Introduction to PROCESS CAPABILITY

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November 17, 1999

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RATIONALE

- Why do Validation ?
- Why apply Process Capability to Validation ?

Why Do Validation ?

- Why ?
  - Common sense and good science requires it.
  - cGMP mandates it !
- How ?
  - Qualify facility and equipment train.
  - Establish extremes and limits of manufacturing process in development through scale-up.
  - Process validation batches on target.
  - If done right, should be the easiest exercise ? !

Why Process Capability?

- Provides a means for common and easily understood language for quantifying the performance of manufacturing process.

- Provides a measure for “High Degree of Assurance”, a key requirement for process validation.

PROCESS CAPABILITY OVERVIEW

- Philosophy
- Literature Review
- Assumptions
- Process Capability Indices
- Example

Philosophy

- Quantification of process location (mean) and variation(standard deviation) is central to product quality.
- Process capability provides a means to compute unitless indices (PCIs) using process location and variation relative to pre-established specifications (target & limits).
- Process capability is the measured reproducibility of the manufacturing process.

Non-Pharmaceutical Literature

- J.M. Juran (1974). Quality Control Hand Book, 3rd edition. McGraw-Hill, New York, NY.
- V.E. Kane (1986). "Process Capability Indices." Journal of Quality Technology, 18, pp 41-52.
- Journal of Quality Technology
- Quality Progress
- B.H. Gunter (1989). "The Use and Abuse of C_{pk}, part 2 and 3. Quality Progress, March and May, 1989.

Pharmaceutical Literature

- J.A. Daley. “A Practical Guide to Sample Selection for C_{pk} Determinations”. Journal of Validation Technology, Volume 2, Number 1, pp 25-28.
- L. Torbeck. “Validation and Process Capability”, Pharmaceutical Technology, June 1998, pp 66-76.
- R. Nash. Pharmaceutical Process Validation, 2 nd edition, Marcel Dekker, Volume 57.

Assumptions

- The process is in a state of statistical control.
- The data are normally distributed.
- The data collected are collected from independent random samples.
- The data are truly representative of the process.

Process Capability Indices (PCI)

- First Generation PCI - Focus of this session
  - → C_p, C_{pu}, C_{pl}, k, C_{pk}
- Second Generation PCI:
  - → C_{pm}
- Third Generation PCI
  - → C_{pmk}
- Robust PCI:
  - → C_θ

Summary of Capability Indices

Index	Term	Equation	Usage
C_p	*Potential Capability*	$\frac{USL - LSL}{6\sigma}$	process potential for two-sided specification limits
CPU	*Upper Capability Index*	$\frac{USL - \mu}{3\sigma}$	process performance relative to upper specification limit
CPL	*Lower Capability Index*	$\frac{\mu - LSL}{3\sigma}$	process performance relative to lower specification limit
k	*Non-centering Correction*	$\frac{2\lvert m - \mu \rvert}{USL - LSL}$	deviation of process mean from midpoint (m) of specification limits
C_{pk}	*Demonstrated Excellence*	*Min { CPL, CPU}* $= C_p(1 - k)$	process performance for two-sided specification limits

Interpretation

Potential Capability - C_p (V. Kane)

Using a $\pm$ 3σ spread, for a process with normal distribution:

- C_p=1.0 $\Rightarrow$0.27% of parts are beyond specification limits.
- C_p=1.33 $\Rightarrow$0.007% of parts are beyond specification limits.

Interpretation (continued)

Demonstrated Excellence - C_{pk} (L. Torbeck)

For Assuming normal distribution:

