ICH Q10
Pharmaceutical Quality System (PQS)

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Three Day Program – 1\textsuperscript{st} day

**Wednesday Morning**
- Introduction to ICH Q10 – Pharmaceutical Quality System
- Management of Deviations/Investigations and CAPA

**Wednesday Morning**
- Change Management
- Equipment Qualification

**Wednesday Afternoon**
- Practical Exercises (Deviations and CAPA)
- Practical Exercises (Change Management)
- Practical Exercises (Equipment Qualification)
Three Day Program – 2\textsuperscript{nd} Day

\textbf{Thursday Morning}
- Controlling Cross Contamination – Biologics Facility
- Risk Management

\textbf{Thursday Morning}
- Supplier Assurance Programs (Qualifying Suppliers)

\textbf{Thursday Afternoon}
- Practical Workshop Exercise
Three Day Program – 3rd Day

Friday Morning
- Viral Inactivation – Industry requirements
- Cleaning and Cleaning Validation in a Biologics Facility
- Microbiological Control

Friday Morning
- Effective Internal Auditing

Friday Afternoon
- Practical Workshop Exercise
PQS - Module Outcomes

On completion of this module the participant should be able to:

- Interpret ICH Q10 expectations
- Develop a Quality Manual (QM) template and Quality Policies (POL)
- Design a pharmaceutical quality system using the QM template
- Strengthen GMP compliance systems
<table>
<thead>
<tr>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basics of Quality and Compliance</td>
</tr>
<tr>
<td>How does a Pharmaceutical Quality System fit together? – ICH Q 10</td>
</tr>
<tr>
<td>Deviations</td>
</tr>
<tr>
<td>CAPA and Continuous Improvement</td>
</tr>
</tbody>
</table>
Major International Codes of GMP

- EU Guide to Good Manufacturing Practices (Eudralex Ch 4)
- World Health Organisation (WHO) c GMPs
- United States - FDA CFRs Part 21
  - CFR 210/211 for Drugs and Biologics - current GMPs
  - CFR 820 Quality Systems for Medical Devices - current GMPs
- ICH Q7 GMP for Active Pharmaceutical Ingredients
- Canadian cGMP (aligned with PICs)
- ISO 13485 : 2003 - Medical Devices
- ICH Guidance Documents – Technical Standards
Some Useful Reference Documents

- EU/PICs/TGA cGMPs – Chapter 1 – Quality Management
- ICH Q10 - Pharmaceutical Quality System
- ICH Q8 – Pharmaceutical Product Development
- ICH Q9 - Risk Management in Pharmaceuticals
- FDA Quality Systems Approach to Pharmaceutical CGMP Regulations (9/2006)
- GHTF - GHTF/SG3/N15R8 - Implementation of risk management within a Quality Management System
Significant Changes
40 Year History of Pharmaceutical Quality Management

- Quality Control (1972)
- Sterile Validation (1975)
- Quality Assurance (1975)
- General Validation (1980s)
- Quality Management (1990s)
- Risk Management (2004+)
- PQS – ICH Q8/Q9/Q10
Quality Control and Sampling

Sampling Plan
Lot Size = 1000
Sample size = 20 (2%)
Quality and Compliance

- **Quality refers to:**
  - **Product Quality** – meeting agreed specifications
  - **Quality Systems** – planned and deployed processes (systems) used to monitor, report and take corrective actions

- **GMP Compliance refers to:**
  - Identification, documentation and deployment of GMP obligations
  - Ongoing verification that GMP obligations are being met, or not.
Compliance Programs

- Executive Commitment
- Objectives
- Identify Obligations
- Assign Responsibility
- Competence & Compliance Training
- Compliance Focused Behaviours
- Controls to Manage Identified Obligations
- Performance Monitored, Measured, Reported
- Demonstrate Compliance (documents, records practices)
- Continuous Improvement and Management Review

