Using Control Charts to Evaluate Process Variability

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PQRI 2015 Annual Meeting
North Bethesda, Maryland
October 5, 2015

Walter Andrew Shewhart (1891-1967)

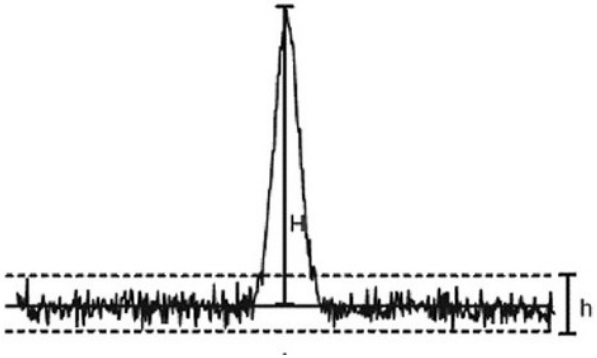
- A physicist, engineer and statistician
- "Father of statistical quality control"
  - "Statistical method from the viewpoint of quality control" (1939)
- "Creator of PDSA (Plan, Do, Study and Act) cycle"
- "Creator of control chart"
- Originator of the "Chance and Assignable variation" concept

"Uncontrolled variation is the enemy of quality"

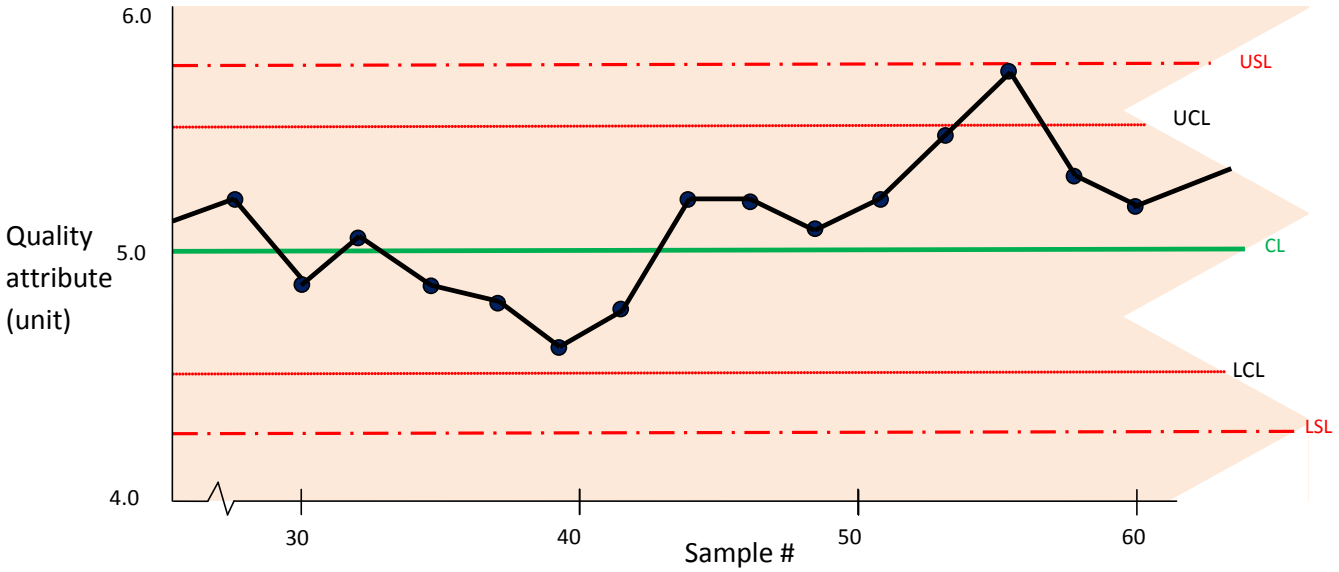
Dr. W. Edwards Deming (1900-1993)

Sources of Variation

- **Variation exists in all processes.**
- **Variation can be categorized as either:**
  - **Chance or Common causes of variation**
    - Inherent to a system, random, always present and hence predictable within statistical limits
    - Eliminate inherent variability (noise) is difficult
  - **Assignable or Special causes of variation**
    - Exterior to a system, non-random, not always present (intermittent)
    - can cause changes in the output level, such as a spike, shift, drift, or non-random distribution of the output.
    - Are usually easier to be detected, controlled or eliminated



Control Chart



- **Definition**: a graphical display of a product quality characteristic that has been measured or computed periodically from a process at a defined frequency
- **Every control chart consists of**:
  - A set of data
  - A central line (CL) (mean)
  - Two **statistical process control limits** (UCL and LCL) (**Is the process Stable**?)
- **Upper and Lower Specification Limits (USL and LSL)**
  - Patient's need (Safety and Efficacy) (**Is the process Capable**?)

