Product Monitoring & Post-Approval Lifecycle Management of Biotech Products

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Presentation Outline

- Background – Need for integrated product quality management
- Process Monitoring and Data Trending – Roche/Genentech Approach
- Post-Approval Lifecycle Management
- Commercial Product Quality Steward role – Product quality oversight by linking system, data, and people

Need for Integrated Product Quality Management

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
- Verify continued operation within a state of control
- Identify sources of variation affecting process performance and product quality for potential continual improvement activities.
- Include feedback on product quality from both internal and external sources

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Product Quality Management at Roche & Genentech

- An End to End view of product quality throughout the product and process lifecycle
- Strong scientific rigor and technical expertise used to evaluate product performance and consistency across sites
- A focus on innovation and continual improvement
- Ensures the safety, efficacy and purity of products produced and supplied to our patients

Product Quality Management: Fundamental Elements

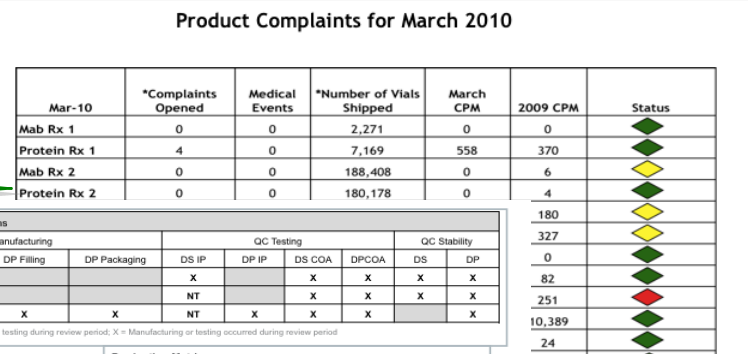
Product Complaints
- Early warning signals of product quality issues in the field

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 health assessment of product to address trends
- Planning provides foresight and proactive approach

QC testing network support
- Harmonized approach to test method execution & support
- Scalability & flexibility to balance test workload across network

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

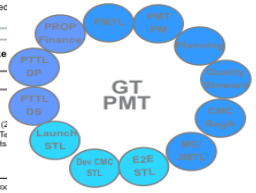

Product Complaints for March 2010

Mar-10	*Complaints Opened	Medical Events	*Number of Vials Shipped	March CPM	2009 CPM	Status
Mab Rx 1	0	0	2,271	0	0	
Protein Rx 1	4	0	7,169	558	370	
Mab Rx 2	0	0	188,408	0	6	
Protein Rx 2	0	0	180,178	0	4	
					180	
					327	
					0	
					82	
					251	
					10,389	
					24	

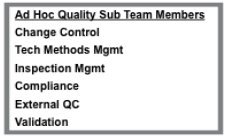
Product Manufacture and Testing Locations

Site	Manufacturing			QC Testing				QC Stability	
	DS	DP Filling	DP Packaging	DS IP	DP IP	DS COA	DPCOA	DS	DP
GNE VV	X (v1.0)			X		X	X	X	X
GNE OCN	NP (v1.2)			NT		X	X	X	X
GNE SSF	NP (v1.0 & v1.2)	X	X	NT	X	X	X		X

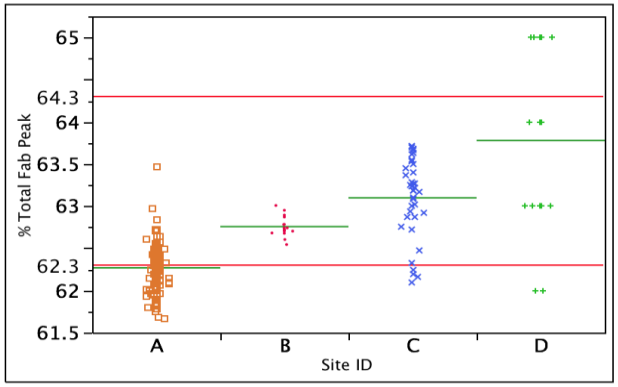
NP = No production during review period; NT = No QC testing during review period; X = Manufacturing or testing occurred during review period



Commercial Product Quality Sub Teams


Ad Hoc Quality Sub Team Members
Change Control
Tech Methods Mgmt
Inspection Mgmt
Compliance
External QC
Validation

fits Of Quality Sub Teams
Provides single point of contact for Quality on



Benefits of Process Monitoring and Trending

- Meets regulatory expectations
- Proactively identifies and reduces variations in the test methods and manufacturing processes
- Provides science and risk - based approach for CAPA activities
- Ensures product consistency from site to site
- Ensures reliability of product supply and guarantees an efficient Supply Chain

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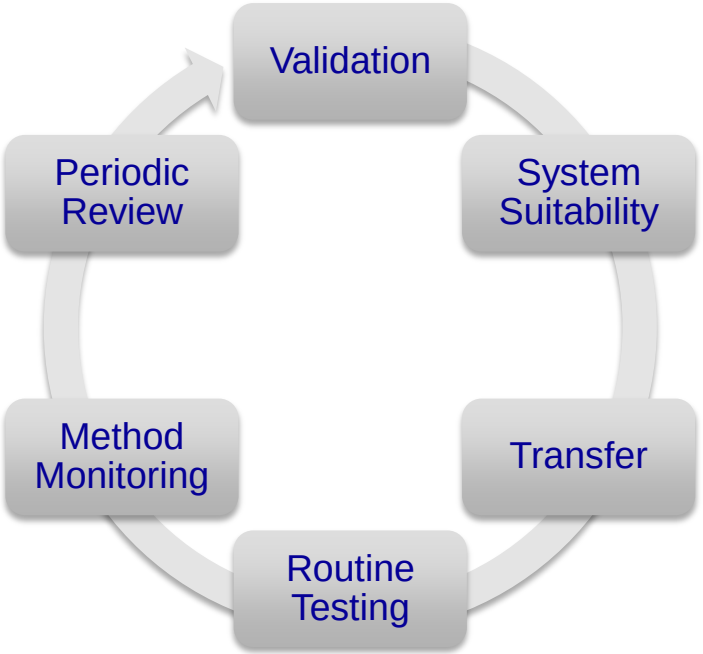
- Background – Need for integrated product quality management
- **Process Monitoring and Data Trending – Roche/Genentech Approach**
- Post-Approval Lifecycle Management
- Commercial Product Quality Steward role – Product quality oversight by linking system, data, and people