Gap Analysis
PQS/Compliance Gap Analysis

- identify and assess compliance obligations and potential failures - not just GMP
- Include external and internal obligations in gap analysis
- Prioritize gaps using use risk principles
- Establish a compliance register or database
- Develop a PQS remediation/ improvement plan
- Establish a system to monitor external changes in PQS & compliance obligations e.g Legislation, cGMP updates …
# Things to look for in the gap analysis

<table>
<thead>
<tr>
<th>Element</th>
<th>What to look for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deviation, OOS System</td>
<td>How effective are the failure investigations</td>
</tr>
<tr>
<td>CAPA System</td>
<td>Does the CAPA system look at root causes or just symptoms</td>
</tr>
<tr>
<td>Audit Programs</td>
<td>Do the audit look at symptoms or root causes – are issues effectively resolved</td>
</tr>
<tr>
<td>Reviews, Trends and Reporting</td>
<td>Are management reviews and APQRs detailed enough and responsive</td>
</tr>
<tr>
<td>Training</td>
<td>Do training programs address compliance obligations</td>
</tr>
<tr>
<td>Management Responsibility</td>
<td>Is compliance a KPI within position descriptions</td>
</tr>
<tr>
<td>Prioritisation and Resource Allocation</td>
<td>Is there a mechanism for resource prioritization e.g., risk based</td>
</tr>
<tr>
<td>Change Management</td>
<td>Does change management include compliance review</td>
</tr>
</tbody>
</table>
How does a Quality System Fit Together?

- Training
- Change Control
- Document Control
- Validation
- Production Control
- Incidents & Deviations
- Failure Investigation
- Quality Control
- Lab OOS
- Management Review
- Annual Product Review
- Complaints & Recall
- Pharmacovigilance
- Audits
- Supplier Assurance
- External
- Internal
- Regulatory
- Change Control
- Monitoring & Trend Analysis
- Audits
- Supplier Assurance
- External
- Internal
- Regulatory
“Linkage” of the QMS system elements

- Each of the major elements are inter-linked to other elements
- Elements either drive or feed others or vice versa
- Linkage of related elements is critical to quality management oversight
  - Without strong linkage identification of problem root cause is difficult
  - With linkages, problems and root causes can be traced through the linked system
- Linkage enables “escalation” of significant issues
**FDA Six Control Systems – Inspection 7356.002**

- **Production System**
  - Batch compounding, dosage form production,
  - In-process sampling and testing,
  - Process validation.
  - Master batch records and manufacturing procedures.

- **Material System**
  - Control of finished products, components, water, gases, containers and closures.
  - Validation of computer inventory control
  - Drug storage, distribution controls, records.

- **Equipment / Facilities**
  - Buildings and facilities & maintenance
  - Equipment qualifications (IQ/OQ);
  - Equipment calibration;
  - Cleaning and validation of cleaning processes.
  - Utilities - HVAC, gases, steam and water

- **Package / Label System**
  - Packaging and labeling operations & controls
  - Label examination and usage,
  - Label storage and issuance,
  - Validation of these operations.

- **Laboratory System**
  - Laboratory procedures,
  - Testing, analytical methods development
  - Method validation or verification,
  - Stability program

- **Quality Assurance**
  - Change control, reprocessing, batch release,
  - Annual product review
  - Validation protocols,
  - Product defect evaluations
  - Evaluation of returns.

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An Overview of ICH Q10
Pharmaceutical Quality System
ICH Q10 - Pharmaceutical Quality System

- Based on ISO 9000/ISO13485/CFR 820 systems model
- Compliments ICH Q8 and ICH Q9
- Applies across the product life-cycle
- Consistent with GMPs - not intended to add new expectations to regulations and compliance
- Applies to APIs, drug products and biotechnology
- Strengthens the link between product development and manufacturing activities
Pharmaceutical Quality System, Quality Assurance, GMP and Quality Control

Pharmaceutical Quality System (ICH Q10)

- Quality Management
- Quality Assurance
- Good Manufacturing Practices
- Quality Control

Quality by Design (ICH Q8)

Quality Risk Management (ICH Q9)

Supply ➔ Manufacturing ➔ Distribution ➔ Customers
ICH Q10 - Some Important Principles

• The size and complexity of the company’s activities should be taken into consideration when developing a new pharmaceutical quality system or modifying an existing one.