Potential Applications

- To proactively monitor and trend a process
- To detect the presence of special cause variation
- To identify continual improvement opportunities
- To maintain the process in a state of statistical control
  - Using science and risk-based approach
  - Take action in a timely manner

Key Considerations for Constructing a Control Chart

Choice of Product Quality Characteristics

- Critical Quality Attributes (CQA)
  - A physical, chemical, biological or microbiological property or characteristic of an output material including finished drug product that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8)
  - Identification of CQA: primarily based upon the severity of harm to the patient (safety and efficacy)
- Critical (input) material attributes and critical process parameters (CMAs/CPPs)
- Other relevant process characteristics that can assist in process monitoring and controlling

Types of Control Chart

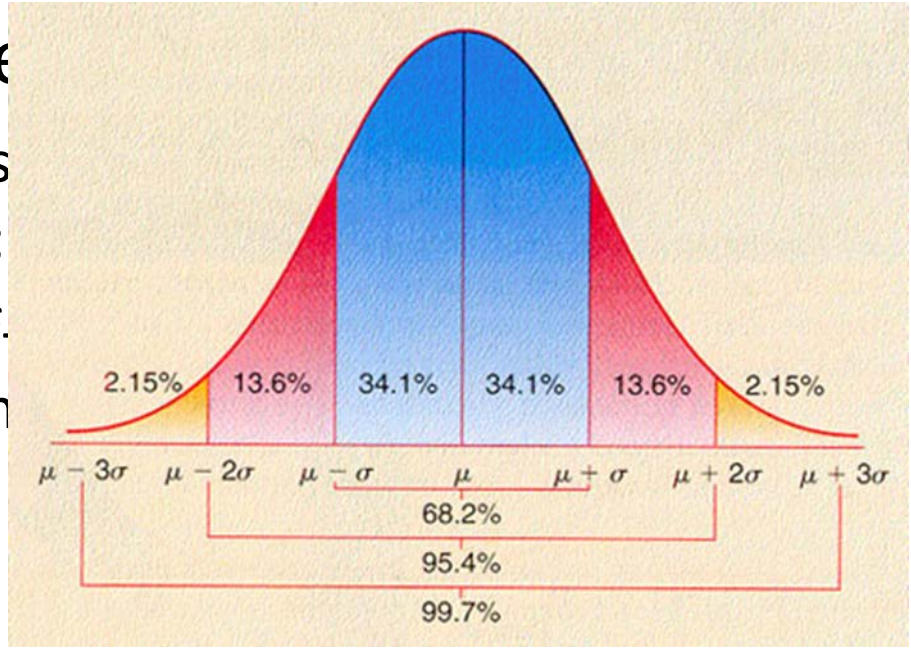
- **Variable Control Chart**
  - Characteristics that can be measured (**continuous numeric data**) e.g. Assay, Dissolution, % of Impurity…
  - The **average** and **variability** charts are usually prepared and analyzed in pairs
    - Average – Range chart (Xbar-R chart, subgroup size 2-10)
    - Average – Standard Deviation chart (Xbar-S chart, subgroup size >10)
    - Individual – Moving Range chart (I-MR chart, n=1)
- **Attribute Control Chart**
  - Characteristics that have **discrete** values and can be **counted**, e.g. % defective, # of failed batches in a month
  - *p* chart / *np* Chart: for fraction of occurrence of an event- Binominal distribution
    - e.g. % of unsuccessful batch at a facility every month
  - *c* chart / *nc* Chart: for counts of occurrence in a defined time or space increment -Poisson distribution
    - e.g. number of particulate matter in an injection vial
- **Other types of control chart**:
  - cumulative sum control chart (CUSUM)
  - exponentially weighted moving average control charts (EWMA)

