Process Capability

Karthik Iyer
Senior Policy Advisor
CDER/OC/OMPQ
October 16th , 2014
QbD/PAT

*** This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.**

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Outline

- WL Example
- ASTM Standard
- Definition and Use
- Key Points

Warning Letter – Equipment Comparability and Process Capability

- Four (4) tablet products, various strengths
  - Initial process qualification used a single-sided tablet press. During routine production, however, these products were also being manufactured using a double-sided tablet press.
  - Compression using the double sided press was not qualified.
  - Firm's response to the FDA 483 attempted to show statistical equivalence between the single and double sides presses.

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Warning Letter – Equipment Comparability and Process Capability

- The firm's written response referenced the Cpk values (point estimates only) for processes using a double-sided tablet press and the single-sided tablet press.

- FDA evaluation of the FDA 483 response
  - The Cpk value alone was not an appropriate metric to demonstrate statistical equivalence. Cpk analysis requires a normal underlying distribution and a demonstrated state of statistical process control. The firm did not address these issues in their response.

  - Statistical equivalence between the two presses could have been shown by using either parametric or non-parametric (based on distribution analysis) approaches and comparing means and variances. Neither of these approaches was employed. Firm did not use the proper analysis to support its conclusion that no significant differences existed between the two compression processes.

Warning Letter – Equipment Comparability and Process Capability

- Issues –
  - Data did not support proper statistical conclusions.
  - Firm did not understand underlying assumptions required to conduct Process Capability calculations.
  - Firm did not conduct proper statistical analysis to demonstrate equivalence between two operations.

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Process Capability

- ASTM E2281 Standard Practice for Process and Measurement Capability Indices.
- Definition – statistical estimate of the outcome of a characteristic from a process that has been demonstrated to be in a state of statistical control.
- This value is usually measured as a capability index.
- The index compares the variability of the process against product specifications or tolerances. (Voice of the process/Voice of the customer).
- Note: Large sample sizes (minimum of 100) are required to estimate C_{pk} with a high level of confidence (95%).

Process Capability/Performance

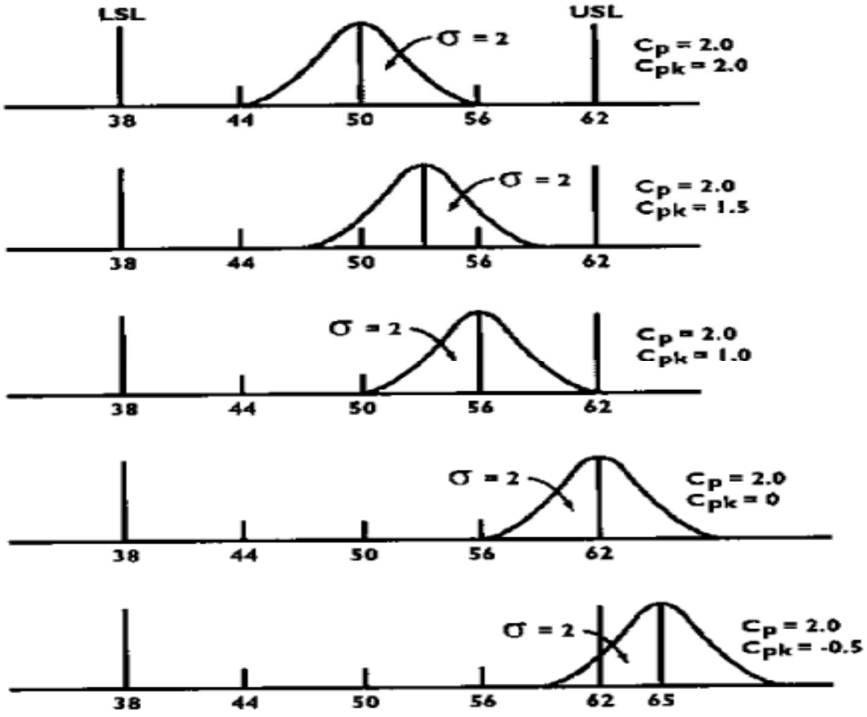
- C_p is for a centered process.
- C_{pk} is for a process that is not centered.
- C_p/ C_{pk} indices assume normality and are for short term performance (i.e. few number of batches of short time period).
- P_p indices do not require normality assumption and are for long term performance. Does not assume that process is in a state of statistical control.
- Process performance represents what the producer makes and process capability represents what the producer could make if the process is in a state of statistical control.

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Process Capability/Performance

