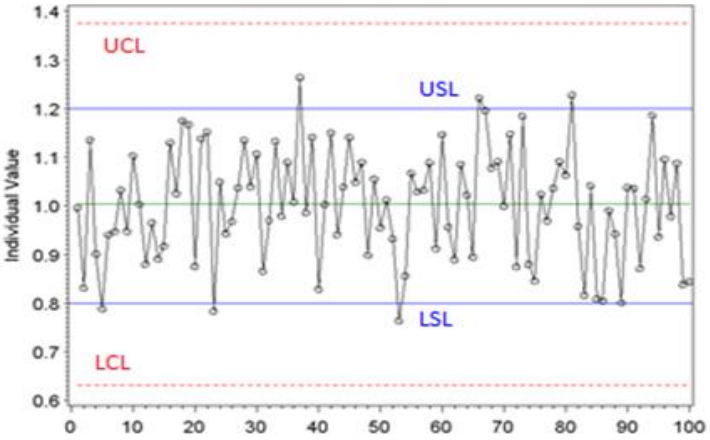
Process Monitoring & Performance Analysis

Capable, Stable

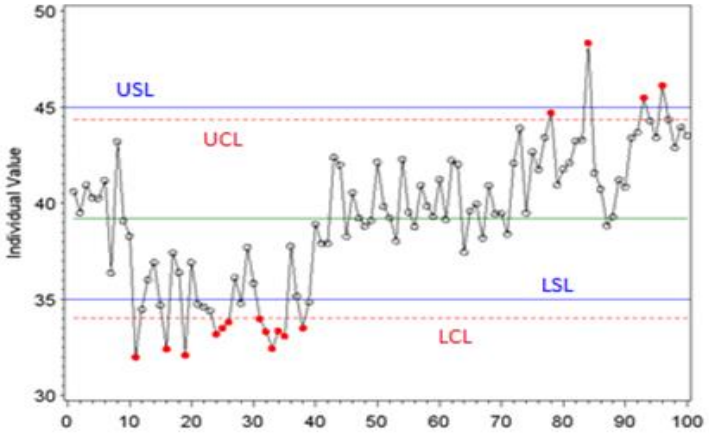


Capable, Not Stable

Not Capable, Stable



Not Capable, Not Stable



Process Monitoring ➔ **stability** of our processes

Performance Analysis ➔ **capability** of our processes

Performance Analysis - Scope

Purpose

- Ensure that a process is capable of consistently delivering quality product
- Identify opportunities for process improvement through risk ranking of CQAs

Scope

- Company-wide – All products
  - Large and Small Molecule
  - API/Drug Substance, Drug Product, Devices
- Many products, Many sites, 5 to 15+ CQA/Product
- ~20-200 lots per product per site per year

Simple Performance metrics are needed for effective PA

Common Process Capability Indices

Symbol	Index Name	Formula (Normal Dist)	Notes
C_P	Potential Capability	$C_p = \frac{USL - LSL}{6\sigma_{ST}}$	Uses short term variability only. Does not consider process location.
C_{PK}	Process Capability	$C_{PK} = \min\left\{\frac{USL - \mu}{3\sigma_{ST}} \text{ and } \frac{\mu - LSL}{3\sigma_{ST}}\right\}$	Uses short term variability, considers location but not process target
C_{PM}	Target Capability	$C_{PM} = \frac{USL - LSL}{6\sqrt{\sigma_{ST}^2 + (\mu - T)^2}}$	Uses short term variation, and also considers location AND target.
P_P	Potential Performance	$P_P = \frac{USL - LSL}{6\sigma_{LT}}$	Uses long term variability only. Does not consider process location
P_{PK}	Process Performance	$P_{PK} = \min\left\{\frac{USL - \mu}{3\sigma_{LT}} \text{ and } \frac{\mu - LSL}{3\sigma_{LT}}\right\}$	Uses long term variability, considers location but not process target
P_{PM}	Performance Target	$P_{PM} = \frac{USL - LSL}{6\sqrt{\sigma_{LT}^2 + (\mu - T)^2}}$	Uses long term variation, and also considers location AND target.

If the data are not normal, the interpretation of Cpk/Ppk is unknown. Many Biopharma processes do not follow normal distribution. We need alternatives.