• While some aspects of the pharmaceutical quality system can be company-wide and others site-specific, the effectiveness of the implementation of the pharmaceutical quality system is normally demonstrated at the site level.
ICH Q10 - Pharmaceutical Quality System

- Pharmaceutical Development
- Technology Transfer
- Commercial Manufacture
- Product Discontinuation

Investigational Products

GMP Regulation

Management Responsibility

PQS Elements

- Process Performance and Product Quality Monitoring System
  - Corrective and Preventive Action (CAPA)
  - Change Management System
  - Management Review

Enablers

- Knowledge Management
- Quality Risk Management

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A Hierarchy QMS/GMP Documentation

- New expectation
- QP
- Objectives
- Quality Manual (Guidance/Policy)
- Systems Quality Management SOPs
- Operating SOPs Master Batch Records
- Operator Instructions
- Manufacturing and Quality Records
- Training Manuals and Records

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Expectation of Skills and Knowledge Development of Personnel

- Quality Knowledge
- GMP Knowledge
- Product and Process Knowledge (Skills Competency)
- GMP Behaviour (Minimising Human Error)
- Training Manuals, Records and Competency Assessments
Integration of PQS and GMP Elements in the Quality System

**PQS**
- Knowledge Management, Training and Education
- Monitoring Systems
- Change Management
- CAPA & Improvement
- Management Review and Responsibility
- Quality Planning & Resources
- Process Performance and Product Quality Monitoring System

**GMP**
- Quality Management/Quality Assurance System.
- Facilities and Equipment System.
- Materials System.
- Production System
- Packaging and Labeling System
- Laboratory Control System
PQS Enablers
Quality Risk Management (QRM)

- **Quality risk management**, in line with ICH Q9, provides an essential component of the Quality System.
- QRM enables both effective and efficient practices.
- Application of QRM ensures the quality system is efficient.
- Provides a systematic approach to escalating and prioritising significant events.
## Risk Management Maturity

<table>
<thead>
<tr>
<th>Risk Maturity Level</th>
<th>Risk Processes</th>
<th>Attitude</th>
<th>Behaviour</th>
<th>Skills &amp; knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Scepticism</td>
<td>No Formal Processes</td>
<td>Risk Avoidance</td>
<td>Fear of Blame Culture</td>
<td>Unconscious Incompetence</td>
</tr>
<tr>
<td>Awareness</td>
<td>Ad hoc use of Stand Alone Processes</td>
<td>Suspended Belief</td>
<td>Reactive, Fire fighting</td>
<td>Conscious Incompetence</td>
</tr>
<tr>
<td>Understanding &amp; Application</td>
<td>Tick Box Approach</td>
<td>Passive Acceptance</td>
<td>Compliance, reliance on registers</td>
<td>Conscious Competence</td>
</tr>
<tr>
<td>Embedding &amp; Integration</td>
<td>Risk Management embedded in Business</td>
<td>Active Engagement</td>
<td>Risk-based decision making</td>
<td>Unconscious Competence</td>
</tr>
<tr>
<td>Robust Risk Management</td>
<td>Regular review &amp; Improvement</td>
<td>Champion</td>
<td>Innovation, Confident Risk taking</td>
<td>Expert</td>
</tr>
</tbody>
</table>
PQS Enablers - Knowledge Management

- **Knowledge management** means the systematic accumulation of information concerning products so that this knowledge can be leveraged in the future.