Process Monitoring and Data Trending: Roche/Genentech Approach

- Key elements in the continuous monitoring of commercial products
  - Process and analytical life cycle validation
  - Align inter-related inputs – process, methods, product quality attributes
  - Definition of statistical state of control (control charts etc.)
- Examples of Data Trending
  - Product Data Monitoring
  - Analytical Method Monitoring
  - Proper assessment of process capability → consistent product quality

Life Cycle Approach to Analytical Method Management

- Method development & qualification throughout clinical stages
- Commercial method validation pre-licensure
- Commercial control system established at first launch
- Analytical method transfer support commercial production globally
- On-going cross-site method monitoring ensures state of control throughout method and product life cycle



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Product Quality Data Evaluation

- Dependent on both Analytical and Process Monitoring
- Proper assessment of manufacturing process capabilities relies on QC method performance assessment
- Product quality assessment, as measured by QC test methods, relies on assurance that analytical methods are consistent and are in a state of control

Fundamental Steps in Monitoring

- Establish statistical monitoring systems:
  - Appropriate monitoring attributes
  - Appropriate statistical method (Control charts, Histogram, Pareto, etc.)
  - Analyze data and establish trend/control limits from historical data
  - Establish Rules for monitoring and trending
  - Timely evaluate of the impact of product and process changes
- Establish business process to assess out-of-trend (OOT) results and to assure that the process is in a state of statistical control
- Formal investigations and communication to stakeholders required for OOT and Out-of-specification (OOS) event to determine root cause (Discrepancy and CAPA)

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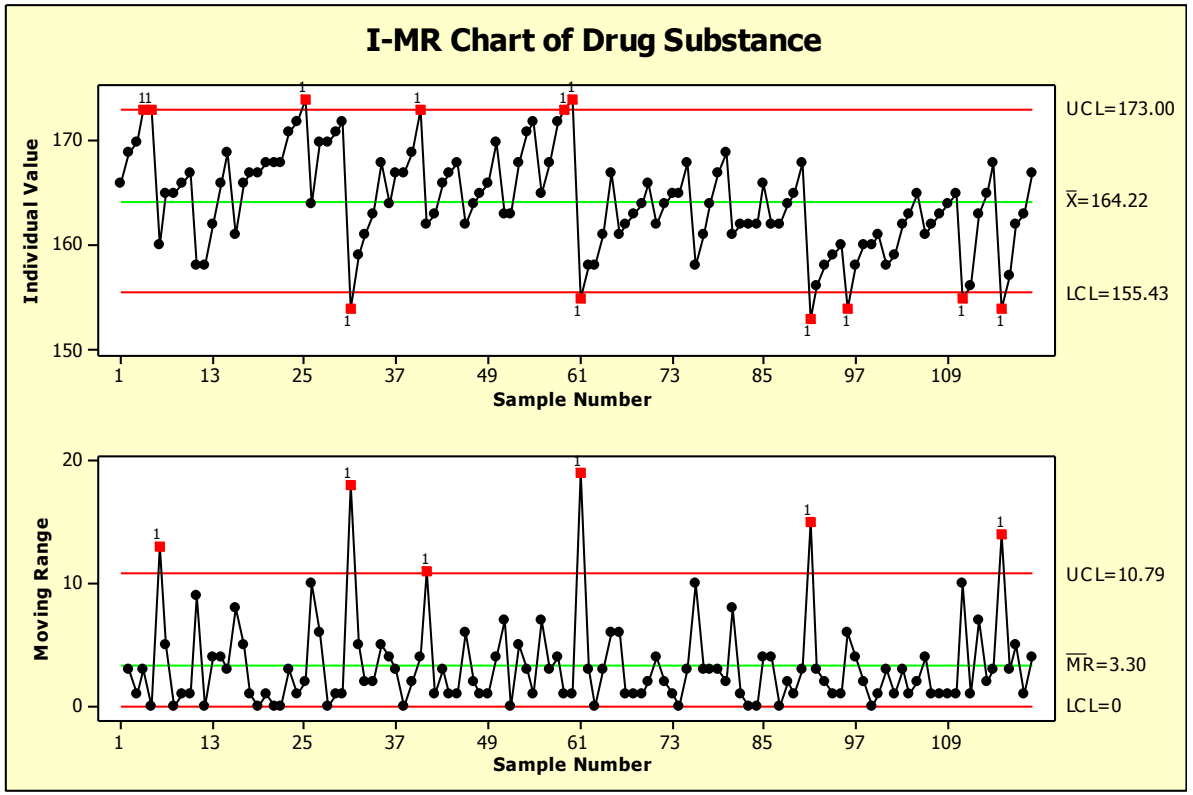
Criteria for Monitoring

- Critical Quality Attributes (CQAs)
- Key QC test methods
- Critical process parameters (CPP)
- Key process performance indicators (KPI)
- Periodic vs. real time monitoring
- Site versus global monitoring

Data Trending: Moving Range Chart

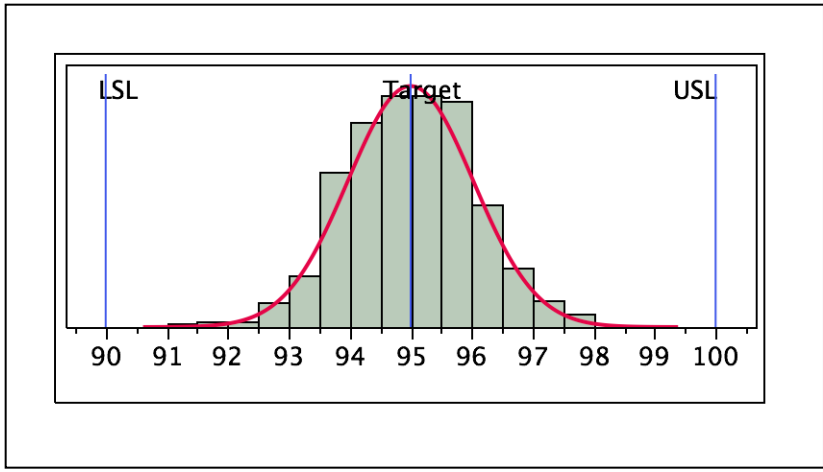
- Moving range chart – used to track process variation and detect the presence of “special causes”.
- The moving range - equal to difference between successive pairs of numbers in a data set.