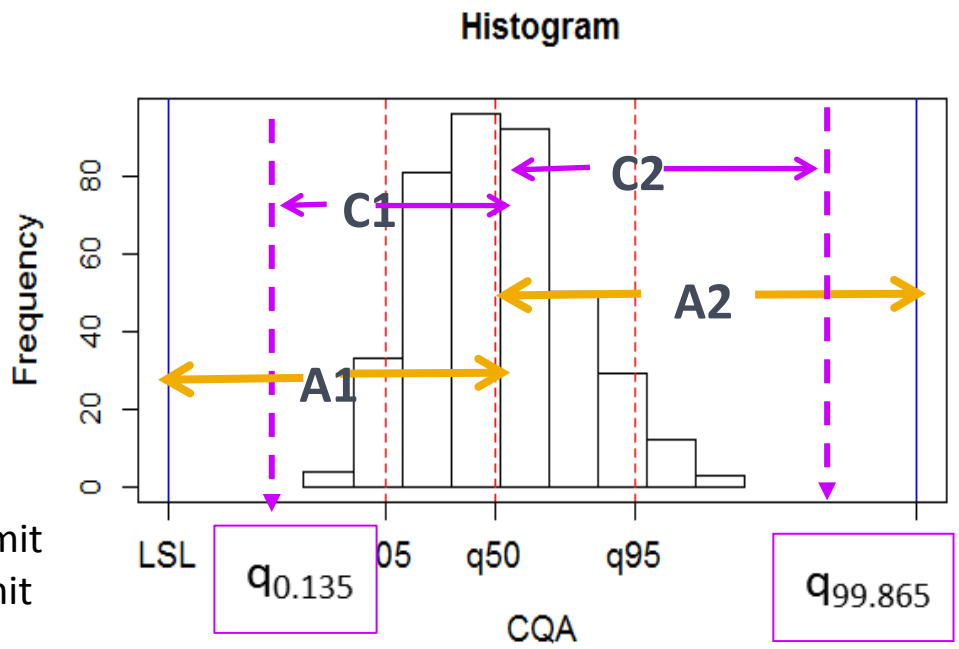
Performance Analysis - Ppq

- Ppq: Quantile-based index from literature [Clements, 1989]
- Based on Kurtosis and Skewness

Definitions for two-sided Spec:

Pp_q = Min{A1/C1, A2/C2}

Ppq is covers 99.73% of the data



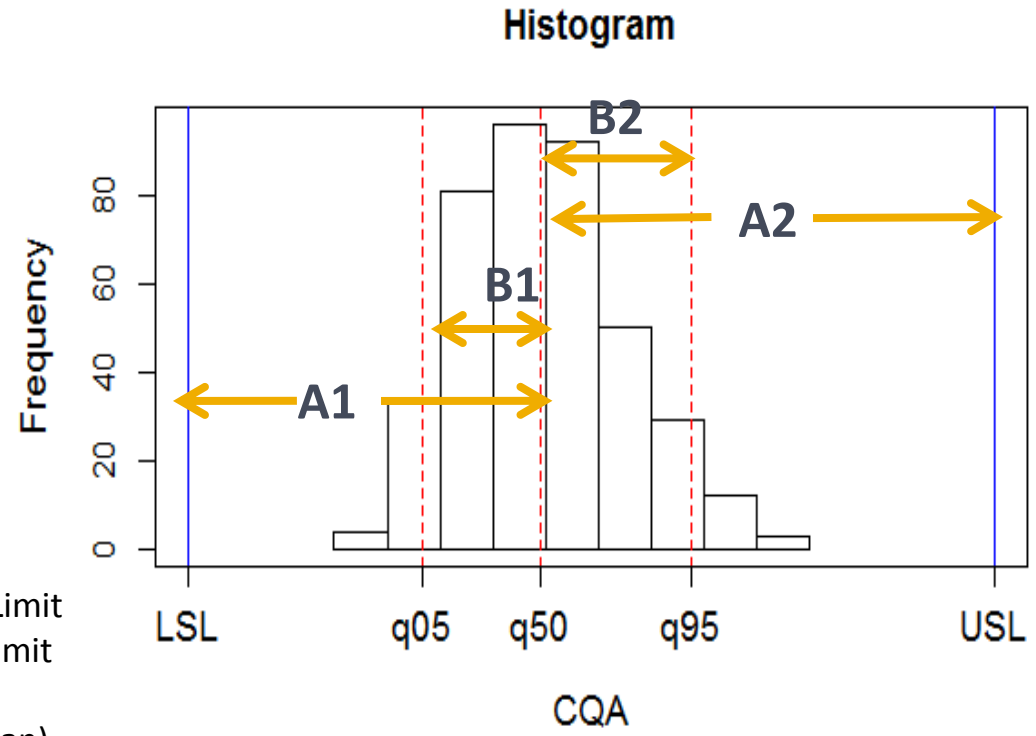
USL = Upper Specification Limit
LSL = Lower Specification Limit
q0.135 = 0.135th percentile
q50 = 50th percentile (median)
q99.865 = 99.865th percentile