- **Knowledge** can be stored in systems such as:
  - Quality Records, including testing, stability studies and reports
  - Registration Dossiers
  - Contracts and Technical Agreements
  - Validation Protocol and Reports
  - Marketplace Events (Complaints, Recalls, Adverse Events etc.)
  - Annual Product Quality Reviews (PQRs)
    - Process control, significant deviations and changes.
ICH Q10 – Pharmaceutical Quality Manual

• A Quality Manual or equivalent documentation approach should be established and should contain the description of the pharmaceutical quality system.

• The description should include:
  i) The quality policy
  ii) The scope of the pharmaceutical quality system.
  iii) Identification of the processes within the pharmaceutical quality system, as well as their sequences, linkages and inter-dependencies.

• Process maps and flow charts can be useful tools to facilitate depicting these in a visual manner.
Example Chapters of a Quality Manual

- MANAGEMENT REVIEW AND RESPONSIBILITY
- DESCRIPTION OF THE QUALITY SYSTEM
- QUALITY PLANNING AND RESOURCE MANAGEMENT
- TRAINING AND EDUCATION
- PRODUCT DEVELOPMENT AND PRODUCT REGISTRATION
- QUALITY ASSURANCE AND COMPLIANCE PROGRAMS
- MONITORING PROGRAMS
  - CAPA / QUALITY AUDITS / PRODUCT QUALITY REVIEWS
  - MARKETPLACE MONITORING: COMPLAINTS AND PHARMACOVIGILANCE PROGRAMS
- QUALITY RISK MANAGEMENT
- KNOWLEDGE MANAGEMENT

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Example Chapters of a Quality Manual

- MATERIAL CONTROL SYSTEM:
  - SUPPLY CHAIN INTEGRITY AND SUPPLIER ASSURANCE

- PRODUCTION SYSTEM
  - PRODUCT DEVELOPMENT, TECHNOLOGY TRANSFER AND MASTER INSTRUCTIONS
  - PROCESS PERFORMANCE AND PRODUCT QUALITY MONITORING SYSTEM
  - PROCESS VALIDATION
  - PACKAGING AND LABELLING
  - DEVIATIONS, INVESTIGATIONS AND NON-CONFORMING PRODUCT

- LABORATORY CONTROL SYSTEM

- CHANGE MANAGEMENT / VALIDATION

- FACILITIES AND EQUIPMENT SYSTEM / CLEANING/ CONTAMINATION CONTROL AND COMPUTERISED SYSTEMS

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PQS Objectives

- Set objectives and clear performance metrics:
  - Objectives are reviewed annually
  - Metrics are measured, time-related and indicate the level of performance required;
  - Metrics are reviewed regularly;
- Define how compliance obligations are embedded in operational practices and procedures.
- Address processes for identifying, reporting and responding to compliance failures.
## FDA View on Quality Metrics

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot Acceptance Rate</td>
<td>Number of lots rejected in a year / number of lots produced</td>
</tr>
<tr>
<td>Right First Time Rate</td>
<td>Number of deviations / lot</td>
</tr>
<tr>
<td>Complaint Rate</td>
<td>Number valid complaints/number of lots released per year</td>
</tr>
<tr>
<td>Invalidated (OOS) Rate</td>
<td>Number of OOS test results invalidated /tests performed</td>
</tr>
<tr>
<td>Annual Product Review (APR) on Time Rate</td>
<td>Number of APRs generated within 30 days of annual due date</td>
</tr>
<tr>
<td>Management Engagement</td>
<td>Most senior manager that signed each annual product review</td>
</tr>
<tr>
<td>Process capability or performance index</td>
<td>Whether performed for each critical quality attribute as part of that product’s APR.</td>
</tr>
<tr>
<td>Corrective and Preventative Action (CAPA) Rate</td>
<td>Number of CAPAs that were initiated due to an APR, divided by the total number of APRs generated.</td>
</tr>
</tbody>
</table>
ICH Q10 – 4.1 Management Review

• Senior management should be responsible for pharmaceutical quality system governance through management review to ensure its continuing suitability and effectiveness.