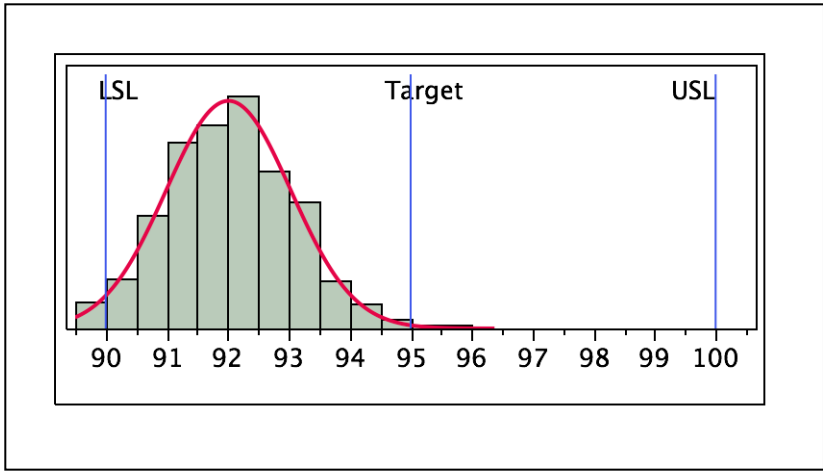


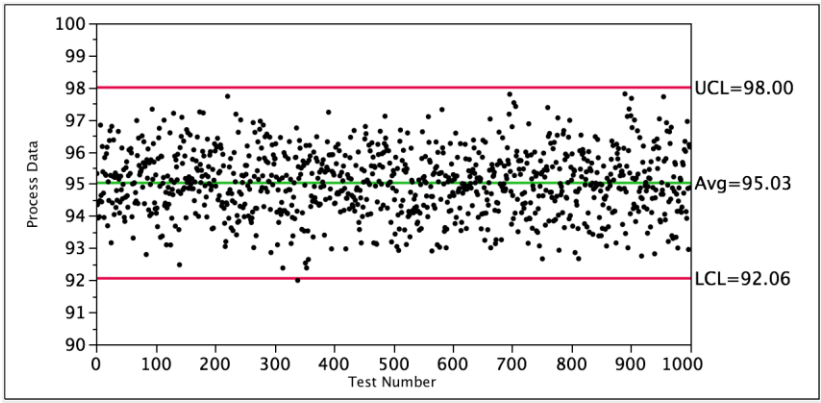
Examples of Process Trend Chart: Process Data

A set of random product data is presented against the acceptance criteria over a period of time:

- Top Histogram: A capable process **(Centered & well- within process limits)**
- Middle histogram: Similar process (with lower mean) against the same limits **(Not centered or contained by limits)**
- Bottom histogram: Actual run chart data for the top process