Subgroup Size and Sampling Frequency

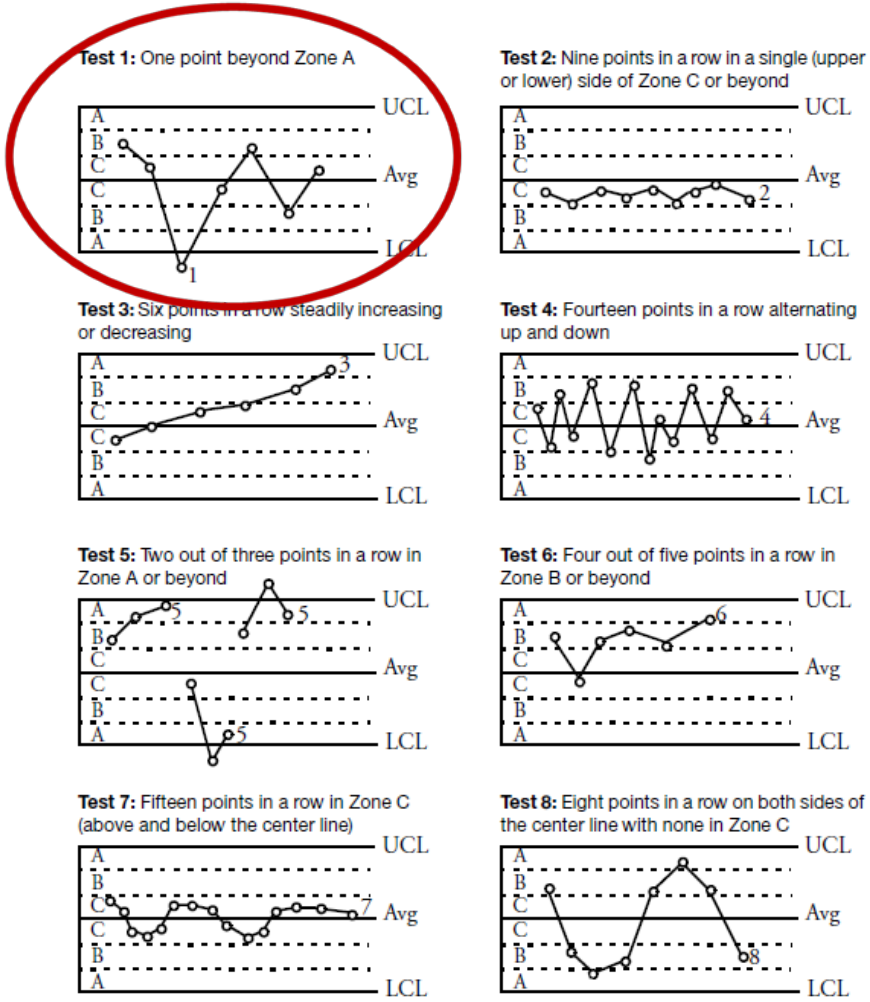
- **Subgroup**: the observations sampled at a particular time point
- **Subgroup Size and Sampling Frequency** (N x K)
  - The number of observations in each subgroup: 1 → n
  - the objective of the monitoring (detect large or small shift)
  - how quickly the output responds to upsets
  - consequences of not reacting promptly to a process upset
  - time and cost of an observation
- **Rational Subgroup**:
  - Minimize the variation of observations within a subgroup
  - Maximize variation between subgroups

Statistical Process Control Limits

- UCL and LCL:
  - the thresholds at which the process output is considered statistically unlikely
  - typically, ±3 SD (Shewhart limits)
- Rationale: to balance
  - Failing to signal the pres cause when one occurs;
  - False alarm of an out-of- the process is actually in control



How out-of-control points are identified?



