Quality systems for continuous manufacturing

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Continuous Manufacturing

A Quality System Approach To Process Monitoring and Control

ICB II

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Ron Branning
President, RBC LLC
Implementing World-Class Production Quality Systems

The Focus of My Career

• J&J – 1968 – Beginning of Modern GMPs
• 45 years of practical, world wide, science and compliance solution implementation:
  J&J, Searle, Boehringer Ingelheim, Serono, Genetics Institute, Aventis Behring, Somatogen, Genentech, Gilead, Genzyme
• VP, SVP Quality and Compliance Issues Experience:
  – Quality Organization and Operational Performance
  – FDA 483s and WW Regulatory Inspection Observations
  – FDA CRLs, WLs, CDs and DOJ Investigations
  – MHRA, IMB, TGA, ANVISA, JMOH, SFDA, PICS Commitments
  – CHMP Oral Presentation: Commitments and Implementation
FDA’s (World Regulator’s) Expectations: Production Quality Systems

“We rely upon the manufacturing controls and standards to ensure that time and time again, lot after lot, year after year the same clinical profile will be delivered because the product will be the same in its quality...We have to think of the primary customers as people consuming that medicine and we have to think of the statute and what we are guaranteeing in there, that the drug will continue to be safe and effective and perform as described in the label”

Janet Woodcock, M.D.
Presentation Outline

• Continuous Manufacturing
• Quality System
• Process Development
• Technology Transfer
• Manufacturing
• Process Monitoring and Control
• Quality Control
• Quality Assurance
Continuous Manufacturing

- Glass, Plastic Manufacturing
- Radiation Sterilization
- McNeil Tylenol Response
- Serono – Perfusion Disks
- GI – Batch Harvest / Re-Feed
- Continuus - MIT / Novartis Collaboration
- DARPA – Tractor / Trailer Sized BioManufacturing
- Genzyme – Integrated Continuous BioMFG Platform
Integrated Product / Process Quality System
Organization Chart – SME’s, Risk Assessment, Culture Building
ICH Q10 Quality System – Organization Chart

Core Quality System Elements™

Development | Engineering & Maintenance | Manufacturing | QC | QA
## Core Quality System Elements

<table>
<thead>
<tr>
<th>Development</th>
<th>Engineering &amp; Maintenance (FEUM)</th>
<th>Manufacturing</th>
<th>Quality Control</th>
<th>Quality Assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Process development</strong></td>
<td>PD experiments define process CQAs, CPPs</td>
<td>Design FEU based on PD CQAs CPPs data</td>
<td>BR development based on CPP data</td>
<td>CQA initial IP TM development</td>
</tr>
<tr>
<td><strong>Test methods</strong></td>
<td>CQA TM development</td>
<td>Design IP&amp;QC TMs sampling capability into FEU</td>
<td>Develop operator training for IP &amp; QC sampling and testing</td>
<td>Initial CQA QC TM review &amp; assessment</td>
</tr>
<tr>
<td><strong>Facility, utilities, equipment</strong></td>
<td>Conduct FEU unit operations risk assessment (RA)</td>
<td>Refine FEU design &amp; Maintenance Program based on PD RA</td>
<td>Verify FEU design incorporates PD RA + Rev &amp; app FEU design</td>
<td>Define initial EM sampling &amp; test requirements</td>
</tr>
<tr>
<td><strong>Personnel</strong></td>
<td>Verify CQAs and CPP’s are included in E,M,QC, QA training material</td>
<td>Include PD RA into FEUM SOPs &amp; training material</td>
<td>Include PD RA into MFG SOPs &amp; training material</td>
<td>Include PD RA into FEU testing QC training material</td>
</tr>
<tr>
<td><strong>Tech transfer</strong></td>
<td>Process Development Report (PDR) includes final CQAs &amp; CPP’s</td>
<td>FEU completion, install, control sys and maintain based on PDR</td>
<td>Assess final MFG process based on PDR data from RA</td>
<td>IP, QC TM transfer</td>
</tr>
<tr>
<td><strong>Process validation</strong></td>
<td>Verify CQAs &amp; CPP’s are in validation protocols</td>
<td>Facility certification, Equipment qual, Utility qualification</td>
<td>Execute validation protocols during MFG qual, validation runs</td>
<td>TM validation + testing process validation (PV) samples</td>
</tr>
<tr>
<td><strong>Routine manufacturing</strong></td>
<td>Verify CQAs &amp; CPP’s are in batch records, ongoing process and test method support</td>
<td>Engineering Maintenance and Calibration support for routine manufacturing</td>
<td>Routine manufacturing</td>
<td>Routine IP, QC sampling and testing</td>
</tr>
<tr>
<td><strong>In process testing</strong></td>
<td>Monitoring and review of in process data</td>
<td>In process sampling capability support</td>
<td>IP sampling, MFG BR process adjustments</td>
<td>IP sampling and testing</td>
</tr>
<tr>
<td><strong>QC testing</strong></td>
<td>Monitoring and review of QC test data</td>
<td>QC sampling capability support</td>
<td>QC sampling</td>
<td>QC sampling and testing</td>
</tr>
<tr>
<td><strong>Product disposition</strong></td>
<td>MFG data and APR rev &amp; assessment to QA</td>
<td>FEU and Maintenance data to QA</td>
<td>MFG BR, deviation, CAPA data to QA</td>
<td>IP and QC data to QA</td>
</tr>
</tbody>
</table>
Quality System - Development