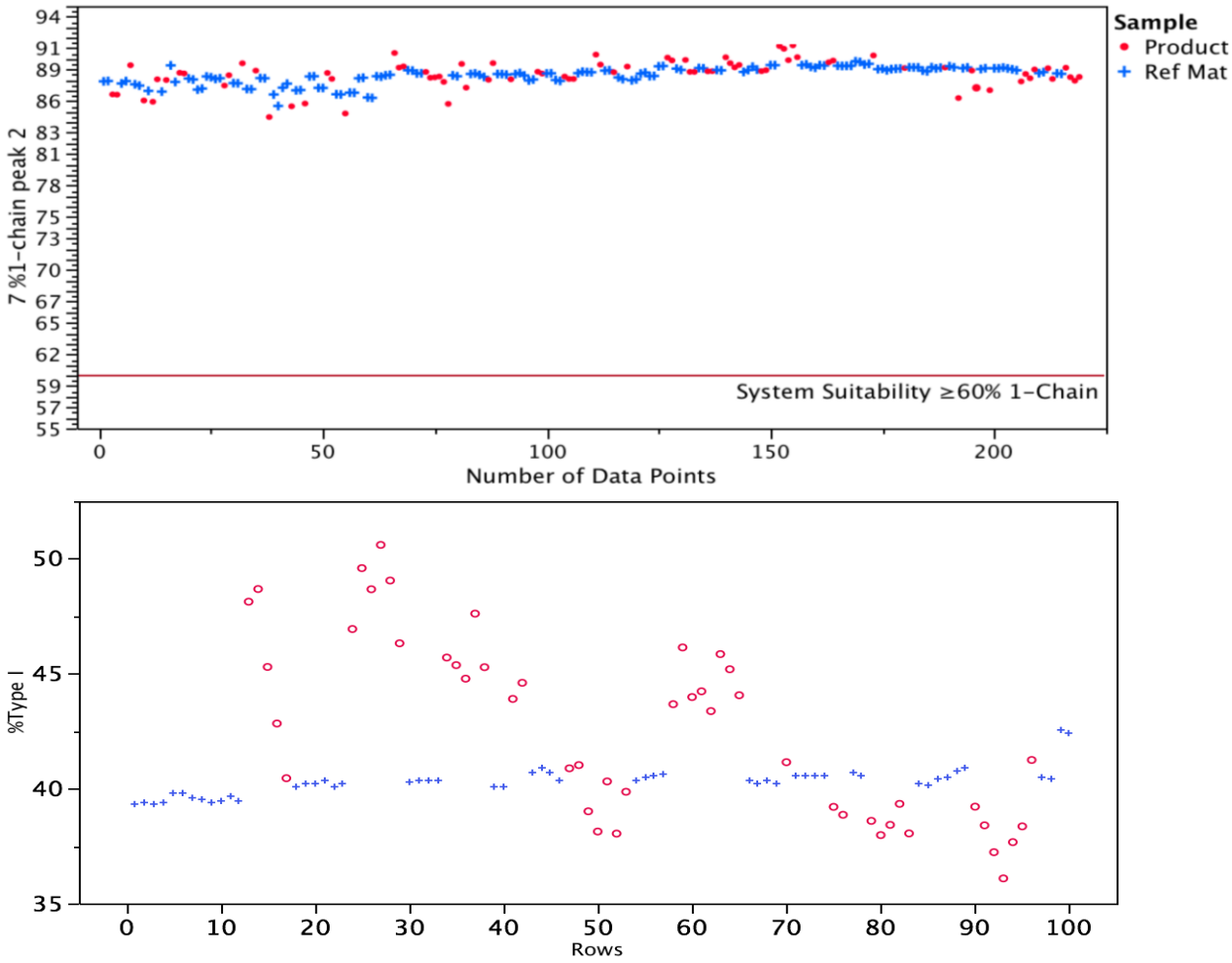






Example of Integrating Process & Analytical Method Monitoring

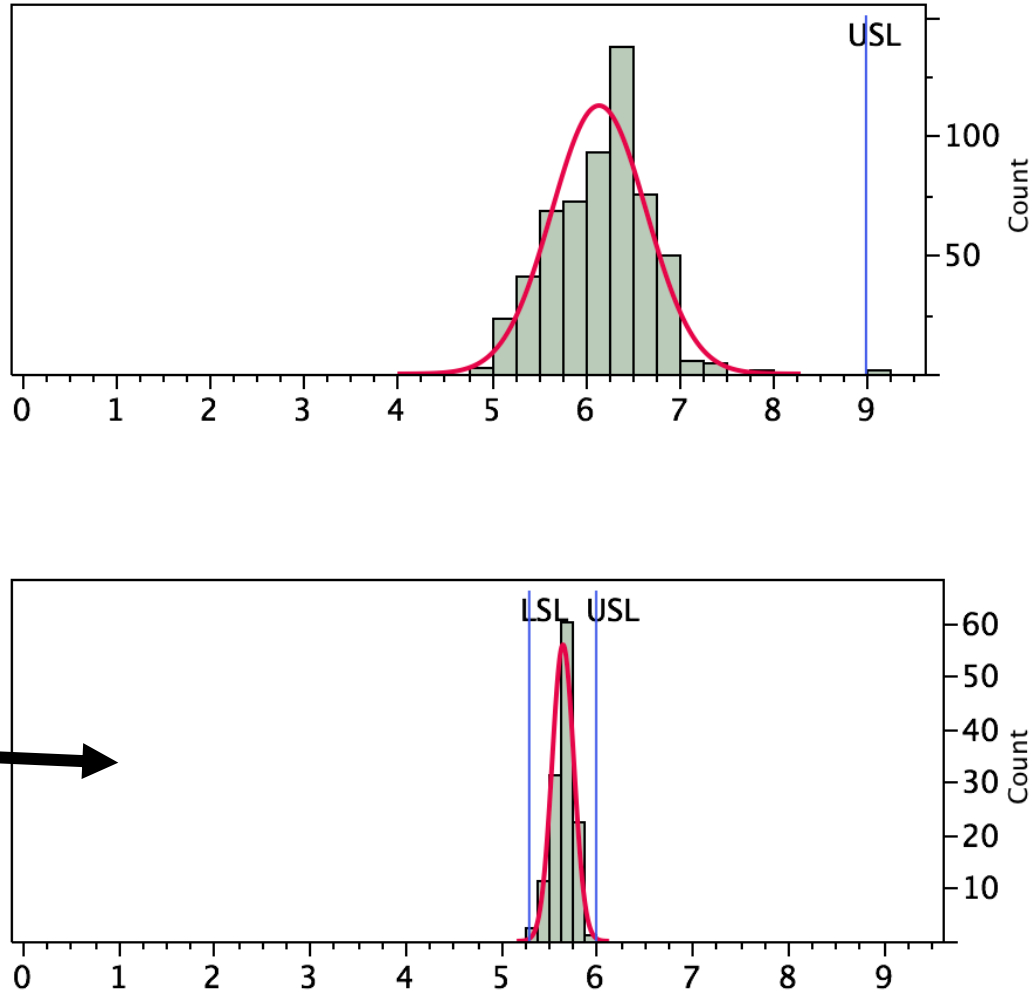
- Top: Product vs. reference material data trend chart demonstrating a robust process
- Bottom: Product vs. reference material data trend chart for a variable process



Example of Process vs. Analytical Method Capability Trend Chart

- Top graph shows a capable process
- Lower graph shows a capable QC method that supports the product specification

A Well behaved Process & Method



QC Method Monitoring Program

- Integral to the analytical method LCM
- Ensures that the method performance across complex manufacturing network & testing sites is consistent
- Provide analytical trending support to process/product trending

Additionally:

- 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

Current Scope of Method Monitoring Program

- Commercial biologics
- All QC testing sites including partners and CMOs
- Incorporates new sites after method transfer
- Currently focus on purity and potency methods
- Monitor key quantitative attributes
- Analysis of data from reference material, assay controls, and product controls

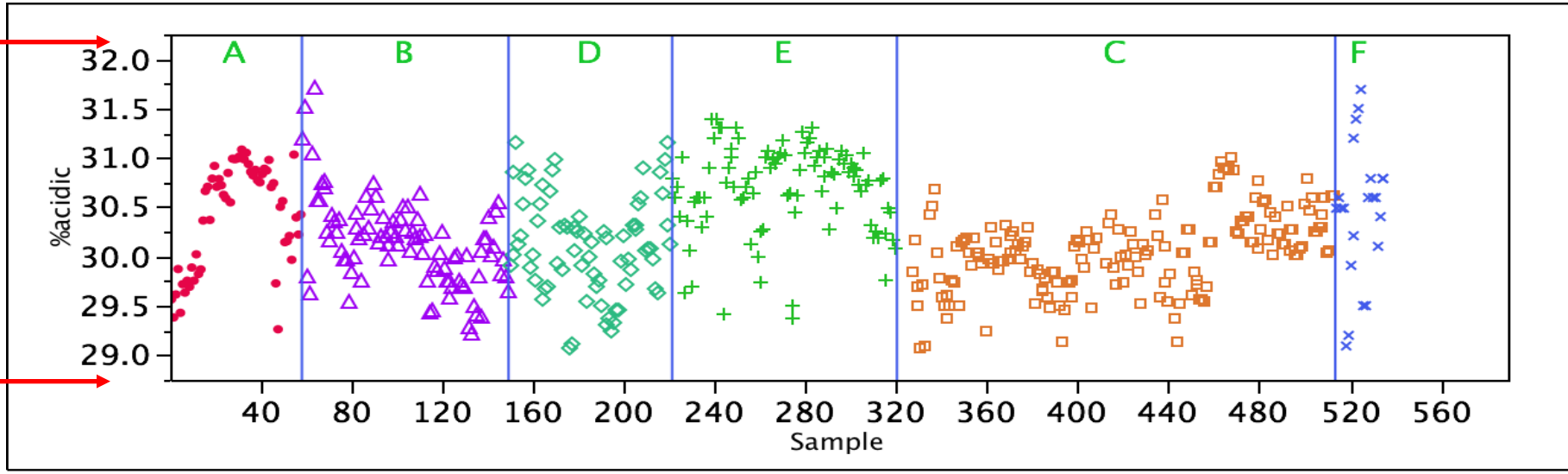
Monitoring Criteria and Data

- Based on available historical data
- Use statistical analysis
- Cross site harmonization of data submission format
- Centralized group to perform trending analysis and report results

