INDUSTRY MATURITY IN THE ASSESSMENT AND USE OF PROCESS CAPABILITY

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ISPE’s Process Capability Team

Team Goals (per Team Charter):

• To develop a position on process capability as a performance and/or compliance metric
  • Reportable to FDA to support a risk-based inspection program as outlined in sections 705 to 706 of US Food and Drug Administration Safety and Innovation Act (FDASIA).
  • Acceptable to industry, addressing challenges for implementation.
• To communicate this position & gain support for implementation across pharmaceutical companies via:
  • A series of articles and/or white papers.
  • Potential baseline guide.
  • Sessions at ISPE and other meetings.
Goal: Improve Quality and Ensure Reliable Supply.

1. Performance and Compliance Applications.
   Self-audit of process performance helps to prioritize improvements
   - Embed a product robustness review process in the organization
     (at site level/ supply chain end-to-end/ for overall product portfolio)

2. Statistical Considerations. Process Capability is an easy and meaningful metric to capture and report but there are challenges:
   - Real life is drastically different from textbook examples
   - Difficult to predict failures using Cpk/Ppk
   - Many failures are not related to Cpk/Ppk

3. Maturity Model Development.
   Such a model can be used to guide through the implementation journey
   - Survey was conducted to assess where companies are today, where they want to be
   - Common opportunities for improvement have been identified

Process Capability Indices:
The Good, The Bad, and The Ugly

ASTM defines process capability as the natural or inherent behavior of a stable process that is in a state of statistical control, which is achieved when the process exhibits no detectable patterns or trends. (ASTM E2281). Statistical tools such as control charts are utilized in the determination of process capability, however capability indices are often commonly used.

The Good: Dimensionless index which can be used to compare across products, attributes, etc.

The Bad: Highly dependent on meaningful specifications and "well-behaved" data sets.

The Ugly: Process Capability is not the whole story. Complexity associated with practical application of these tools limits their effectiveness as a compliance requirement.
Three Levels of Product Robustness Monitoring
Rely on Associates with Product Understanding

1. Drug Product Manufacturing Site
   - Approximately Monthly inter batch data reviews
   - Voice of the Process at the Shop Floor
   - Site Focused…but also feeds data upward

2. End to End Product Reviews
   --Cross functional team across Drug Substance, Drug Product, Analytical, Stability and Quality
   --Deeper Statistical Analysis applied to Hot Spots

3. Quarterly Portfolio Review
   Sr. Management Scorecard looking at all sites and products

Product Robustness Involves Many Elements

Process Robustness – Continuous Improvement Over Time

Release Attributes Summary

Significant improvement in robustness performance observed over the past 5 years

Example from Peter G. Millili, BMS. Y-axis: proportion of CQAs with high/medium/low Cpk

Statistical Considerations

Gap between Reality and Textbook

A simple interpretation of process capability metrics is often not possible

Must understand details of the data, and how results will be used.

Otherwise, actions may be improper!

ISPE Discussion Paper focuses on: 1) use of process capability for risk based decisions for action and 2) identification and practical treatment of non-textbook situations
Using Ppk for Risk Based Decision for Action

- Set predefined “acceptable threshold” for Ppk to decide whether additional action is required.
- Data is normally distributed, no outliers.
- Use of a single attribute from within the process.
- Statistical analysis confirms the process is under control.
- Further analysis required. Maybe action required to remediate risk. Maybe accept risk based on cross-functional review.

Here risk is acceptable hence no further action required.

Here risk is negligible hence no further action required.

Statistical Considerations: Textbook Example

- Process Data Analysis:
  - Chart Data: 102.5, 100.0, 97.5, 95.0
  - StDev: 1.563
  - Cp: 1.07
  - Cpk: 0.86
  - PPM: 4881.59

- Overall Data Analysis:
  - Chart Data: 102.5, 100.0, 97.5, 95.0
  - StDev: 1.527
  - Pp: 1.09
  - Ppk: 0.88
  - Cpm*: 0.88
  - PPM: 4080.77
Statistical Considerations - Reality

- Small data sets
- Small number of unique values, including case with many values less than LOQ
- Non-independence resulting from non-random use of sources of variability
- Non-normality
- Specifications based on process performance, not customer driven (clinically relevant)

Process Shifts
Due to Non Random Use of Sources of Variability
Process Shifts Due to Non Random Use of Sources of Variability

Data with underlying non-normal distribution
Statistical Considerations - Other Topics

- Influence of Measurement Variability
- Manipulated Data
- Survey of Other Methods

Why a Maturity Model?

As shown in the example, continuous improvement success comes after a multi-year effort.

During the course of the program,
- Sponsor and workstream leaders may change
- Culture changes slowly
- Systems contribute to inertia
- New ways of working need to be implemented

→ A compass is needed to find true north
What is a Maturity Model?

A maturity model points out areas for improvement starting from a current (■) level, going to a target level (□).

Level 1 - Initial. Exclusively a business process, not in quality systems. Lacks rigor. Ad hoc, reactive, driven by users or events.

Level 2 – Repeatable. Proactive within some organizations/groups. Proactive but selectively applied.

Level 3 – Defined. Proceduralized. There are sets of defined and documented standard procedures established and subject to some degree of improvement over time.

Level 4 – Managed. Rolled out across sites, networks, organizational units and functions.

Level 5 – Optimizing. Proactive, integrated into the culture and operations management review. Comprehensive view of leading indicators and recurring root causes.

Maturity Matrix Consists of Nine Key Process Areas

In order to use process capability and concept tools optimally, it is important to achieve a certain level of proficiency and/or clarity in 9 specific areas:

- Policy – SOPs are established.
- Data Management – a system for collecting, managing and accessing data.
- Frequency – how often process capability indices are calculated.
- Basis for Specification – manner in which specifications are developed and linked to clinical studies.
- Calculation Consistency – use of process capability approach, calculations and metrics.
- Response – thresholds with action required, attention is shifted to products with low capability.
- Organization Skill Set and Execution – level of process capability knowledge across the organization.
- Risk-based Context – part of an overall risk management framework.
- Commercialization – sources of variability are well understood. Process capability at initial launch is high and site resources focus on continuous improvement.
ISPE Process Capability Maturity Model: Key Process Areas

For each key process area five levels of maturity are defined with detailed descriptions.

Maturity Model Survey - biggest opportunities according to participating companies are “Commercialization” and “Data Management”

Publication submitted to Pharm Eng
Main Areas for Improvement

Commercialization challenges
- Small data set before/after commercial launch
- Little experience with applying process capability at this stage in the lifecycle

Data Management challenges
- Complex IT system landscape
- Manual data management
- Cost of IT system upgrade

survey responses:
“Majority of data is CQAs, some CPP data available. Overall, program is in early stages of maturity, starting to integrate risk based methods, using scale up models for site transfers and commercialization.” (5 yrs)*

survey responses:
“Some databases are structured; some are manually entered/updated. Network roll-up not available (100% manual). Product specific, may or may not be automated.” (5 yrs)*

“On demand pull of capability data” (15 yrs)*

(*Number of years using Process Capability Measurements)

KEY TAKE AWAYS

• Process Capability is only a small part of the story
• A sustainable business process is needed to be successful
• Textbooks are good to get started…
• It takes years to reach maturity
• … and some already got there!