Application of Process Capability in Pharmaceutical Manufacturing

Alex Viehmann

Pharmaceutical Quality Symposium 2016

July 21, 2016

Agenda

- Background
  - Concept / Why? / Requirements / Assumptions
  - Calculation
  - Process Capability vs Process Performance
- Role of Statistical Process Control
- Examples
  - Continuous
  - Discrete

Concept of Process Capability

- Defined as “the natural or inherent behavior of a stable process that is in a state of statistical control”
  - A “state of statistical control” is achieved when the process exhibits no detectable patterns or trends, such that the variation in the data is believed to be random and inherent to the process.
- The process capability index relates the process capability to the customer’s specification tolerance.

Why is Process Capability measured?

- The capability of a process should be constantly measured and analyzed. Capability analysis can help you answer the following questions:
  - Is the process meeting customer specifications?
  - How will the process perform in the future?
  - Are improvements needed in the process?
  - Have you sustained these improvements, or has the process regressed to its previous unimproved state?

Assumptions

- Underlying distribution is normal
  - Transformations
  - Distribution fits
  - Distribution – free calculations
  - Discrete data (e.g. Binomial, Poisson)
- Process is in a state of statistical control
  - No significant between-subgroup variability
    - Cpk vs Ppk

Process Capability Calculations

- Process Capability Index (Cp):

$$C_p = \frac{\text{Specification Tolerance}}{\text{Process Capability}} = \frac{USL - LSL}{6\sigma_{ST}}$$

- Short-term standard deviation:

$$\hat{\sigma}_{ST} = \frac{\overline{R}}{d_2} \text{ or } \frac{\overline{MR}}{d_2} \quad \text{or} \quad \hat{\sigma}_{ST} = \frac{\overline{s}}{c_4}$$

- Process Capability Index (considering the process average):

$$\hat{C}_{pk} = \min[\, \hat{C}_{pku}, \hat{C}_{pkl}]$$

$$\hat{C}_{pku} = \frac{USL - \bar{X}}{3\,\hat{\sigma}_{ST}}$$

$$\hat{C}_{pkl} = \frac{\bar{X} - LSL}{3\,\hat{\sigma}_{ST}}$$

Formulas

$$CPU = \frac{(USL - \mu)}{(3 * \sigma_{Within})}$$

$$PPU = \frac{(USL - \mu)}{3 * \sigma_{Overall}}$$

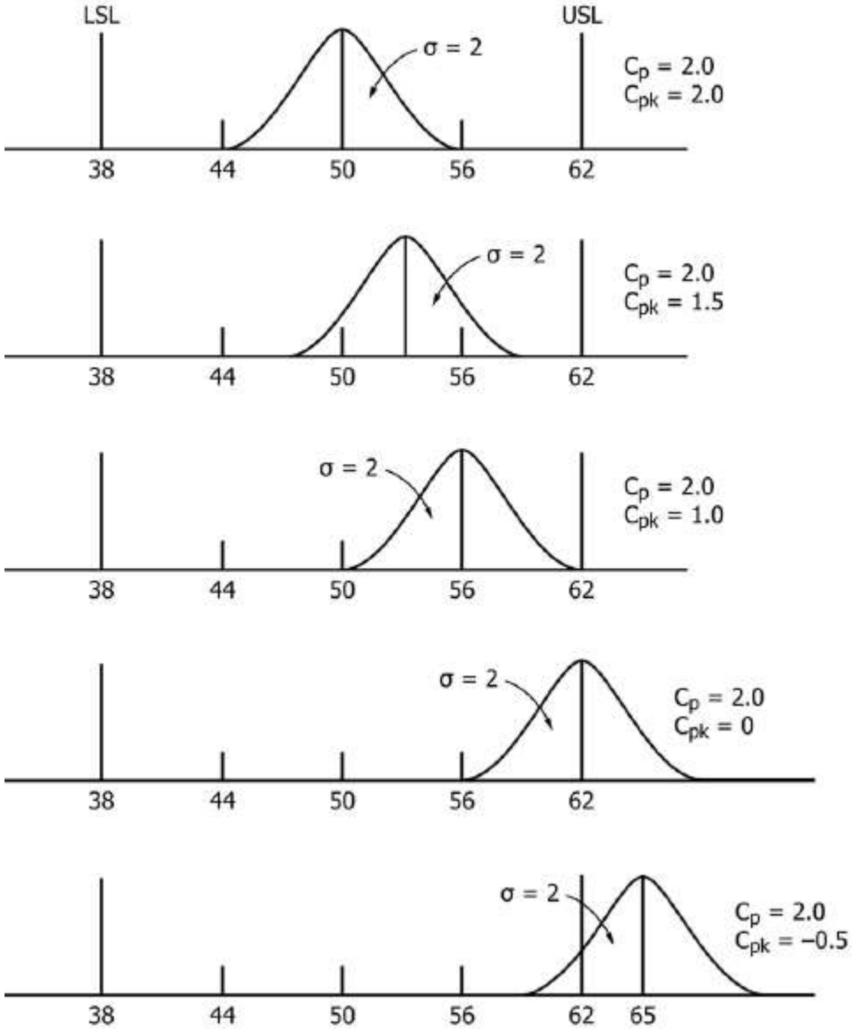
$$CPL = \frac{(\mu - LSL)}{(3 * \sigma_{Within})}$$

