Pharmaceutical Quality System (ICH Q10) Conference
October 4-6, 2011 | Crystal Gateway Marriott | Arlington, Virginia
November 14-16, 2011 | Sheraton | Brussels, Belgium

Product Quality Management

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Presentation Outline:

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- 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

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- 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

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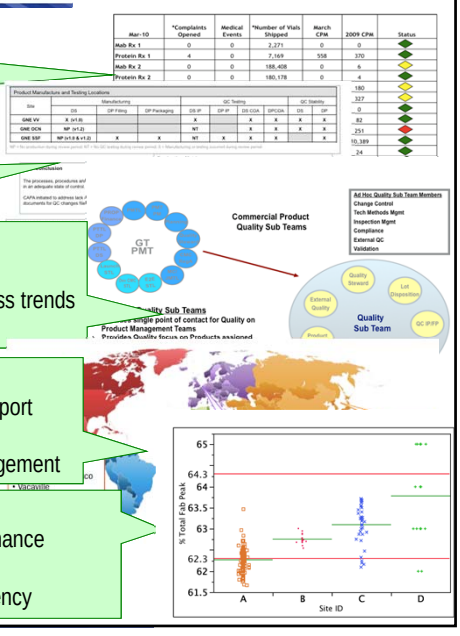
Product Complaints
- Identifying early warning signals of product quality issues in the field

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

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- 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

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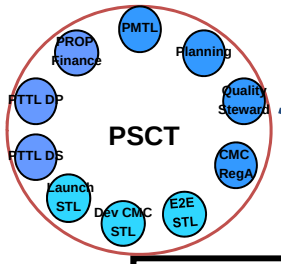

Ad Hoc Quality Sub Team Members

- Change Control
- Methods Mgmt and Technology
- Inspection Mgmt
- Compliance
- External QC
- Validation

Product Quality Steward Role
Leadership & Accountability

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- 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

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- *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

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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):

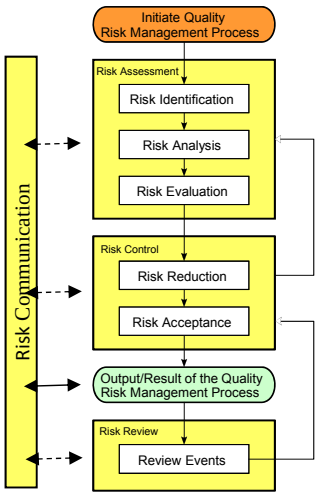
- Up to DP: Quality/Regulatory scoring matrix
- For distribution and on: Patient Safety scoring matrix

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

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- 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*

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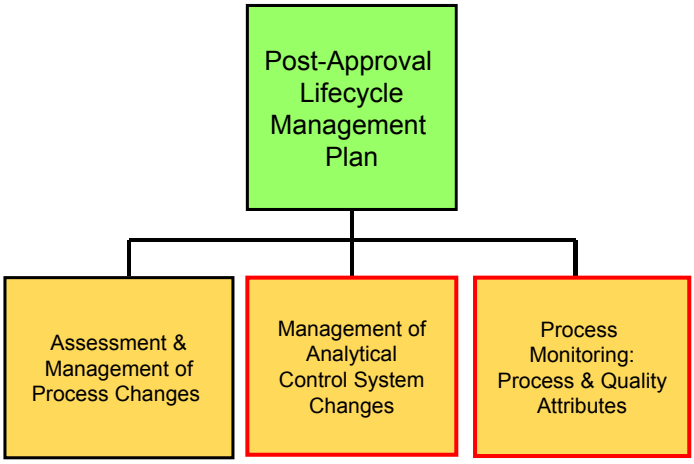

- Health Authority expectation that commercial products ***are monitored and continuously improved post-approval***
- ***License claims are expected to be updated*** as sponsor learns more about the product and process

Management of Analytical Control System Changes

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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