8 Western Electric Rules

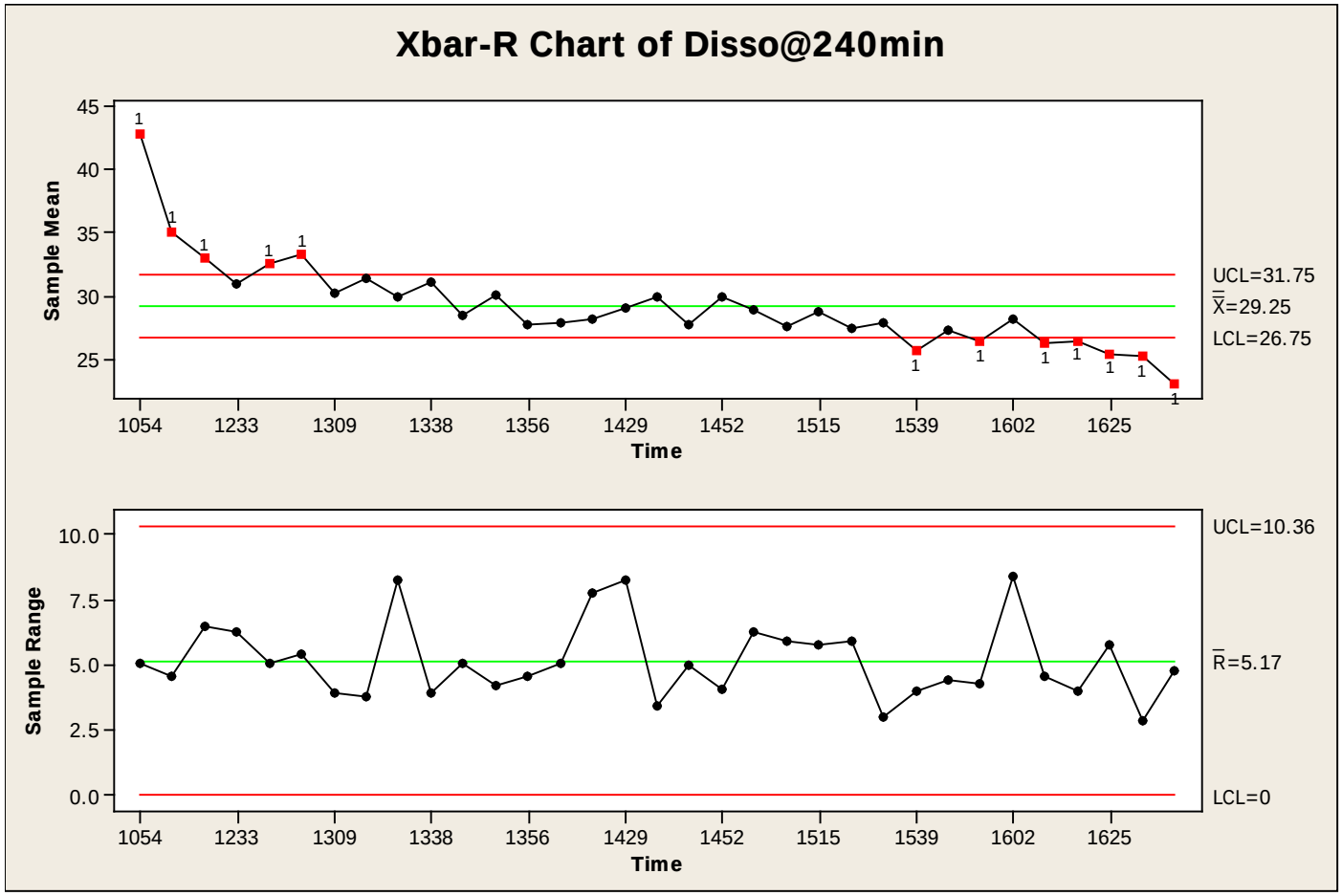
- Rule No.1
  - any point falls outside UCL/LCL
- Other Rules
  - certain nonrandom patterns of the plotted data
  - Use it judiciously
- Risk of “false alarm”