Risk Index Tool for Performance Analysis

Introducing a new quantile-based capability risk index: Rpk

Definition for two-sided Spec

- R_{pk} = Max{B1/A1, B2/A2}
- Rpk is the proportion of (A) allowable range used by the bulk (B) of the data
- **R_{pk} is based on the 90% (B1+B2) of the data**



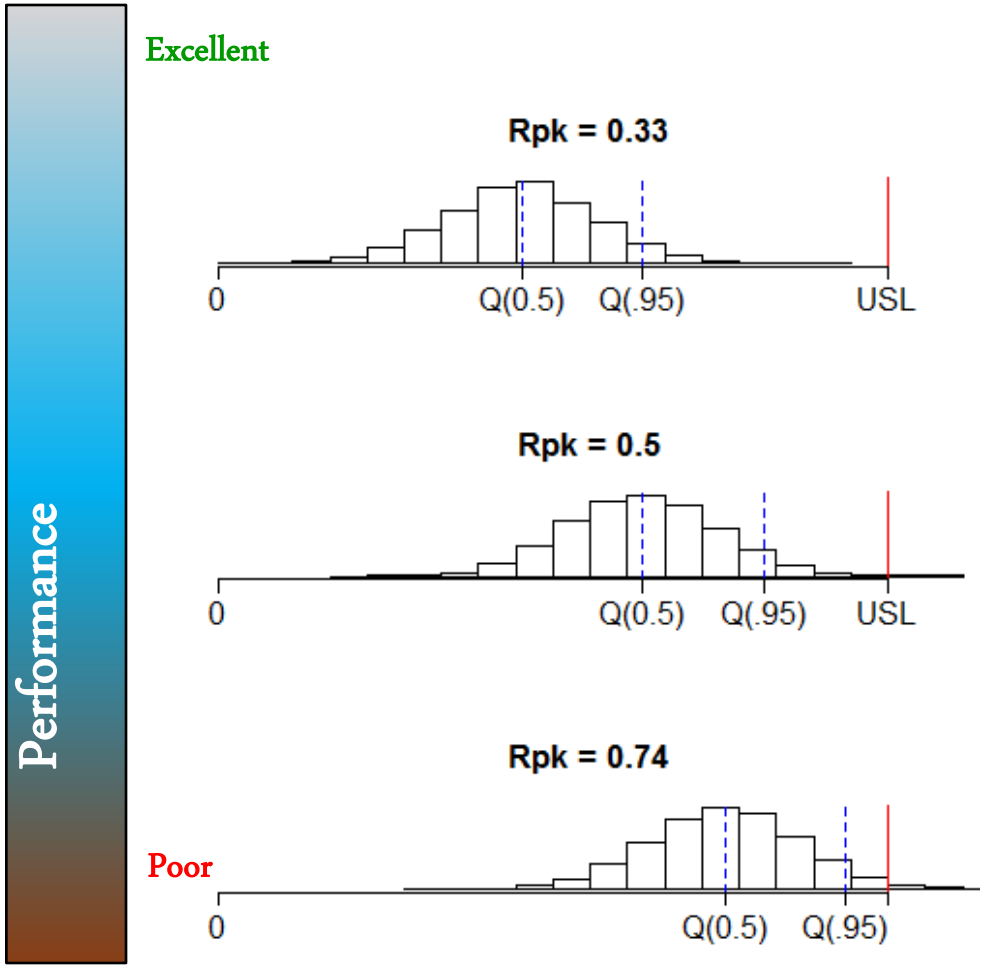
USL = Upper Specification Limit
LSL = Lower Specification Limit
q05 = 5th percentile
q50 = 50th percentile (median)
q95 = 95th percentile