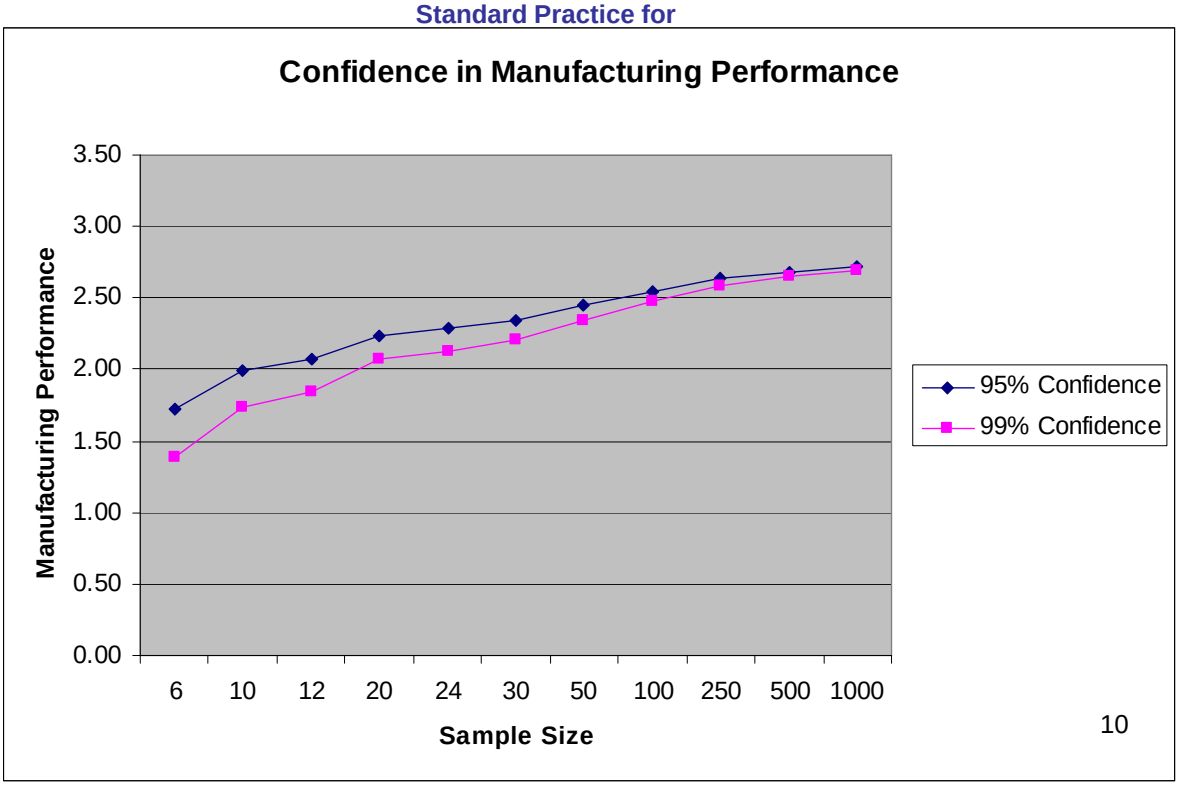
- Report indices with a lower confidence bound.
- Lower confidence bound accounts for the amount of samples that the index was based upon.
- Indices should be based on individual values (unless the reportable value is based on sample means).
- Can be applied for data based on Incoming, In-process, or Lot release samples.

Process Capability C_p vs C_{pk}



ASTM E2281

Standard Practice for



ASTM E2281 Explanation

Standard Practice for
Process and Measurement Capability Indices

- Slide shows the relationship between a reported Process Performance Index (P_{pk} (2.79)) and sample size. A positive relationship exists - as sample size increases, so does the reported P_{pk}.
- When reporting a P_{pk}, a lower 95 or 99% confidence bound should always be the value reported. As this value accounts for the sample size in which the P_{pk} was estimated.
  - For example: If you sampled 30 units and estimated a P_{pk} of 2.79, then the value reported should be ~2.2 (that is I am 99% confident that the P_{pk} for my process is at least 2.2). The analysis was done using ASTM E2281-08.

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

P_{pk} vs. C_{pk}

- C_{pk}
  - Data normally distributed
  - State of Statistical control
  - Sigma estimated using Control chart methods
  - Short-term
- P_{pk}
  - Data Normally Distributed
  - Sigma estimated using standard formula
  - Long-term
- Both indices can be applied to non-normal data through transformation, distribution fit or non parametric approaches
- Note: There may be cases where the calculation and application/interpretation of C_{pk} and P_{pk} are different

Key Points To Consider

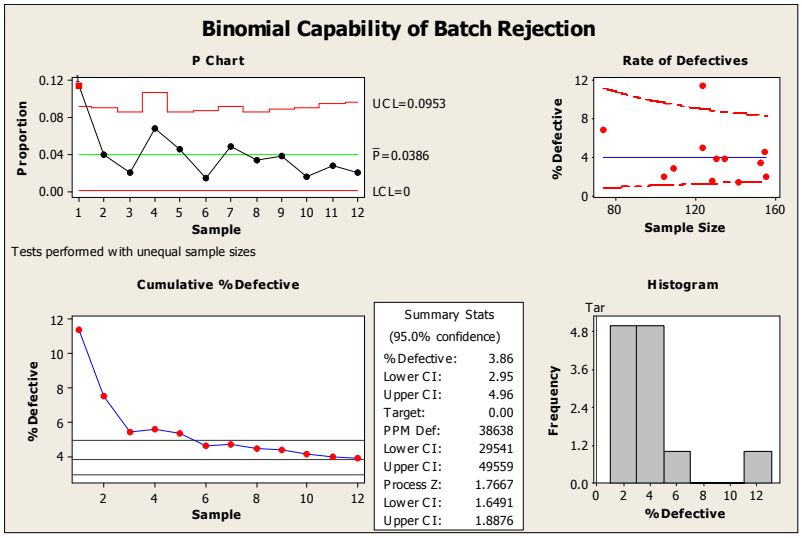
- Interpret the result, what is the lower bound? (Performance or Capability?)
- How many data points (observations) were used in the derivation? (Individual or means?)
- Were any points excluded and why?
- Was the distribution evaluated?
- Can Statistical Process Control be reasonably established?
- How is the final result being utilized?
- How do the Tolerance Intervals Compare vs. Specifications?
- Is the assessment for 1 CQA or multiple?

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Key Points

- Are the variables continuous or discrete?
- Binomial and Poisson Process Capability Analysis can be conducted
- Is there an overall or joint assessment?

Binomial Capability Example



Acknowledgements

- Alex Viehmann – CDER/OPS
- Grace McNally – CDER/OC