Over-Reaction vs. No-Reaction

Control chart and process capability analysis often go hand-in-hand

Illustrative Examples

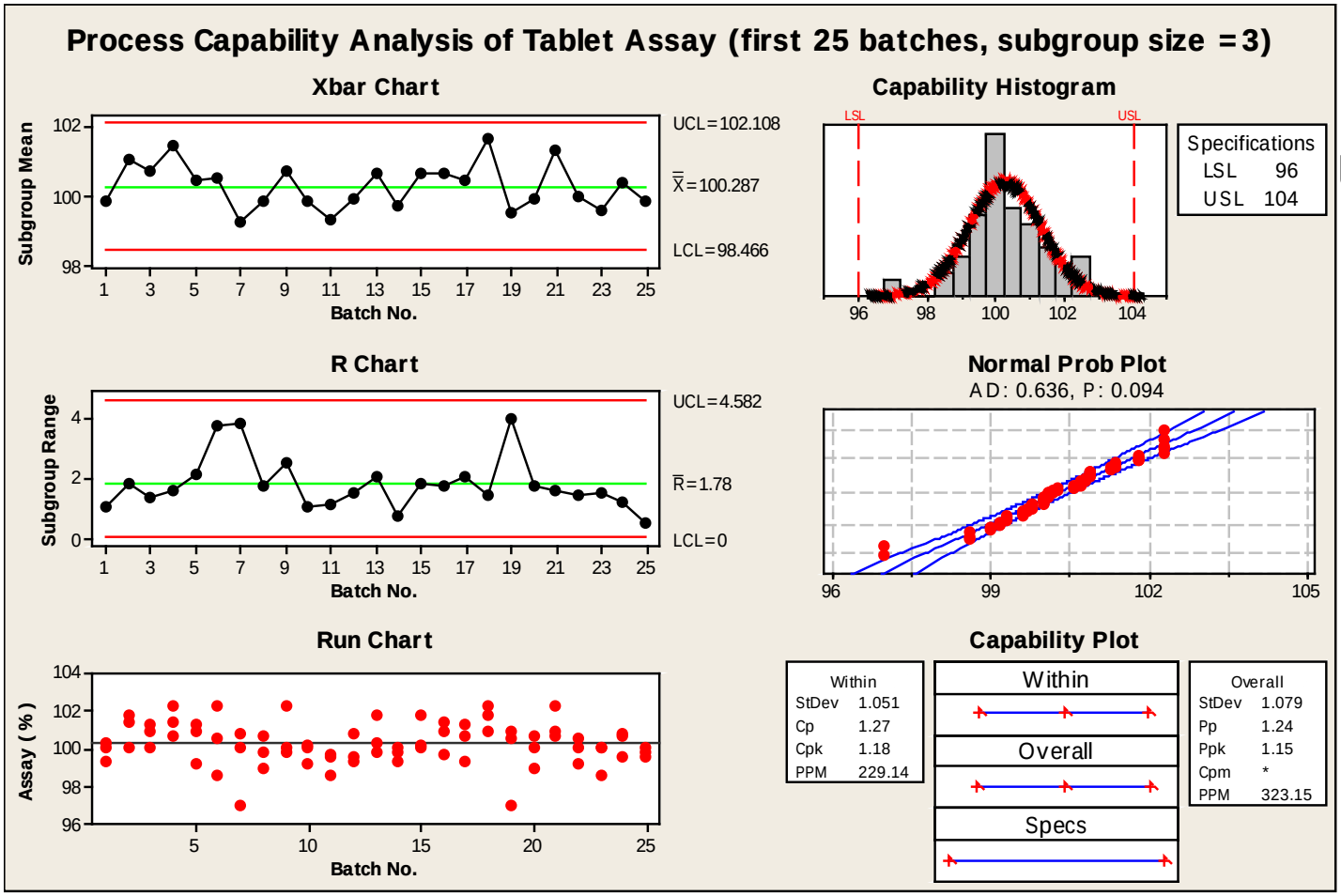
Within Batch Variability Example



Not Stable
&
Not Capable

ER coated beads, mixed with extra-granular cushioning excipients and compressed into tablets
Compression: ~ 5h, sample frequency: every 8-10 min (total 33 subgroups), subgroup size= 6