Novel Tool : Rpk is Simple and Interpretable

Rpk: Non-parametric, proportion of allowable range used by process

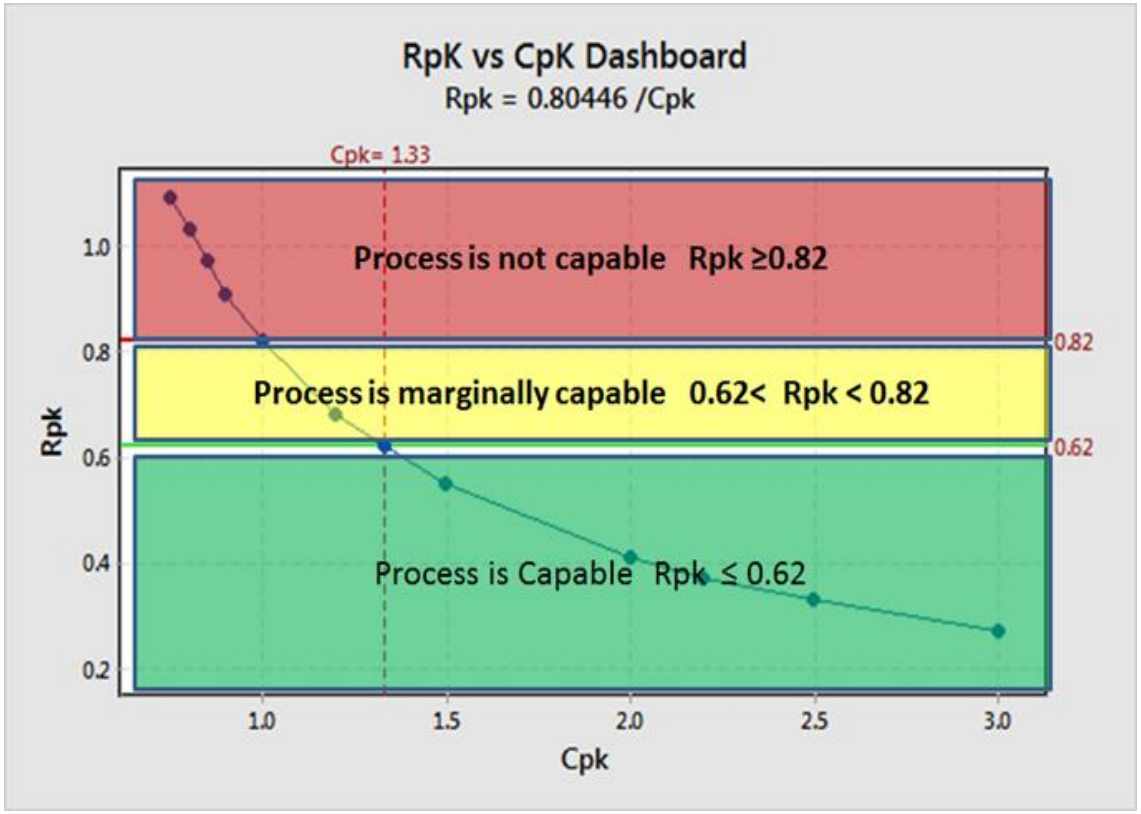
- Rpk typically between 0 and 1
- 0 indicates high process performance
- 1 indicates low process performance
- Small is Beautiful, Big is Bad!
- Useful when process data do not meet normal distribution assumptions
- Gives best result with smaller sample size

Examples with USL:



Risk Index Dashboard

- **CpK Assumption**
  - The CQA data have to satisfy the normality assumption
  - Cpk based on variation from mean.
  - It could be a predictor of future defect rates or ppm
- **RpK Assumption**
  - The CQA data does not have to satisfy the normality assumption
  - Rpk based on variation from median
  - Process does not have to be centered
  - Rpk is not a predictor of future defect rates or ppm



For normally distributed data, Rpk has an inverse relationship to Cpk

Capability/Performance Indices Comparison

	Cpk	Ppk	Ppq [6, Clements]	Rpk
Indices Type	Capability	Performance	Performance	Performance
Utility	Predictive	Retrospective	Retrospective	Retrospective
Variance Type	Short Term	Total Variance	Total Variance	Total Variance
Data Coverage /Stat Base	**99.73 % Mean, SD** $_{\text{Short Term}}$	99.73% **Mean, SD** $_{\text{ALL}}$	99.73% Quantile from Median	90% Quantile from Median
Normality Assumption	**Yes**	**Yes**	**No**	**No**
Application	Predict non-conformance rate	**Past performance**	**Complete Process data coverage e.g. robustness**	**process robustness to shifts of distribution**