$$PPL = \frac{(\mu - LSL)}{3 * \sigma_{Overall}}$$

$$Cpk = \text{minimum}\{\text{CPU, CPL}\}$$

$$Ppk = \text{minimum}\{\text{PPU, PPL}\}$$

Cp vs Cpk


LSL
USL
σ = 2
C_p = 2.0
C_{pk} = 2.0
38
44
50
56
62
σ = 2
C_p = 2.0
C_{pk} = 1.5
38
44
50
56
62
σ = 2
C_p = 2.0
C_{pk} = 1.0
38
44
50
56
62
σ = 2
C_p = 2.0
C_{pk} = 0
38
44
50
56
62
σ = 2
C_p = 2.0
C_{pk} = −0.5
38
44
50
56
62
65

Role of SPC

- Process Capability calculations assume the process is stable (i.e. no significant between location variability).
  - Standard deviation calculation accounts for within subgroup variation.
  - If the process is not stable, then the process capability estimate is not valid and overestimated.
    - Must account for the overall variation and calculate Process Performance (not indicative of future production).

Process Performance Calculations

- Process Performance Index (Pp):

$$P_p = \frac{\text{Specification Tolerance}}{\text{Process Performance}} = \frac{USL - LSL}{6\,\hat{\sigma}_{LT}}$$

- Long-term standard deviation:

$$\hat{\sigma}_{LT} = \sqrt{\frac{\Sigma(x_i - \bar{x})^2}{n-1}}$$

- Process Performance Index (considering the process average):

$$\hat{P}_{pk} = \min\left[\hat{P}_{pku}, \hat{P}_{pkl}\right] \rightarrow \hat{P}_{pku} = \frac{USL - \bar{X}}{3\,\hat{\sigma}_{LT}}$$

$$\hat{P}_{pkl} = \frac{\bar{X} - LSL}{3\,\hat{\sigma}_{LT}}$$

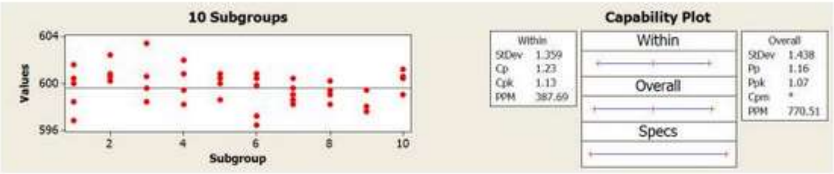
Ppk vs Cpk

- Cpk
  - Only accounts for variation WITHIN the subgroups
  - Does not account for the shift and drift between subgroups
  - Represents the potential your process has – predict future production

- Ppk
  - Accounts for the OVERALL variation of all measurements
  - Includes both the variation within and between the subgroups
  - Represents the actual performance level of the process – not intended to predict future production