Between Batch Variability Example



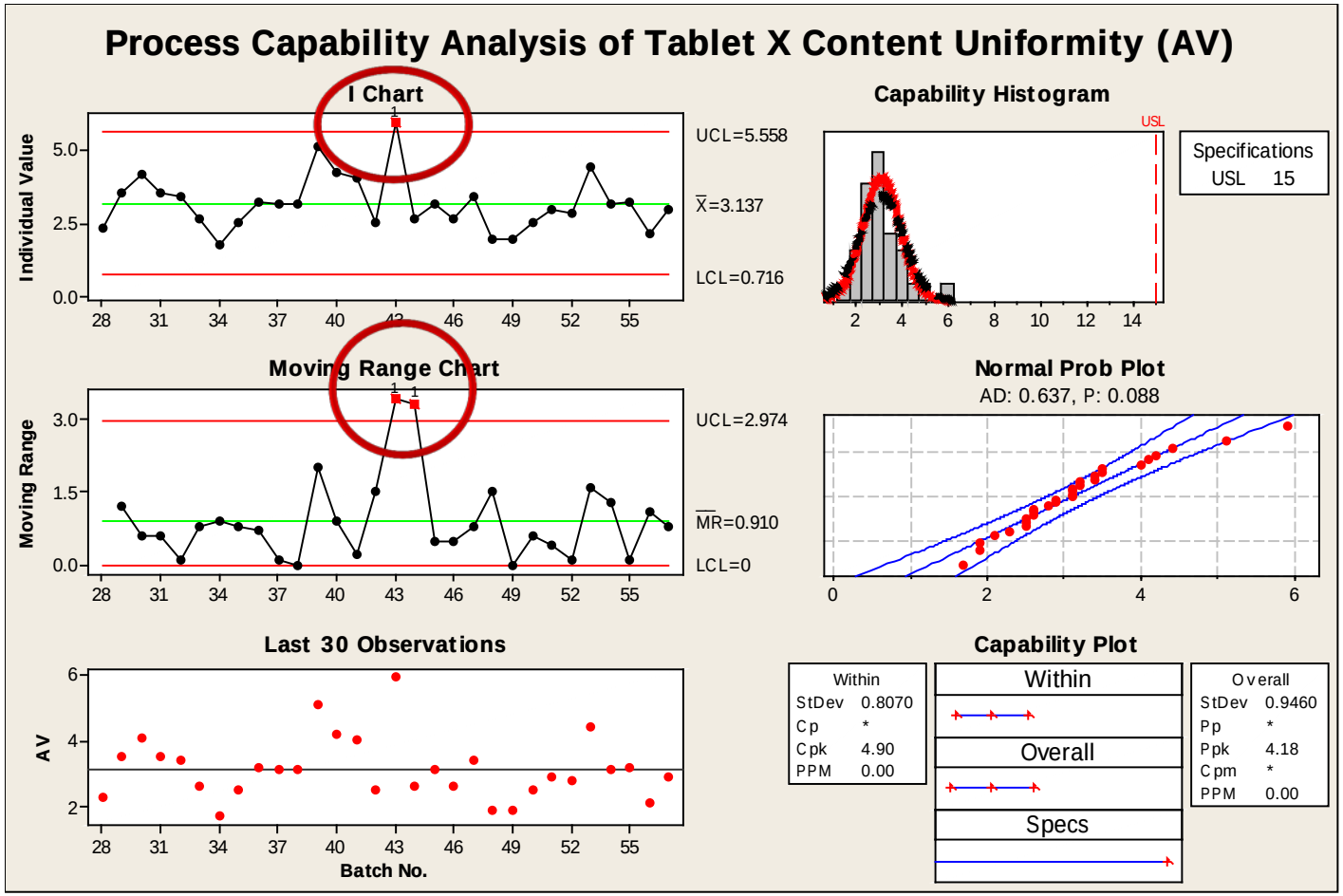
USP: 90-110

Cpk: 2.95

Stable & Capable

Data source: Chopra, V., Bairagi, M., Trivedi, P., et al., "A case study: application of statistical process control tool for determining process capability and sigma level," *PDA J Pharm Sci and Tech,* 66 (2), **2012**, pp. 98-115