Quantile-based metrics provide robust performance assessment

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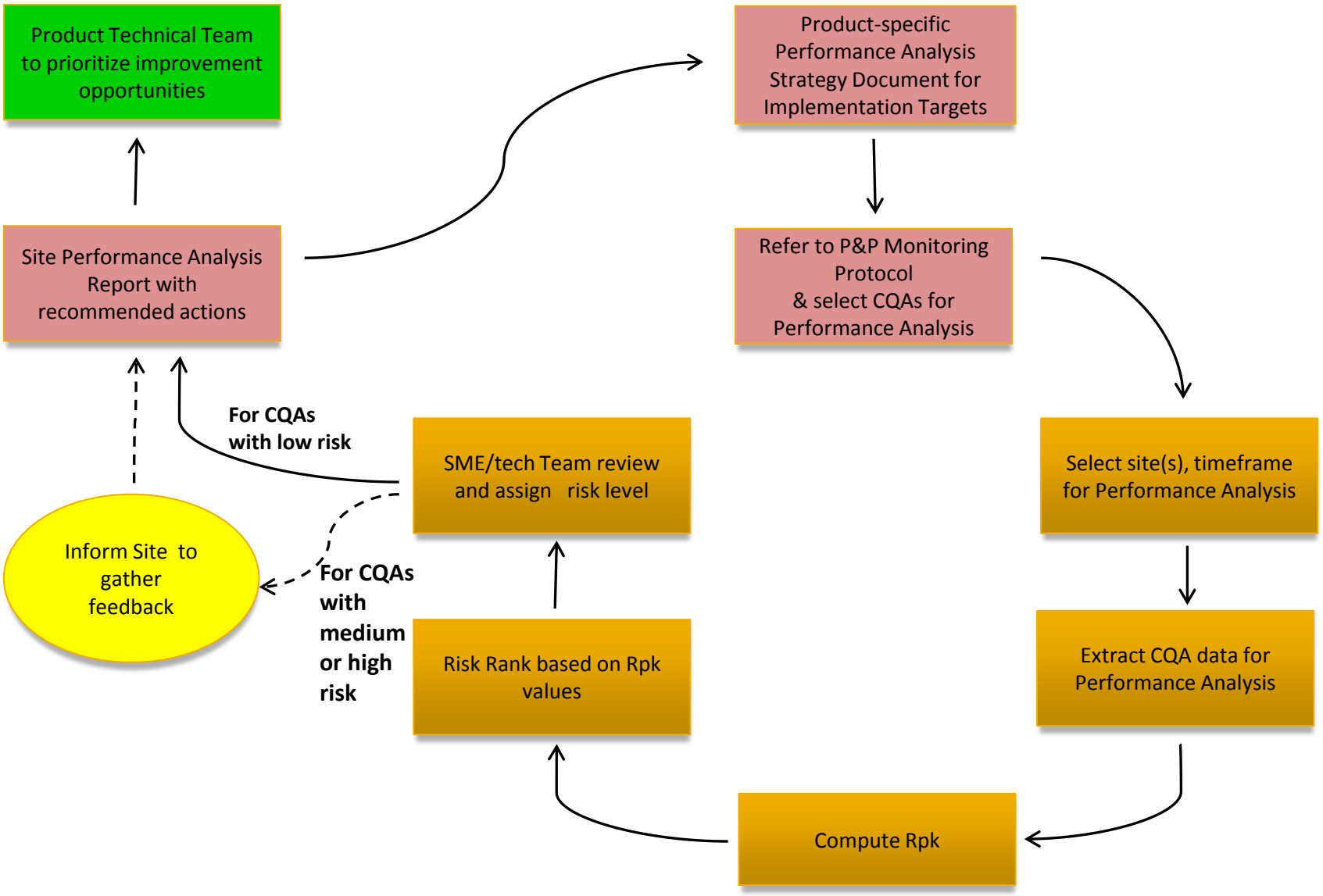
Overview of Performance Analysis at Roche