Examples of QC Method Monitoring Results

A MAb product, Ion Exchange Method

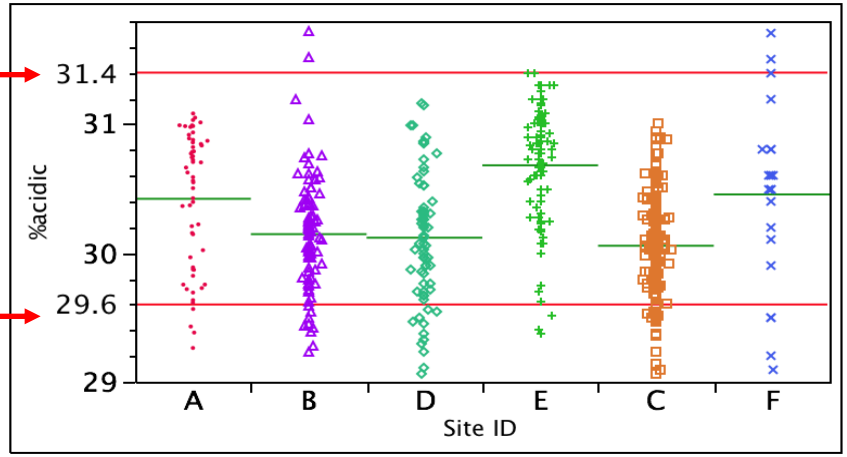
System suitability limits



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

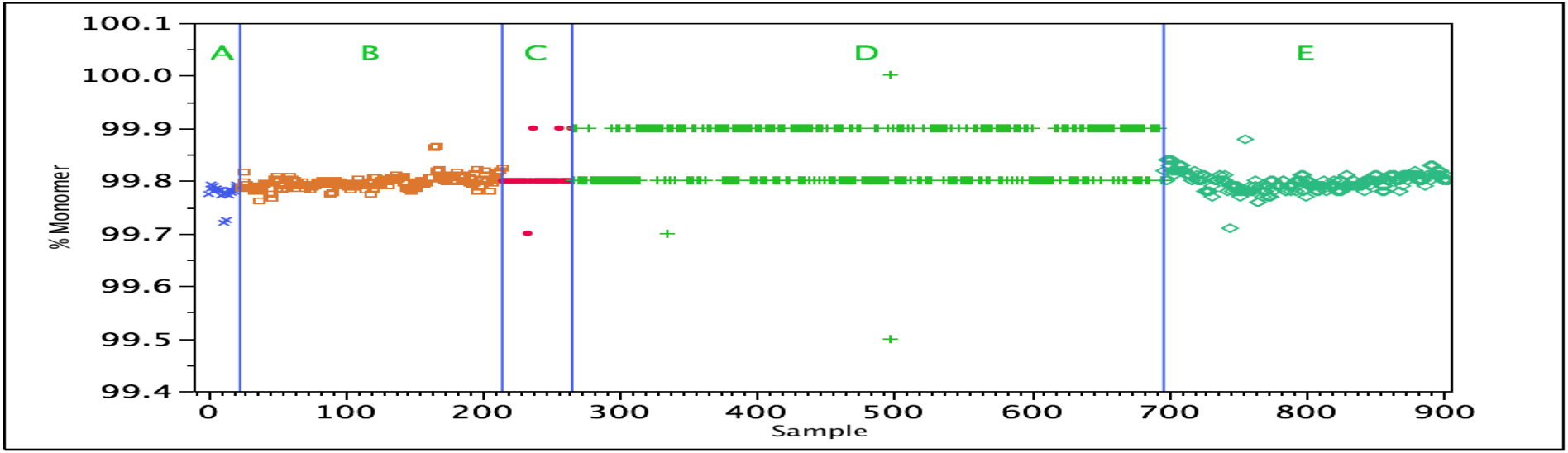
Bottom: Site Mean trend chart for the 6 sites showing that the method performance is consistent throughout all sites

Method Monitoring limits



Example: Method Monitoring Supports Inspection Response

A MAb product: Size Exclusion Method



- Concern regarding lack of quantitative system suitability criteria for a chromatography method
- Method monitoring provided strong evidence that method performance in a state of control, and sufficiently supporting release specification (≥ 98%)

