Process Capability and relationship to Quality management

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Barbara Allen, Ph.D.
Global Quality Systems
Eli Lilly and Company
Core Objective

‘Safely & **reliably** manufacture quality medicines for our **patients**’
Implementation of a Quality System should result in achievement of three main objectives:

• Achieve Product realisation:
  • Delivery of product with the quality attributes to meet the needs of patients.....

• Establish and maintain a state of control:
  • Develop and use effective monitoring & control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes.

• Facilitate Continual Improvement
  • Identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and quality system enhancements, thereby increasing the ability to fulfil quality needs consistently.

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Manufacturing – converting inputs to outputs

**Inputs**
- People
- Equipment
- Materials
- Methods
- Facility

**Processes**
- Step 1
- Step 2
- Step 3
- Step 4

**Outputs**
- Drug Substance
- Drug Product

**Built on scientific and technical excellence**
**Supported by effective quality system**
**Driven by Continuous Improvement Mindset**

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Scientific & Technical Excellence

Facilities, Equipment
• Capital investment: Recapitalization and maintenance repair
• Process monitoring equipment
• IT infrastructure: Data Management

Process & Analytical Methods
• Validations and revalidations
• Cpk metric: must have active project if < 1.33 (goal > 2.0)

Sterility Assurance
• Detailed review and EM program
• Dedicated sterility assurance team

Expertise and Knowledge (key roles)
• Microbiologist, Batch Release, Analytical Chemists, Engineers, Physician, Statistician

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Product and Process Knowledge & Understanding

- Formal, consistent approaches.
- Clearly and consistently documented.
- Accessible / retrievable.
- Feedback loop to future design.
- Capable, curious people.
Continuous Improvement - Variability reduction

- The **Control Strategy** is a planned set of controls, derived from current product and process understanding, that assures process performance and product quality.

- Cpk metric: must have active project if < 1.33 (goal > 2.0)

- Integrated action plans

<table>
<thead>
<tr>
<th>Inputs</th>
<th>Process</th>
<th>Outputs</th>
</tr>
</thead>
<tbody>
<tr>
<td>People</td>
<td>In Process Control</td>
<td>API or Drug Product</td>
</tr>
<tr>
<td>Equipment</td>
<td>Parameter X</td>
<td>CQA’s</td>
</tr>
<tr>
<td>Materials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facility</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Monitoring and Continuous Improvement

<table>
<thead>
<tr>
<th>( C_{pk} )</th>
<th>Expected # OOS Batches per 100</th>
<th>Expected # OOS Batches per 1000</th>
<th>Expected # OOS Batches per 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>0.00</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2.0</td>
<td>0.00</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>1.3</td>
<td>0.00</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>1.0</td>
<td>0.13</td>
<td>1.3</td>
<td>13.5</td>
</tr>
</tbody>
</table>

**2014 Data**

- \( 3.0 \leq C_{pk} \) 310
- \( 2.0 < C_{pk} \leq 3.0 \) 93
- \( 1.3 < C_{pk} \leq 2.0 \) 76
- \( 1 < C_{pk} \leq 1.3 \) 29
- \( C_{pk} \leq 1 \) 11
- Qualitatively Capable 302
- Qualitatively Not Capable 3

Well understood and controlled processes deliver consistent quality with statistical capability to meet quality attributes.
Swiss Cheese Model

• Used to demonstrate and analyze many types of adverse outcomes
  • Industrial Accidents
  • Plane crashes
  • Emergency services organizations
  • Health Care field

• Defensive layers are put into place to prevent errors from doing harm

‘Swiss cheese model’ Orlandella & Reason 1990
Pharmaceutical Quality System

Combination of controls reduces the overall risk of error occurring and/or not being detected.
Quality System Role Example

**Materials**

**Input Material Requirement**
- X kg of y specification

**Quality Management process**
- Specification Management
- Supplier Quality Management
- Materials management: receipt, storage & dispensing

**Output**
- Correct quantity of the right material of the appropriate quality … everytime
Lilly Quality System

Integrated Standards

- Right people
- Right role
- Right span of control
- Clear accountability

Business Processes

- Effective
- Efficient
- Simple
- Owned by the business with Quality input

Governance/Management Oversight

- Management involvement
- Escalation
- Decision Making
- Auditing

Organization

- Clear requirements to meet both compliance and patient needs
- Owned by Quality with business input

People Capabilities

Owned by the business with Quality input

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### Quality System Structure

**Consistent Architecture.**

<table>
<thead>
<tr>
<th>Standards</th>
<th>Procedure/Practices</th>
<th>Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fundamental Global requirements, e.g., Lilly requirements, regulatory, legal, customer expectations</td>
<td>• Step by step process or instructions that must be followed to meet quality requirements</td>
<td>• Useful reference information or best practices</td>
</tr>
</tbody>
</table>

#### Logical Indexing to facilitate ease of use

- 100 Quality
- 200 Facilities & Equipment
- 300 Materials
- 400 Production
- 500 packaging & labelling
- 600 laboratories

#### External Monitoring & internal feedback loops capture knowledge & facilitate improvement

- Regulatory
- Business Environment
- Internal Operations
Management Reviews: Product and Quality System Review

Review Performance of the product and process and the effectiveness of the quality systems

Cross-functional leadership involved at every level of the enterprise to assess
Product & Process Performance Reviews

- **Global Product Assessment (GPA)**
  - Global view across all supply chains
  - State of validation, process control and capability (CpK), stability
  - Complaints, rejects, significant events, changes
  - Prepared by Global Molecule Stewards (API, drug product, packaging, device)
  - Reviewed and discussed at meeting of Senior Leaders from Manufacturing, Operations, Technical Services, Quality Unit, and Regulatory Affairs

- **Annual Product Review (APR)**
  - Site level, with input related to upstream and downstream
  - Detailed review of state of validation, process control and capability, effectiveness of control strategy, stability, complaints, rejects, significant events, changes, supply chain, analytical data, deviation trends
  - Reviewed and discussed at Site Quality Lead Team and approved by Site Quality Leader, Technical Services Site Leader and Plant Director
Relationship

Focusing on Product and Process Capability:

- Reduces errors, losses, and deviations
- Drive deep technical understanding
- Drives expectations for new products

Implementing an effective quality system

- supports achieving control and capability

Culture moves from minimal compliance and meeting specifications to understanding, controlling and reducing variability. This drives continuous improvement.

*True Quality Culture*
Results

Comparison of 2013 Performance to 2007 Baseline

Activity Indicators

- 50% increase in Portfolio Complexity
- 30% increase in Production Volume

Performance Improvement

- 50% reduction in Injury Rate
- 40% reduction in Deviation Rate
- 90% reduction in Backlog
- Sustained Customer Service

Productivity Improvement

- 10% reduction in Inventory
- Neutral Expense
- 30% reduction in Headcount
- 20% reduction in Capital
- 10% reduction in Losses
- 10% reduction in COPS

"Take what you find here and make it better and better."

- Colonel Eli Lilly

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Achieving Product Quality Reliably

**Scientific and Technical Excellence**
- Well developed process and product control strategies
- In control, capable
- Meets patient needs

**Management Systems**
- Defined governance
- Efficient and effective business processes
- Disciplined execution

**Continuous Improvement Mindset**
- Broad ownership and accountability
- Visibility
- Sense of urgency
- Curiosity

Elements of Operational Excellence