Between Batch Variability Example

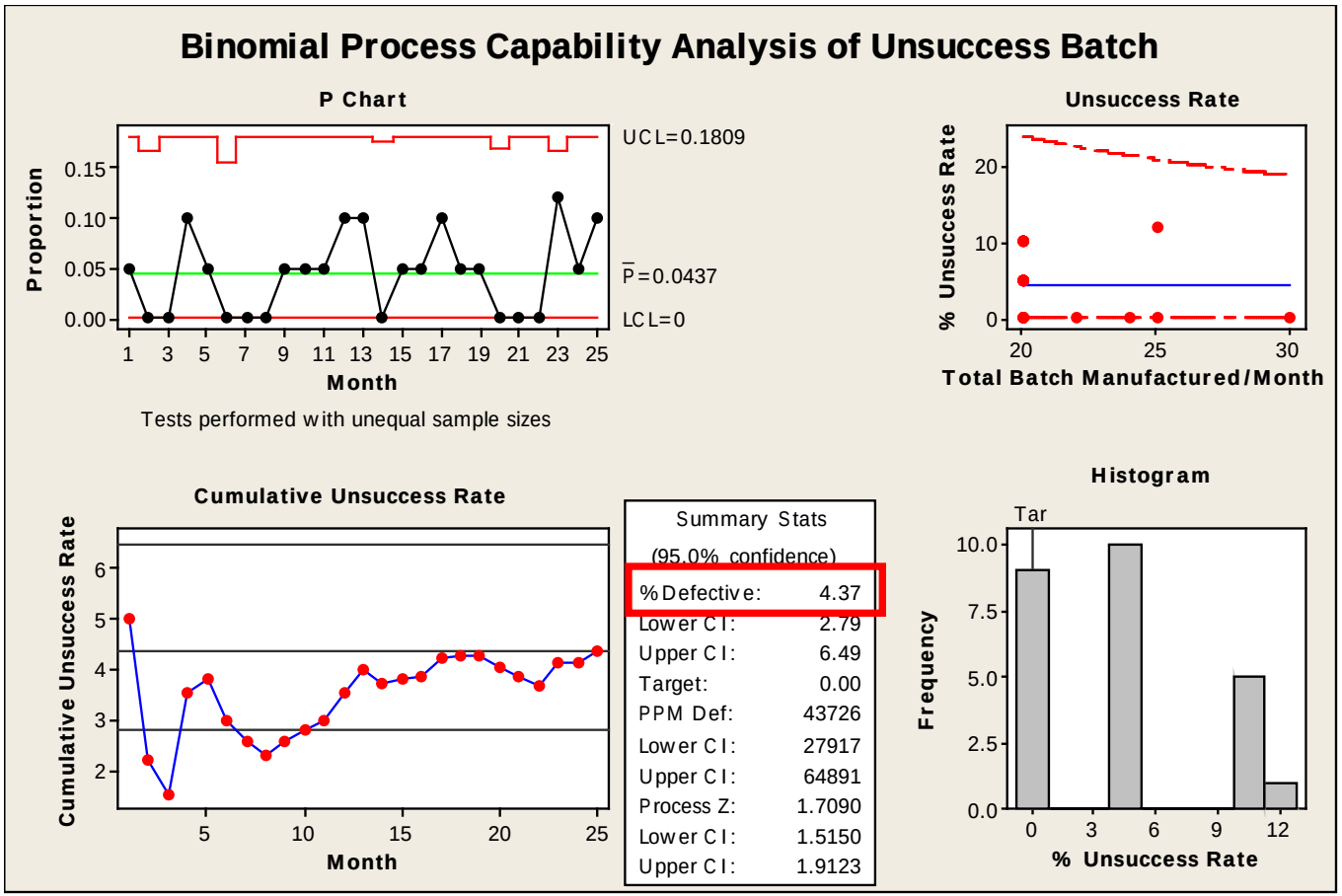


Not Stable but Capable

Tablet content uniformity (AV) of last 30 commercial batches of Tablet X manufactured by Firm Y (subgroup size =1, I-MR chart)

Site Performance Monitoring Example

% of "unsuccessful batch"/month at Site A (# of lots attempted: 20-30/month)



Stable but Not Capable

Binomial process capability index: 0.569

Paradigm Shift – "Culture of Quality"

- Manufacturers take full responsibility for quality of their products
  - Focus on meeting patients' expectations
  - Regulators' expectations considered minimal approach
- Strive for continual improvement
- Management and organizational commitment to prioritizing quality
- Each person in organization understands and embraces their role in quality

Summary

- **Brief introduction of control chart:** history, definition, types
- **Key considerations for constructing a control chart:**
  - Choice of drug product quality characteristics
  - Subgroup size and sampling frequency
  - Statistical process control limits (UCL and LCL)
- **Illustrative examples for process monitoring and control**:
  - Within batch variability
  - Between batch variability
  - Site performance monitoring
- **Control Chart can be a valuable tool to:**
  - Proactively monitor and trend a process
  - Detect the presence of special cause variation
  - Identify continual improvement opportunities
  - Maintain the process in a state of statistical control

Acknowledgements

- Dr. Christine Moore
- Dr. Naiqi Ya
- Dr. Ubrani Venkataram

Thank You for Your Attention!