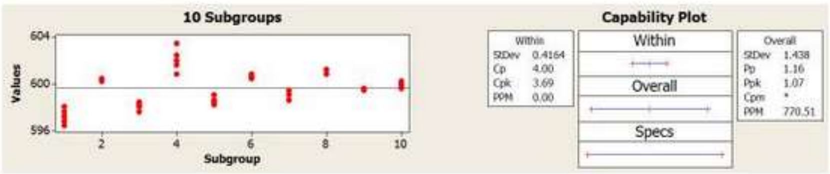
Ppk vs Cpk

Similar Cpk and Ppk



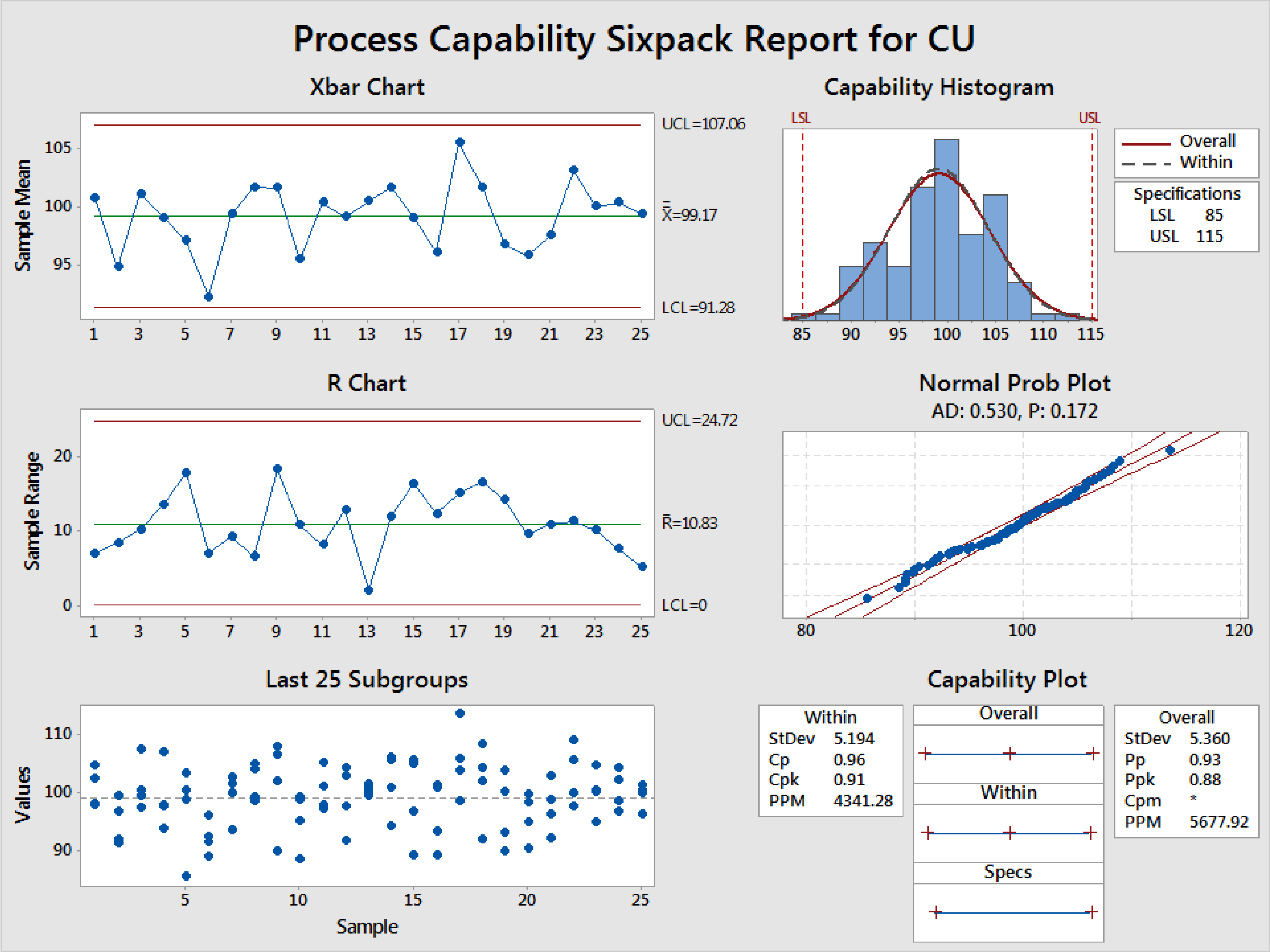
There is not a lot of shift and drift between subgroups compared to the variation within the subgroups. Therefore, the within and overall SDs are similar, which means Cpk and Ppk are similar.

