Product Quality Management

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Presentation Outline:

• Product Quality Management – Regulatory landscape and need for integrated product quality management

• Role of the Product Quality Steward – Product quality oversight by linking systems, data, and people

• Product Lifecycle Management - Commercial Product Lifecycle approach

• Conclusions
Regulatory Landscape
Growing Expectations for Modern Manufacturing

- Quality is built in
- Lifecycle approach from Development to Product Discontinuation
- Understand complex supply chain CMO networks
- Robust process measurement & analytical tools
- Real-time assessment of product & process capability
- Maintaining “state of control” throughout commercial lifecycle

Product Quality Management: 
Fundamental Elements

Product Complaints
- Identifying early warning signals of product quality issues in the field

Product Assessment & Trending
- Proactive assessment of product quality attributes across the manufacturing process

Product Quality Stewards
- Single point of Contact for Quality to key stakeholders
- Routine assessment of product control plans to address trends
- 8 Qtr Plan provides foresight and proactive approach

QC testing network support
- Harmonized approach to test method execution & support
- Raw Materials & Stability Program Management
- Critical Reagent & Reference Material Program Management

Analytical methods management
- Scientific rigor engrained in analytical method performance
- Product control systems based on science
- Seamless product transfers & assessment of consistency
Product Quality Management

Benefits

• Proactively minimize risks to patients, operations, and supply chain through early detection and end-to-end product oversight

• Meets Regulatory expectations of science- and risk-based product knowledge management
  – Risk assessment of product quality attributes linked to control strategy
  – Proactive monitoring & trending of product data
  – Product specific control plans across the global Mfg network
  – A focus on innovation, lifecycle management and continual improvement

• Maintain reputation as a trusted source of high quality product among patients, regulators, and industry

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Supply Chain Teams: 
**Product Quality Steward Role**

- **Ad Hoc Quality Sub Team Members**
  - Change Control
  - Methods Mgmt and Technology
  - Inspection Mgmt
  - Compliance
  - External QC
  - Validation

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**Product Quality Steward Role**

**Leadership & Accountability**

- Own monthly product-specific Health Assessment Report & escalation of risks to senior management
- Own Product-specific Risk Assessments & accountable to drive completion of risk reduction activities
- Lead Product Quality Supply Team
- Quality SPOC on Product Supply Chain Team; responsible for ensuring that Quality requirements are met
- SPOC for Quality for Tech Transfer Teams
- Review APQR’s and AR’s for accuracy and completeness as well as for lifecycle management commitments
Product Quality Steward Role

Key Accountabilities

- **Knowledge & Lifecycle Management**
  - Manage product commercialization with IMP Quality
  - Conduit of Information within Quality for Product Knowledge
  - Own and manage E2E Control Plans and Quality Lifecycle Management (continual improvement) for product

- **Decision Making, Investigations & Issues**
  - Manage team of Quality SMEs for cross-site investigations/issues
  - Influence and drive decisions at Product Quality Supply Chain Teams
  - Escalate product-specific product quality and compliance issues for review at relevant Quality Review Boards and/or Senior Management
  - Decision maker for lifecycle management and product control plans

Quality Risk Management

Understanding E2E Supply Chain

Scope: End-to-end supply chain for commercial products

Data collection checklist: complaints, investigations, stability, QC, lot disposition, audits, supplier quality, APQR, validation, facilities, warehousing, distribution, PQST input, etc.