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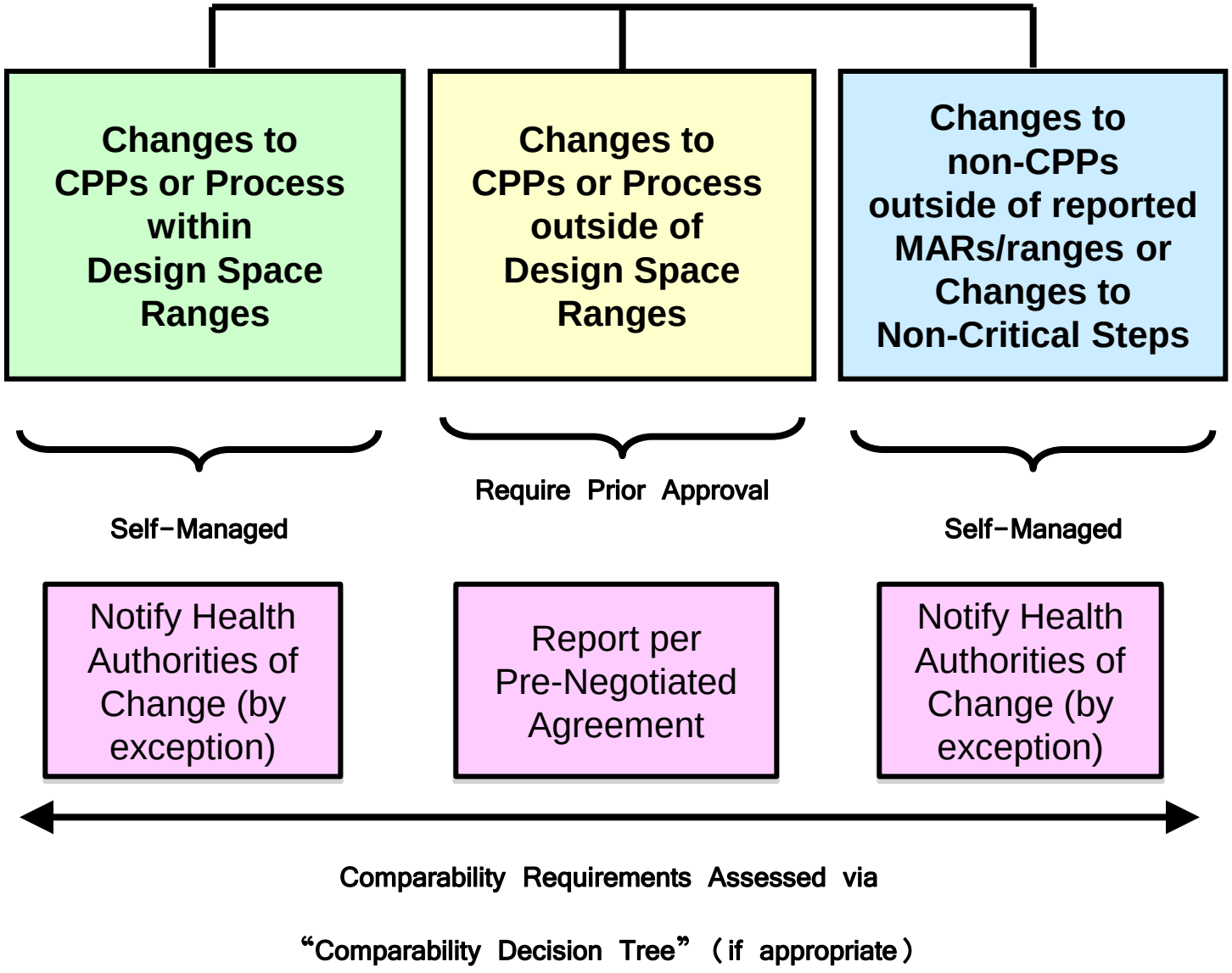
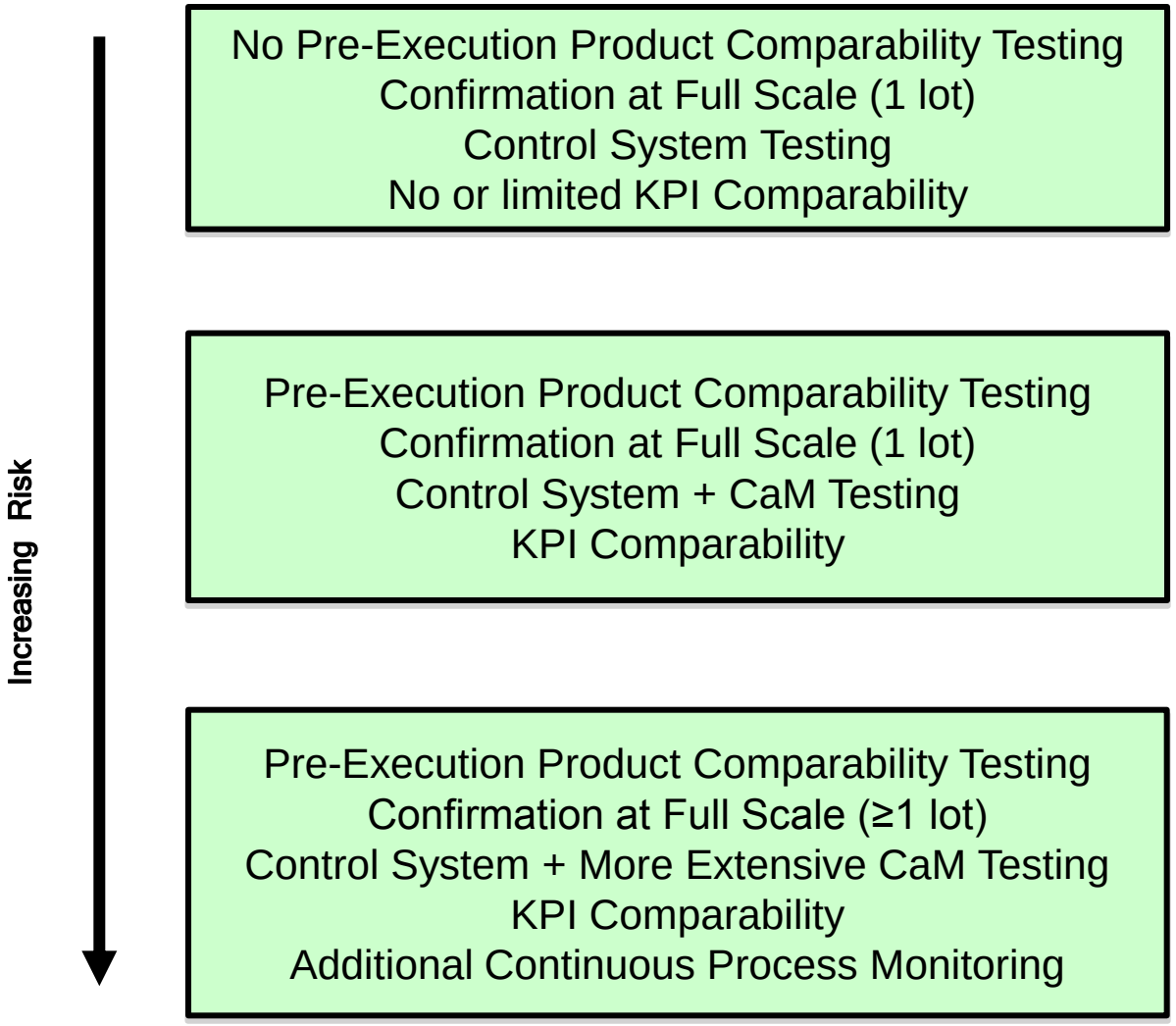
Post-Approval Lifecycle Management

- Process changes to improve yield
- Process changes to improve product quality
- Process monitoring/continual process verification
- Control system