Product & Process Monitoring

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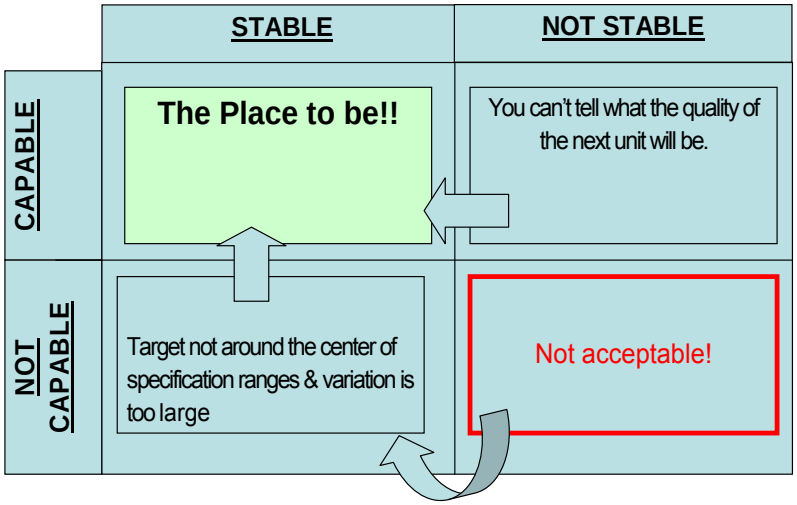
Goal of Product Monitoring: Ensuring a Continued State of Control of Process Performance and Product Quality Delivered!



Process Capable Chart: Capable vs. Un-capable Process

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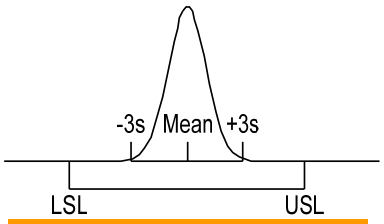
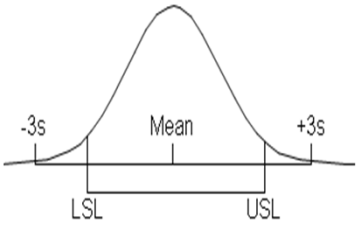
- **Process Capability: …is a statistical estimate of the outcome of a characteristic from a process that has been demonstrated to be in a state of statistical control.**
- **Process Capability Index: a statistical measure of process capability**
- **CpK = Ratio of Spec Range to Total Data Variation**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



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



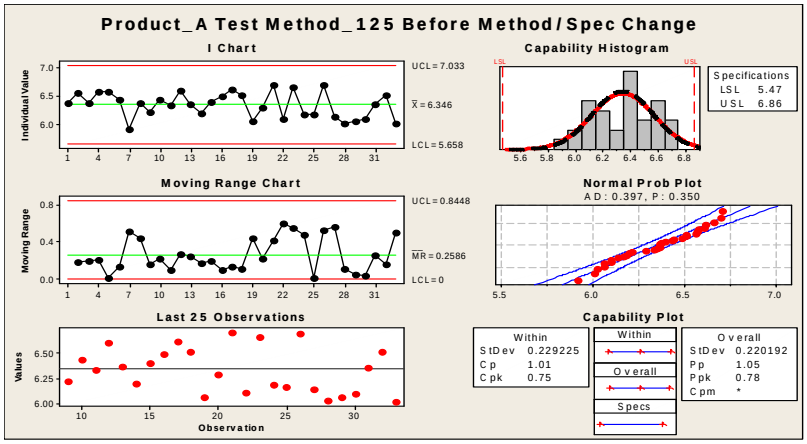
- Not a capable process, even though it centers around the target
- CpK<1