• PD Experiments Define Process CQAs, CPPs
• CQA Test Method Development
• Production Operations Risk Assessment (RA)
• Process Development Report (PDR)
• Verify CQAs & CPPs – Validation Protocols
• Verify CQAs & CPPs – Batch Records,
• Ongoing Test Method Support
• Monitor Process Data
• Monitor QC Test Data
• APQR Assessment
Development of Product Attributes, Process Parameters, Design Space & Control Strategy
Quality System – Engineering
Basis: Process Development Report

• Design Facilities, Equipment, Instruments, Utilities

• Develop Engineering, Cal/ Maintenance Program

• Install Control System

• Qualification

• Routine Manufacturing Support

• Engineering, Cal/ Maintenance data to QA
Quality System – Manufacturing

Basis: Process Development Report

- Drive Process Validation
- Finalize Process Monitoring and Control
- Complete Production Batch Record
- Deviations
- Investigations
- Corrective and Preventive Action (CAPA)
- Manufacturing
- Data to QA
Quality System - Quality Control
Basis: Process Development Report

- Define Environmental Monitoring Requirements
- Test Method Transfer Validation
- Routine IP, QC Sampling and Testing
- IP and QC data to QA
Quality System - Quality Assurance Oversight
Basis : Process Development Report

• Engineering Design
• Training Materials
• Calibration and Maintenance Program,
• Manufacturing BR & SOPs
• In-Process and QC Test Methods
• Process Validation
• CPPs and Critical Unit Operations
• Review IP and QC Test Results
• QA Production Data Review – Product Disposition
FDA Quality Metrics - Reporting

- Lots Attempted
- Rejected Lots
- Attempted Batches
- OOS (Including Stability)
- Lot Release Tests
- Stability Tests
- Invalid OOS (Including Stability)
- Product Quality Complaints
- Lots Attempted
- APR (QPR) On Time Completion
- AQRs (PQRs) Required
Management Governance

- Corporate Product Quality & Compliance Goals
- Routine Production Monitoring and Control
- Deviations, Investigations
- Rejected Materials / Products
- Product Complaints
- Adverse Events
- Recalls
- Annual/Periodic Product Quality Reviews
- Corrective and Preventive Actions
- Continuous Improvement
- Periodic Management Reviews – Goals / Progress
Final Thoughts

• Put in Place an ICH Q 10 Based QS
• Understand the Product (CQAs)
• Understand the Process and its Impact on the Product (CPPs, QbD and Control Strategy)
• Validate QC Test Methods
• Validate, Monitor and Control the Process
• Investigate and CAPA all Deviations
• Continuously Improve all Operations
Thank You

Questions?

Comments?