Post-Approval Lifecycle Management: Process Parameters



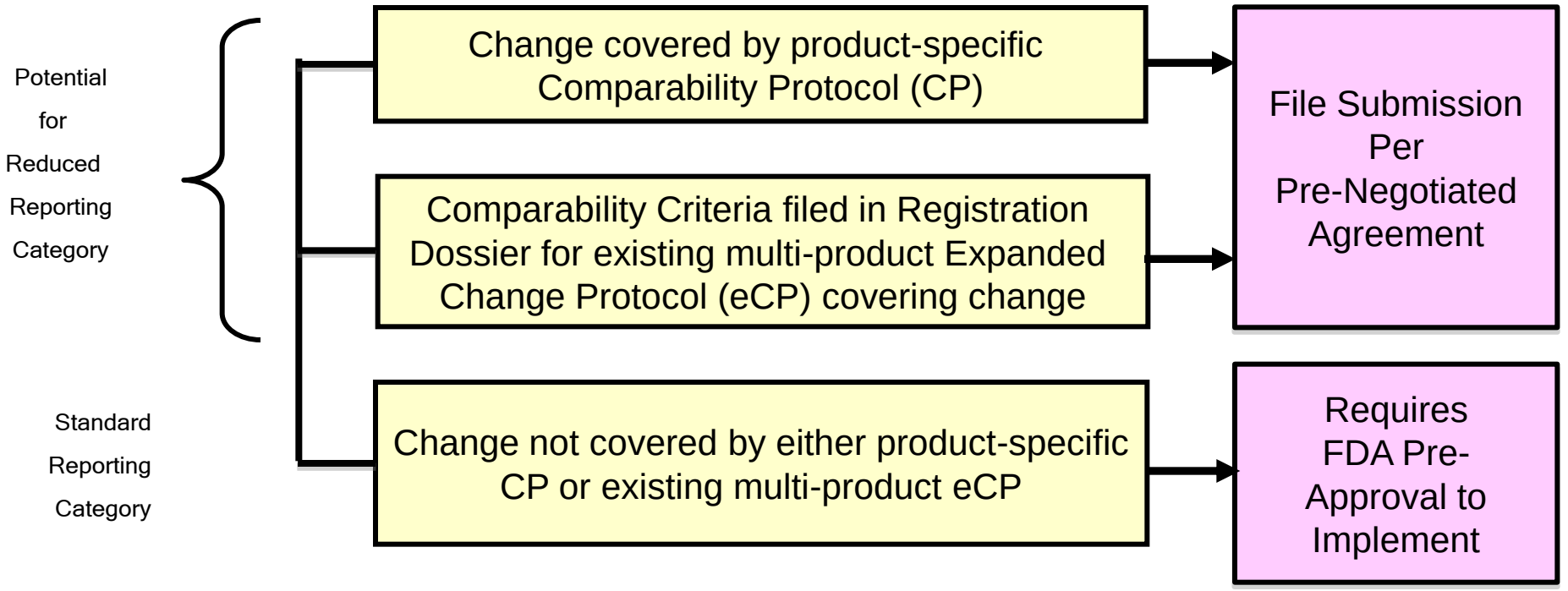
Post-Approval Lifecycle Management: Comparability Decision Tree



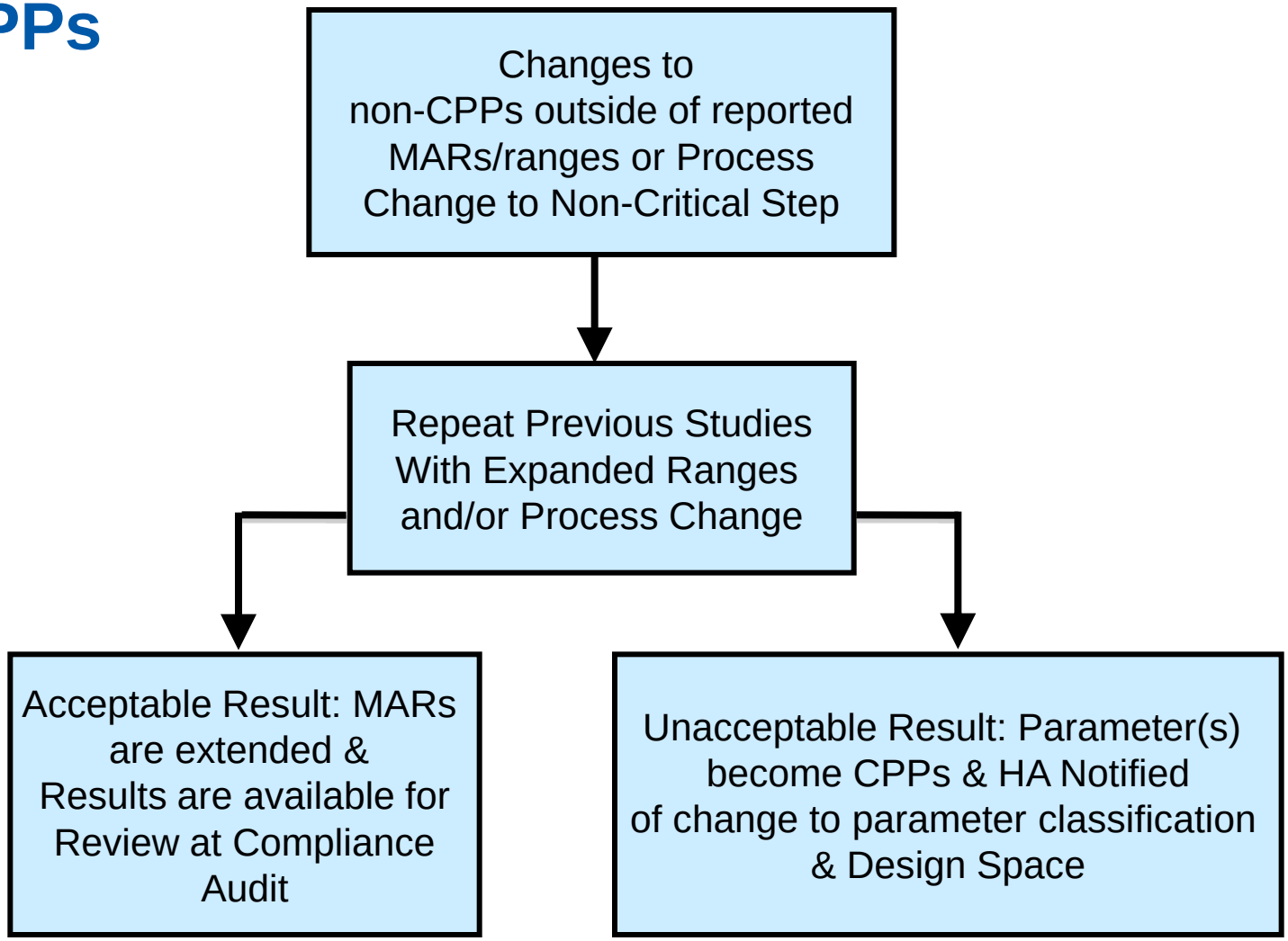
CaM = Comparability and Monitoring Testing

[a] May include stability testing of 1 or more full scale lots.