Gather data & reconfirm risk is still relevant

Score each risk for severity, occurrence & detectability (S, O and D):
  - Up to DP: Quality/Regulatory scoring matrix
  - For distribution and on: Patient Safety scoring matrix

Cross-product review to identify additional risks

“Not acceptable/intolerable” risks need risk reduction actions identified

When risk reduction activities are completed, a rationale for acceptance of residual risk is documented

CAPAs initiated and tracked within Quality System
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ICH Q10 Elements

Product Quality Assessment

• ICH Q10 Pharmaceutical Quality System, Process Performance and Product Quality Monitoring System 3.2.1:
  — Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained.
  — Use quality risk management to establish the control strategy.
  — Provide the tools (e.g., data management and statistical tools) for measurement and analysis of parameters and attributes identified in the control strategy
  — Identify sources of variation affecting process performance and product quality for potential continual improvement activities
  — Knowledge management
Post-Approval Lifecycle Management Plan (PALM)......Leveraging QbD

- Health Authority expectation that commercial products are monitored and continuously improved post-approval
- License claims are expected to be updated as sponsor learns more about the product and process

Management of Analytical Control System Changes

Leveraging PALM Approach for Control System Re-Assessment

Assay Specific Triggers
- Recommendation in response to out-of-trend results
- Recommendation as a result of Annual Product Review (APR/PQR) process
- Implementation of “better” assay for other commercial products
- Assess suitability of assay
- Determine if options exist to improve current assay performance
- Determine suitability of new assays

Control System Triggers
- Recommendation in response to out-of-trend results
- Recommendation as a result of Annual Product Review (APR/PQR) process
- A significant process change or new device being implemented
- New knowledge from additional clinical/non-clinical studies for this product
- Mandated every 5 years if no other triggers require assessment
**Goal of Product Monitoring:** Ensuring a Continued State of Control of Process Performance and Product Quality Delivered!

<table>
<thead>
<tr>
<th>STABLE</th>
<th>NOT STABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAPABLE</strong></td>
<td><strong>NOT CAPABLE</strong></td>
</tr>
<tr>
<td>The Place to be!!</td>
<td>You can’t tell what the quality of the next unit will be.</td>
</tr>
<tr>
<td>Target not around the center of specification ranges &amp; variation is too large</td>
<td>Not acceptable!</td>
</tr>
</tbody>
</table>

**Process Capable Chart:**

**Capable vs. Un-capable Process**

- **Process Capability:** ...is a statistical estimate of the outcome of a characteristic from a process that has been demonstrated to be in a state of statistical control.
- **Process Capability Index:** a statistical measure of process capability
- **CpK** = Ratio of Spec Range to Total Data Variation
- **CpM** = Measurement of how “centered” around the “target” the process can deliver

<table>
<thead>
<tr>
<th>CpK</th>
<th>% Defective Product</th>
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<tbody>
<tr>
<td>0.8</td>
<td>0.819</td>
</tr>
<tr>
<td>1.0</td>
<td>0.135</td>
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<tr>
<td>1.33</td>
<td>0.0033</td>
</tr>
<tr>
<td>1.8</td>
<td>0.00033</td>
</tr>
</tbody>
</table>

A capable process that delivers on target for this CQA:
- CpK>1
- Process delivers right on target.

Not a capable process, even though it centers around the target:
- CpK<1

Correlation of CpK value with % Defective Product
Example 1: A Un-Capable Process for Potency Assay (Cpk <1.0, and not centered)

Analytical method and specification not optimized
Excessive OOSs and OOTs observed

Example 1 continued:
Reconfigured Capable Process

- Both analytical method and specification have been optimized in order to achieve a capable (CpK=1.29) and centered process for the potency assay.
QC Method Monitoring Program

- Integral to the analytical method life cycle management
- Focus is on purity and potency methods
- Ensures method performance across complex manufacturing network & testing sites is consistent
  - Analysis of reference material, assay & product controls data
- Provides analytical trending support to process/product trending
- A key component of the Annual Product Review (APR)
  - Regulatory requirement by Health Canada
- Stability investigation support
- Serves as an inspection tool for analytical methods

Example: QC Method Monitoring Results

**Top:** Reference Material data trend chart for all valid assays across 6 global testing sites

**Bottom:** Site Mean trend chart for the 6 sites showing that the method performance is consistent throughout all sites
PALM & Annual Product Review

Product Quality Management:
- The end-to-end quality review and control of Roche’s products throughout the supply chain
- Drives continual improvement throughout the product and process lifecycle to ensure a reliable supply of quality products to our patients