Different Cpk and Ppk

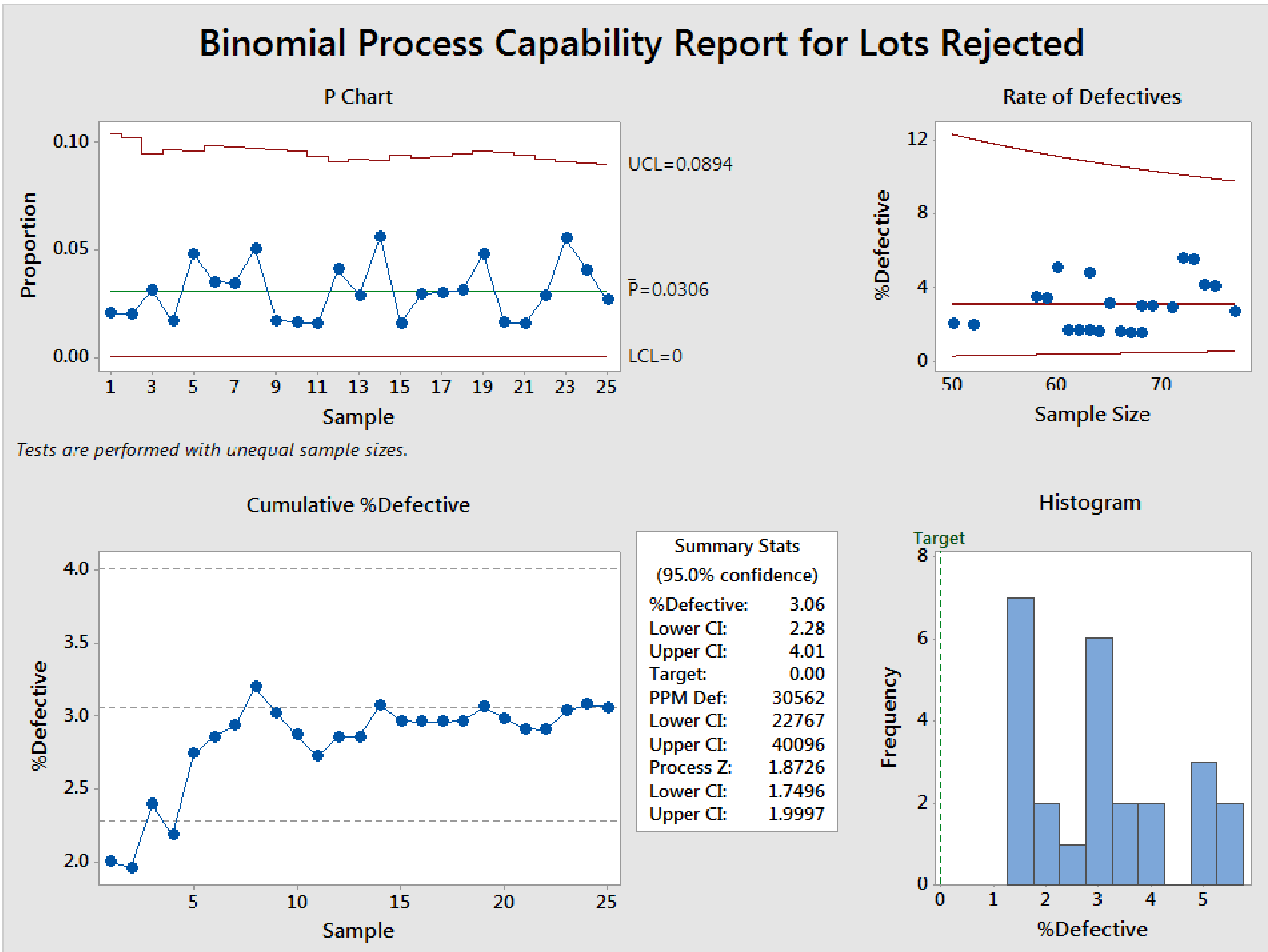


The above graph shows that the points within each subgroup are much closer together. This process is exhibiting significant between subgroup variation compared to the within SD.

Example I: Content Uniformity



Example II: Batch Failure



Resources

- ASTM E2281-15: Standard Practice for Process Capability and Performance Measurement
- ASTM E2587: Standard Practice for use of Control Charts in Statistical Process Control
- Minitab 17 was used for all examples and graphics

Acknowledgements

- Karthik Iyer
- Daniel Peng
- Lawrence Yu

Please evaluate this session:

surveymonkey.com/r/PQS-D2S8