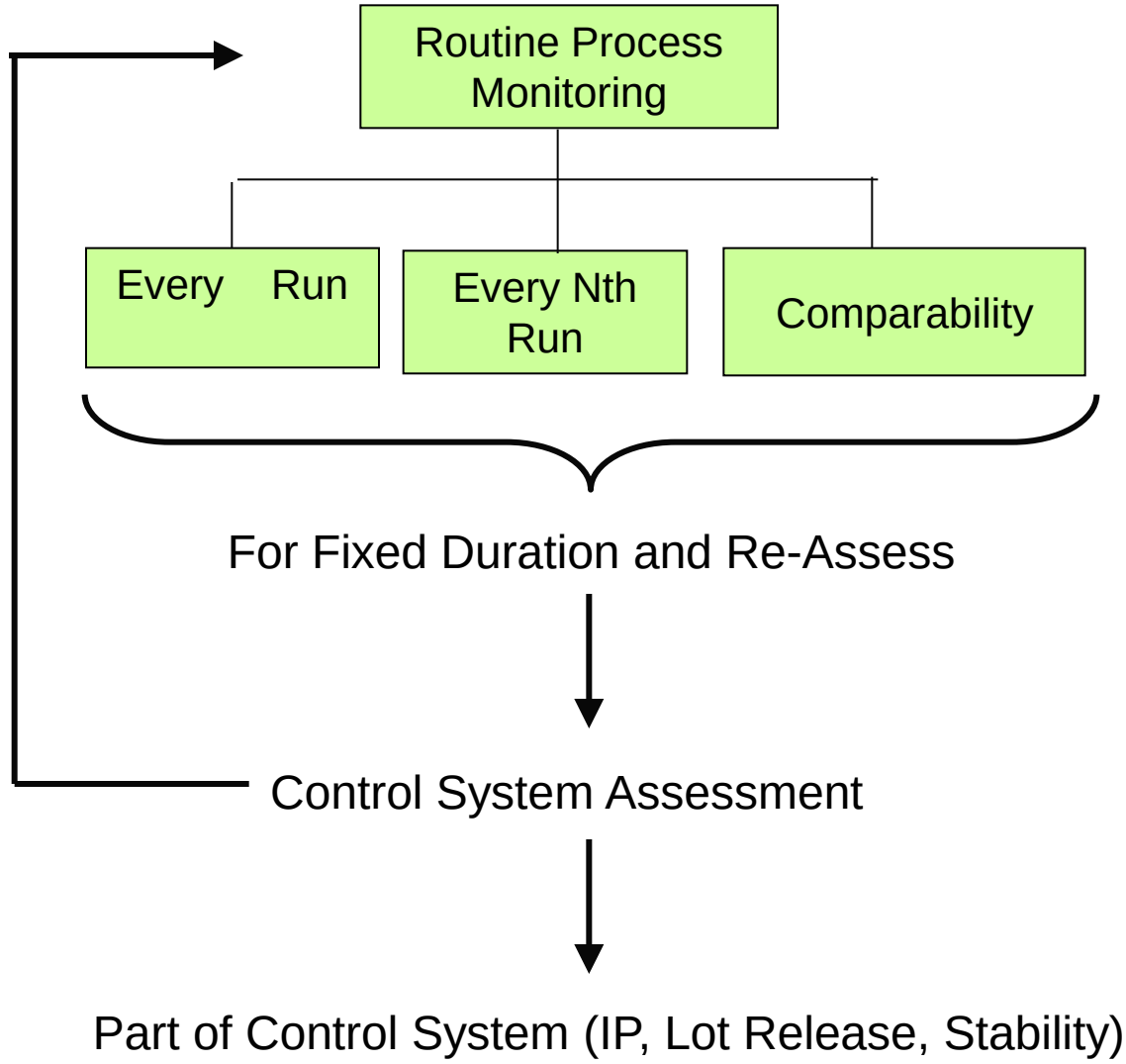
Post-Approval Lifecycle Management: Pre-Negotiated Change Management



Post-Approval Lifecycle Management: Changes to non-CPPs



Post-Approval Lifecycle Management: Continuous Process Monitoring



- Done under a validation protocol
- Pre-defined acceptance criteria for monitoring
- Frequency and duration indicated
- Monitoring done using validated or suitable assays

Post-Approval Lifecycle Management: Control System

- Over the product lifecycle, the QA criticality and testing strategy will be re-evaluated at a regular interval incorporating the following:
  - new knowledge about the Quality Attributes gained from additional clinical, non-clinical and characterization studies
  - trending of Quality Attributes from both the process (via IP, lot release, process monitoring testing) and stability testing
  - assay performance
  - availability of new assays
- Re-evaluation could result in the change of criticality of a QA, the testing strategy (IP, lot release, stability, monitoring or none) and potentially, the assay used to monitor the QA
- Any of these changes would be reportable and require prior-approval before implementation
- Evaluation is done in response to out-of- trend results, as a result of the Annual Product Review (APR) process or every 5 years or as part of a significant process change

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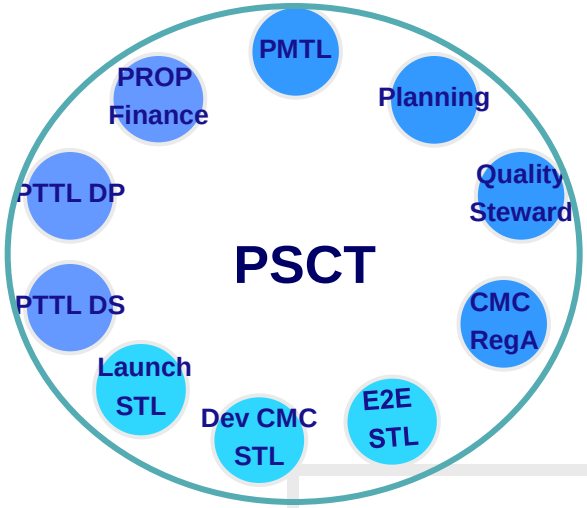
Commercial Supply Chain Teams: Product Steward Concept



Ad Hoc Quality Sub Team Members

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

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Role of the Commercial Product Quality Steward

Product Supply Chain Team

- Acts as the Voice of Quality (QA & QC) and provides Quality expertise and leadership on Product Supply Chain Team (PSCT)
- Serves as the communication conduit between PSCT and Quality functional areas/departments
- Develops and manages the implementation of Quality-related activities required to meet the product strategy and priorities
- Ensures Quality requirements are met during PSCT driven activities and changes

Role of the Commercial Product Quality Steward

Product Quality Monitoring:

- Monitors and reports on product quality across the End-to-End (E2E) network
- Partners with Quality subject matter experts (SMEs) to resolve product quality issues to ensure no impact to patient/product supply
- Conducts an annual Product Quality Risk Assessment; drives resolution of identified risks
- Generates the monthly Product Quality Report
- Reviewers of Annual Product Review (APR)

Role of the Commercial Product Quality Steward

Lifecycle Management

- Drive changes to ensure appropriate product quality life cycle management spanning across the network, contract sites, and partners
- Own and maintain the Process Specification File: Quality-controlled document that is a summary of current license ranges and commitments
- Accountable to ensure lifecycle commitments are completed
- Knowledge management
- Sharing of best practices

Conclusions

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Acknowledgements

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