• Management should assess the conclusions of periodic reviews of process performance and product quality and of the pharmaceutical quality system.
Commitment to Quality by Management

- Governing Body and CEO are engaged
- The Quality Policy is aligned with business objectives
- Compliance and Quality obligations are embedded in position responsibilities
- Resources are allocated to Quality / Compliance
- Top level engagement in compliance/quality metrics and reviews
PQS, Compliance and Quality Organisation

- Assign compliance and quality responsibilities to individual managers – set out in position descriptions
- Ensure all management “walk the talk”
- Appoint a senior Compliance/Quality executive:
  - direct access to the Board/CEO
  - Access to expert advice (internal and external)
  - Establish compliance/quality objectives and KPIs
- Ensure compliance/quality function has the authority to act
ICH Q10 - Management Reviews – should include

- A timely and effective **escalation** process to senior management;
- Measures of customer satisfaction - complaints and recalls;
- Conclusions of process performance and product quality monitoring;
- The effectiveness of process and product changes including those arising from CAPA;
- Any follow-up actions from previous reviews;
Management Reviews, Trend Analysis and Feedback

Management Reviews
- SOPs & Reports
- Periodic Meetings

- Risk Assessment
- PQRs Conducted
- Report KPIs and Quality Metrics
- Verification of PQS Effectiveness
- Trend Analysis and Feedback
ICH Q10 Quality System
Section 3 - Continual Improvement of Process Performance & Product Quality

- Process performance and product quality monitoring system:
  - Well defined systems
    - Process control
    - Identification of improvement areas
- Corrective action and preventive action (CAPA) system
  - In place and effectiveness evaluated
  - Focus on Continuous Improvement
- Change management system:
  - QA oversight
  - Utilizes science and risk-based assessment
- Management review of process performance and product quality
  - Periodic reviews of performance against metrics
  - Supports continual improvement
ICH Q10 Quality System:
Section 4 - Continual Improvement of the QS

- Management Review of the Pharmaceutical Quality System
  - Measurement of achievement of QS objectives
  - Assessment of Metrics

- Monitoring of Internal and External Factors impacting the QS
  - Emerging regulations, guidance and quality issues
  - Innovations
  - Changes in business strategies and objectives.

- Outcomes of Management Review and Monitoring
  - (Re)allocation of resources and/or personnel training
  - Timely and effective communication of the results
## Compliance and Improvement

<table>
<thead>
<tr>
<th>Element</th>
<th>Compliance is a cost ($)</th>
<th>Regulation Driven</th>
<th>Improved Compliance</th>
<th>Integrated Compliance</th>
<th>Competitive Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Focus</td>
<td>Testing (QC)</td>
<td>GMPs</td>
<td>Processes and Systems</td>
<td>ICH Q8, 9, 10 Started</td>
<td>ICH Q8,9,10 Embedded</td>
</tr>
<tr>
<td>CAPA</td>
<td>Correction (Reactive)</td>
<td>Corrective Action</td>
<td>Prevent. Action (RCA)</td>
<td>Management Reviews</td>
<td>Drive down COQ</td>
</tr>
<tr>
<td>Continuous Improvement</td>
<td>Absent</td>
<td>Event Driven (Reactive)</td>
<td>QA Focus (Predictive)</td>
<td>Operations Focus</td>
<td>Company Wide - Part of Culture</td>
</tr>
<tr>
<td>Compliance</td>
<td>QA/QCs role - minimal Audits</td>
<td>Compliance / GMP Audits</td>
<td>PQS Systems driven audits</td>
<td>Prepare for Regulatory Audits</td>
<td>Welcome External Feedback</td>
</tr>
<tr>
<td>Knowledge &amp; Training</td>
<td>Basic GMP Training</td>
<td>Knowledge is anecdotal</td>
<td>Systematic Training Evaluated</td>
<td>Knowledge is Documented &amp; Organised</td>
<td>Knowledge is Leveraged</td>
</tr>
</tbody>
</table>