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- PA Team: Pia zur Loye (nee Krieger), Mike Siani-Rose, Dan Coleman, Theo Koulis, Yiming Peng, Marie-Odile Schneider, David Cate, Jodi Fausnaugh-Pollitt, Raquel Iverson, Aaron Goerke
- References: Brenda Ramirez, David Griffiths

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[2] *Process monitoring using statistical quality metrics: Application to biopharmaceutical processes* Keith A. Britt, Brenda Ramirez, and Tom Mistretta, Quality Engineering, 2016 Vol. 28 No 2. 193-211

[3] *A Quantitative Approach for Detection of Unstable Processes Using a Run Chart* Quality Technology &Quantitative Management Vol. 7, No. 3, pp. 231-247, 2010 Susanta Kumar Gauri

[4] *Quantitative Techniques to Evaluate Process Stability* -B. Ramirez, G. Runger Quality Engineering 18:53-8, 2006

[5] *The Probability of an Out of Control Signal from Nelson's Supplementary Zig-Zag Test* Griffiths, David; Bunder, Martin; Gulati, Chandra; and Onzawa, Takeo,, Centre for Statistical and Survey Methodology, University of Wollongong, Working Paper 11-10, 2010, 9p.

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[7] *Process Capability Calculations for non-Normal Distributions* John A. Clements - Quality Progress, September 1989 p95-100.

[8] *Embrace Special Cause Variation During CPV* - Tara Scherder, Pharmaceutical Engineering ISPE Magazine May-June 2017, Vol. 37, Number 3, pp. 66-69

Abstract submitted

Keywords: SPC Quality Capability Monitoring Control Chart Quantile Cpk Continuous Verification Ppk
Purpose: Demonstrate application of novel statistical metric tools that enhance robustness of process monitoring and enable reliable assessment of process capability in biopharmaceutical industry
1. Motivation: Increased robustness in process monitoring is being demanded by regulators to meet Continuous Process Verification (FDA, ICH) guidelines. Biopharmaceutical industry faces a significant
challenge in application of conventional SPC techniques due to short run lengths, questionable conformance to underlying SPC assumptions and increased occurrence of false alarms. As SPC run (Nelson) rules are added to
distinguish special cause situations from common cause, the false alarm rate increases. Novel tools are needed to increase robustness of process monitoring and to make reliable capability assessment
so that high quality drug products are manufactured efficiently.
2. A new paradigm for PM/PA (Process Monitoring/Performance Analysis) is proposed for reliable and efficient process monitoring and process capability assessment. Easy-to-use metrics are described to
reliably and efficiently detect true quality trends. We propose that the stability of the process be first evaluated using stability metric tests. If the process is stable, capability assessment can be done with traditional Cpk analysis
for normally distributed data and with quantile-based capability index for the dataset that is not normally distributed. If the process is not stable, capability assessment should not be done. Process must be
fixed remove “special causes” of poor process stability.
3. Significance: We provide new point of view and simple novel tools for reliable SPC and capability analysis. Utilization of these tools will eliminate wasted efforts and increase accuracy of process monitoring
investigations in biopharmaceutical industry.

Session Preference: Statistics, Target Audience: Quality
Material Presented Before: No
Previous Presentations: (1) International Six Sigma Conference (Orlando, FL, March 11-12, 2009): Quality Engineering and Statistics at the Heart of Success of Lean Six Sigma and OE Programs at Roche. (2)
ASQ Fall Technical Conference (Jacksonville, FL, October 11-12, 2007): Multiple Linear Regression Methods with Collinear Datasets, (3) ASQ Innovation Conference (Sacramento, CA, October 26, 2013) and
ASQ Section 613 Meetings 2013, Statistical Tools for Innovation