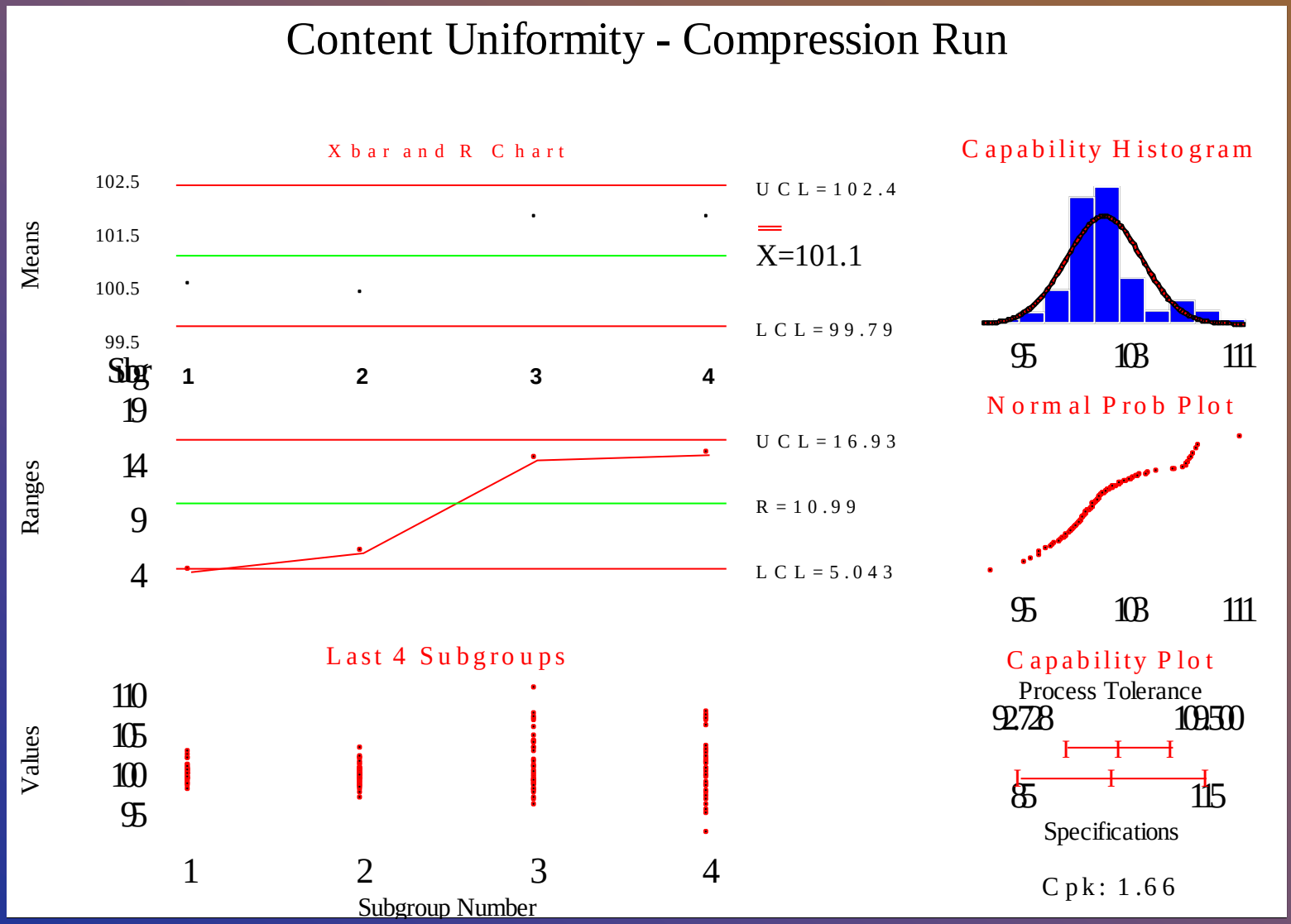
C_{pk}	Units Outside of Specifications (Billion)	(Percentage)
0.5	70,000,000	7
1.0	1,300,000	0.13
1.33	30,000	0.003
1.67	1000	0.0001
2.0	1	0.0000001

- C_{pk} for potency should be targeted at 1.33.
- To consistently achieve a C_{pk} of 1.33 during routine production, $C_{pk} > 1.33$ should be obtained in validation.

Example

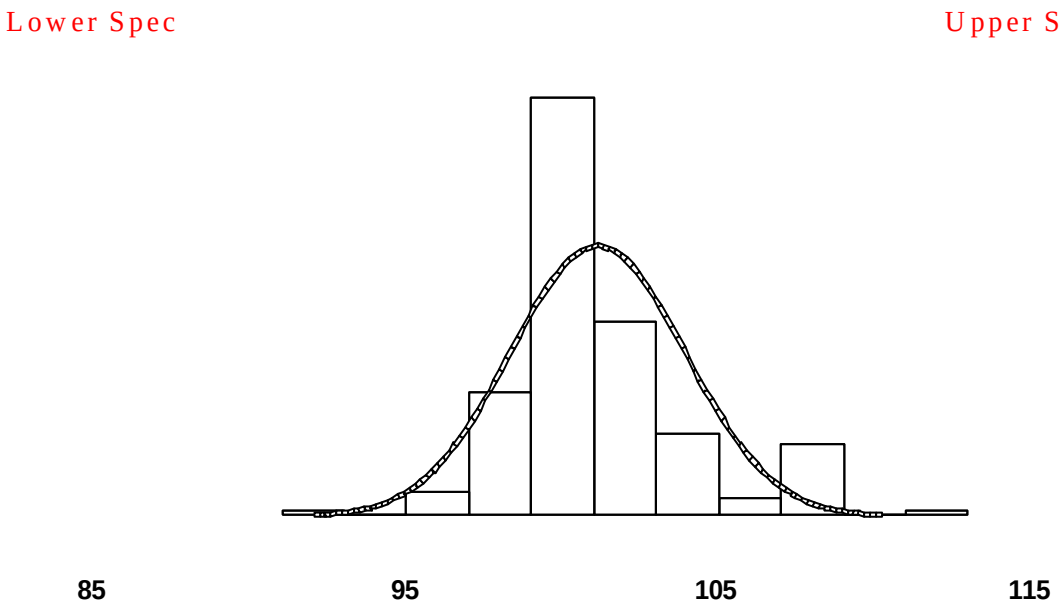
- OTC Product; B.S: 500.0 kg
- Drug Loading: 4.65%; Compression Stage
- Collect random sample of tablets representing the entire compression run
- Test 5 tablets/sample; 40 tablets/batch; 4 batches (overall n=160)
- Check Process Capability for 85-115 % CU limits

Example (continued)



Example (continued)

Content Uniformity - Compression Run



Active

Cp	1.79	Targ	100.000	Mean	101.114	%>USL Exp	0.00	PPM>USL Exp	0
CPU	1.66	USL	115.000	Mean+3s	109.500	Obs	0.00	Obs	0
CPL	1.92	LSL	85.000	Mean-3s	92.728	%<LSL Exp	0.00	PPM<LSL Exp	0
Cpk	1.66	k	0.074	s	2.795	Obs	0.00	Obs	0
Cpm	1.64	n	160.000						

SUMMARY

Knowledge of Pharmaceutics, Manufacturing Processes, etc.

Prerequisite

Apply Process Capability

High Degree of Assurance

Process Validation