Correlation of CpK value with % Defective Product →

Cpk	% Defective product
0.8	0.819
1.0	0.135
1.33	0.0033
1.8	0.00033

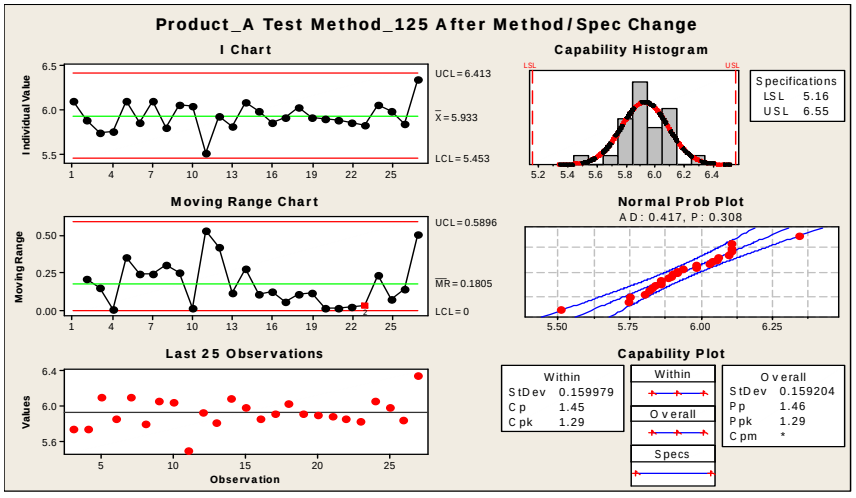
Example 1: A Un-Capable Process for Potency Assay (Cpk <1.0, and not centered)

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

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- 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

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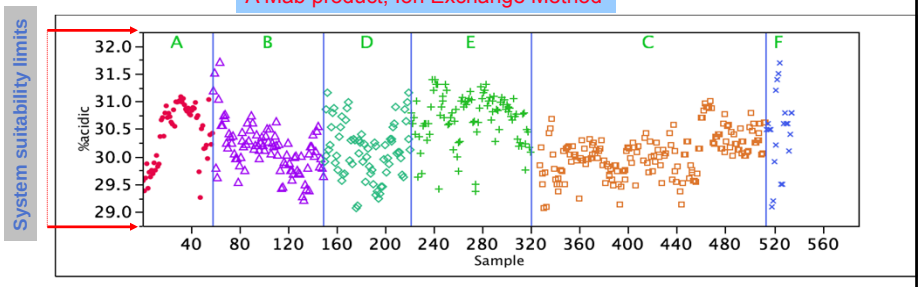
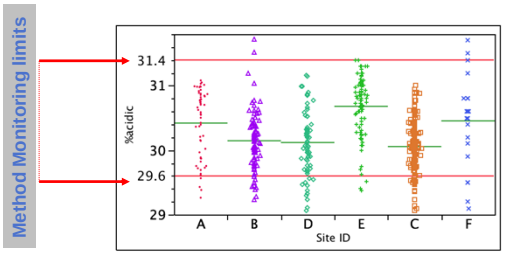
A Mab product, Ion Exchange Method



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

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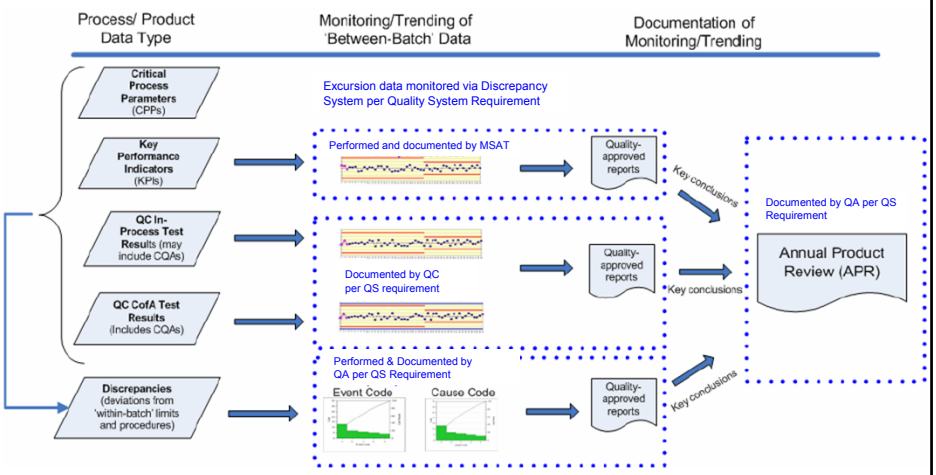
Figure 1. Process Monitoring Data Flow for a Commercial Product



- Product Quality Monitoring Information would be documented with APR

Conclusion

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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




Raw Materials **Drug Substance** **Drug Product** **Testing** **Distribution**

End to End