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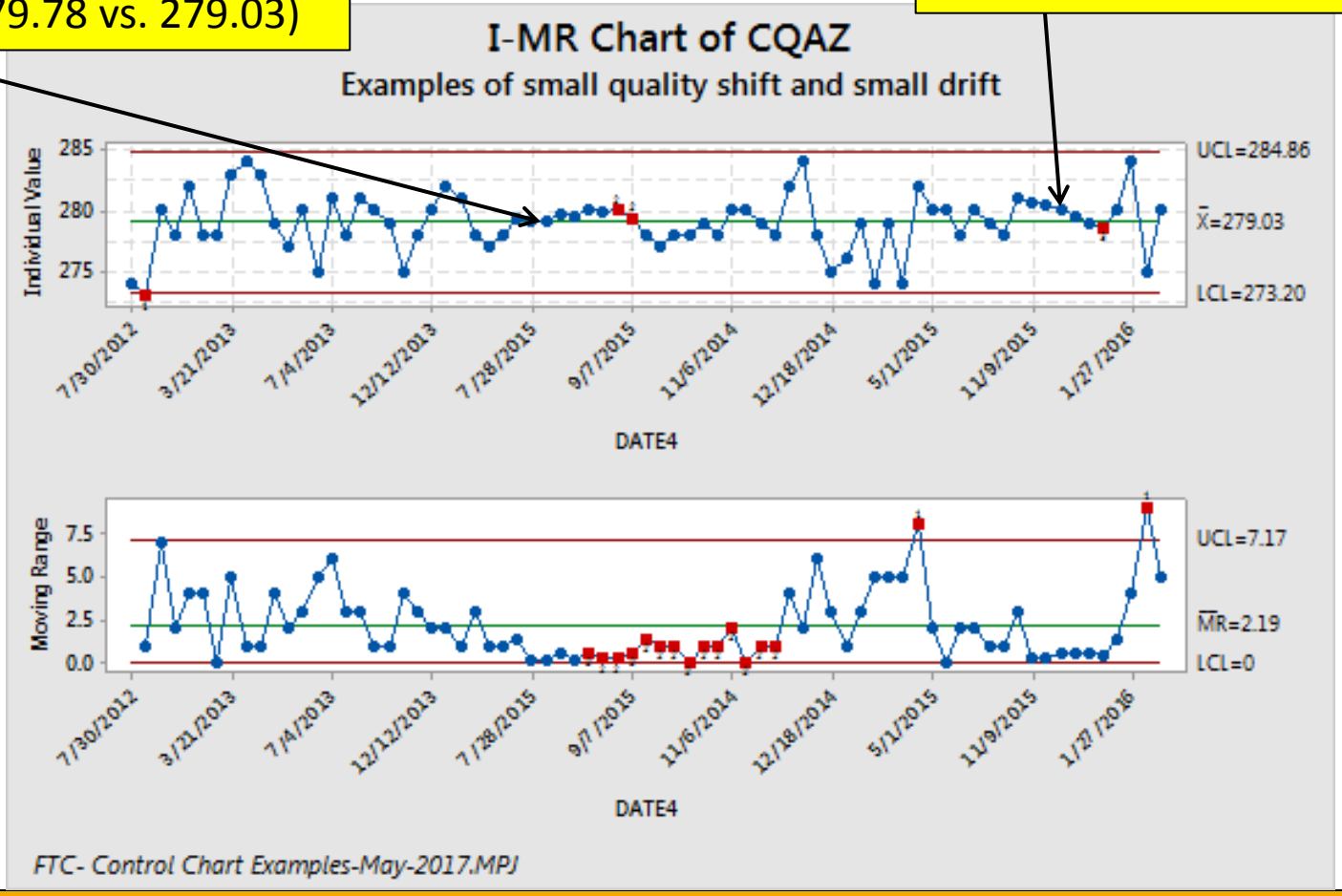
Examples of quality shift and drift
Test of Practical Significance

Shift of 0.75 (279.78 vs. 279.03)

Drift of 1 (from 281 to 280)



SMEs decide how much change is practically significant

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Performance Analysis
An integrated approach Inspiring Innovation for Reliable Supply (Pia's poster [6])

Performance Analysis – An integrated approach Inspiring Innovation for Reliable Supply

Pia Krieger, David Cate, Dan Coleman, Elvin Varghese, Jodi Fausnaugh-Pollitt, Maxim Zehe, Michael Siani-Rose, Ray Arnold, Sam Salari, Theo Koulis, and Yiming Peng

Roche
Changing the way we cure disease

Abstract

Ensuring reliable supply of bio/pharmaceuticals to our patients is the priority for Roche Pharma Technical Operations. Understanding the capability of manufacturing processes to generate product lots, which conform to release specifications, is one of the keys to uninterrupted supply. Global Manufacturing Science and Technology is working in close collaboration with Global IT, Global QC, Non-clinical Biostatistics, and manufacturing site staff to establish systems to enhance transparency, unity, and engagement.

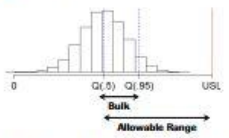
The **Roche Enterprise Manufacturing Intelligence (REMI) system** is an automated data management solution to acquire, analyze, and report global manufacturing data near real-time. **Performance Analysis metric Rpk** is a unique statistical approach to identify and prioritize improvements in process and analytical method performance.

These innovative solutions will enable rapid acquisition and analysis of data to enhance understanding and drive timely and well-informed decision making.

Rpk: Risk-Based Performance Index

Introduction

Rpk is the proportion of the allowable range used by the bulk of the data.



CQAs with one-sided limit
R_{pk} = B/A

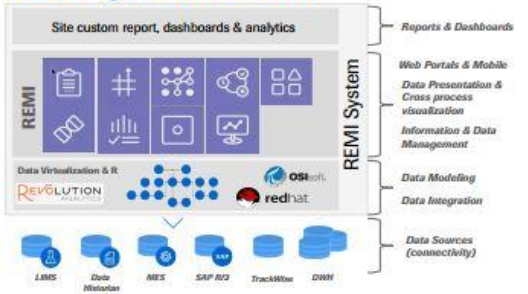
CQAs with two-sided limits
R_{pk} = Max (B1/A1, B2/A2)

- Rpk ~ 0 → low risk
- Rpk ~ 1 → high risk

B = Bulk of data, Proportion of the data between q50 and q95
A = Allowable Range, interval between q50 and USL

With Rpk, one metric used across network allows risk ranking within and across sites, products, manufacturing stages to identify areas of highest risk

REMI – System Architecture

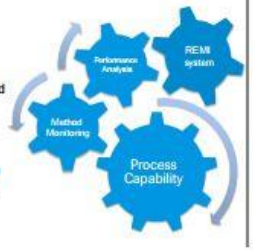


Integrated Enterprise Intelligence Suite

Performance Analysis: uses metrics, such as Rpk, with statistical analysis and visual feedback to assess performance, sources of variation and improvement opportunities.

Method Monitoring: evaluates the reference standard and product control results generated during routine, commercial QC testing to ensure that test methods are performing according to their original validated state.

Roche Enterprise Manufacturing Information (REMI): is a Centralized IT System framework to automatically acquire, analyze and report global manufacturing data for Product & Process Monitoring



Rpk: Risk-Based Performance Index

Rpk provides distinct advantages compared to Cpk, Ppk

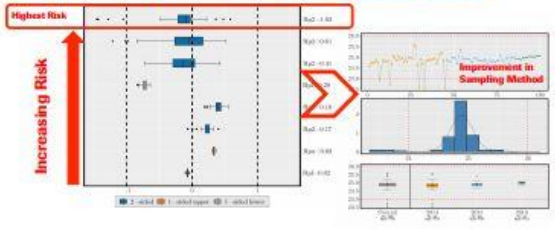
	Cpk	Ppk	Rpk
Indices Type	Capability	Performance	Performance
Utility	Predictive	Retrospective	Retrospective
Variance Type	Variance around trend line	Total Variance	Total Variance
Common usage	Process in statistical control	All processes	All processes
Index assumes normal distribution	Yes	Yes	No
Interpretation	Predicts proportion of non-conforming units	Same interpretation as Cpk when process in statistical control	Indicates process robustness to shifts of distribution

Cpk/Ppk assume normal distribution. The tails of the distribution are described using +/- 3 std. dev. If data is not normally distributed, interpretation is unknown.

REMI generates Performance Analysis Report

CQA Dashboard

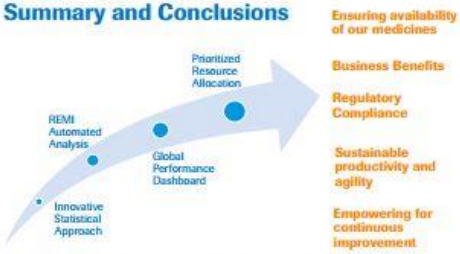
CQAs sorted by risk and drilling down to Control Charts



RpK as metric for Performance Boards

Change of Mindset

Summary and Conclusions



Deliver best in class tools and engage across our network to capture enterprise-wide data and build enterprise-wide thinking.

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