CBE
Centre for Biopharmaceutical Excellence

ICH Q10
Pharmaceutical Quality System (PQS)

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Three Day Program – 1st 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 – 2nd Day

Thursday Morning

- Controlling Cross Contamination – Biologics Facility
- Risk Management

Thursday Morning

- Supplier Assurance Programs (Qualifying Suppliers)

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

PQS Module Topics

- Basics of Quality and Compliance
- How does a Pharmaceutical Quality System fit together ? – ICH Q 10
- Deviations
- CAPA and Continuous Improvement

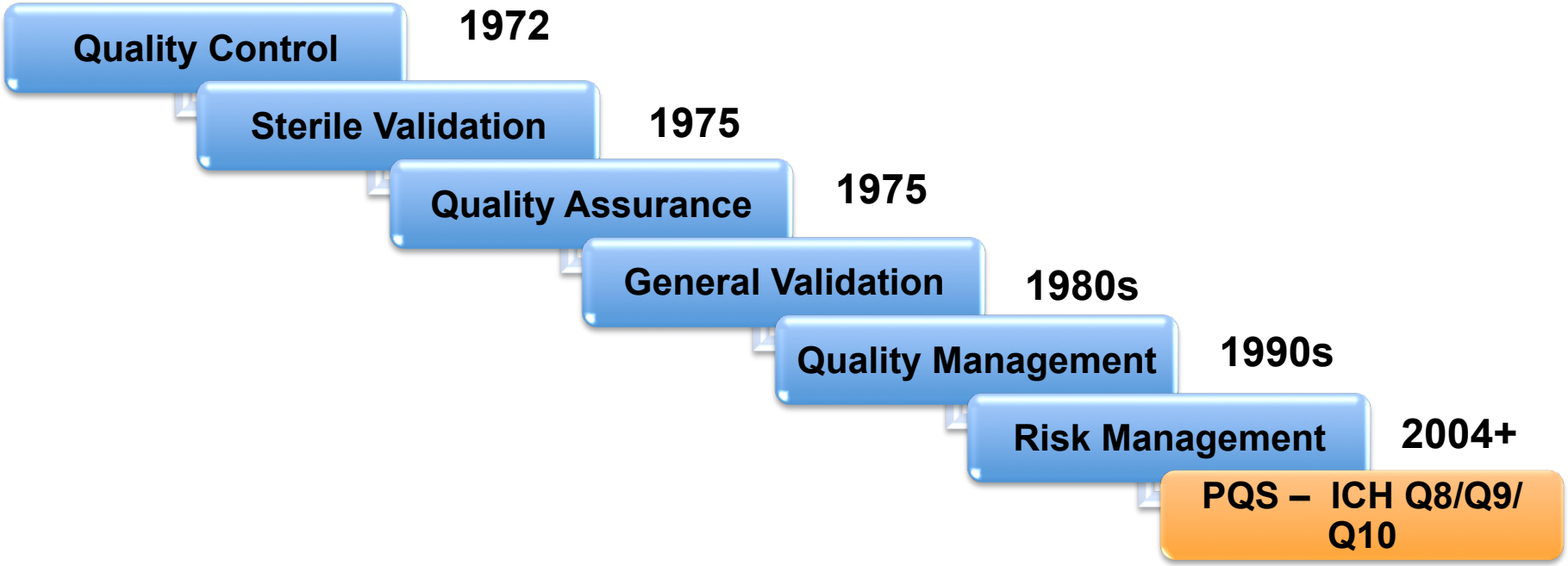
Major International Codes of GMP

- **PIC/S Guide to Good Manufacturing Practices - PE 009 - 2014**
- **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

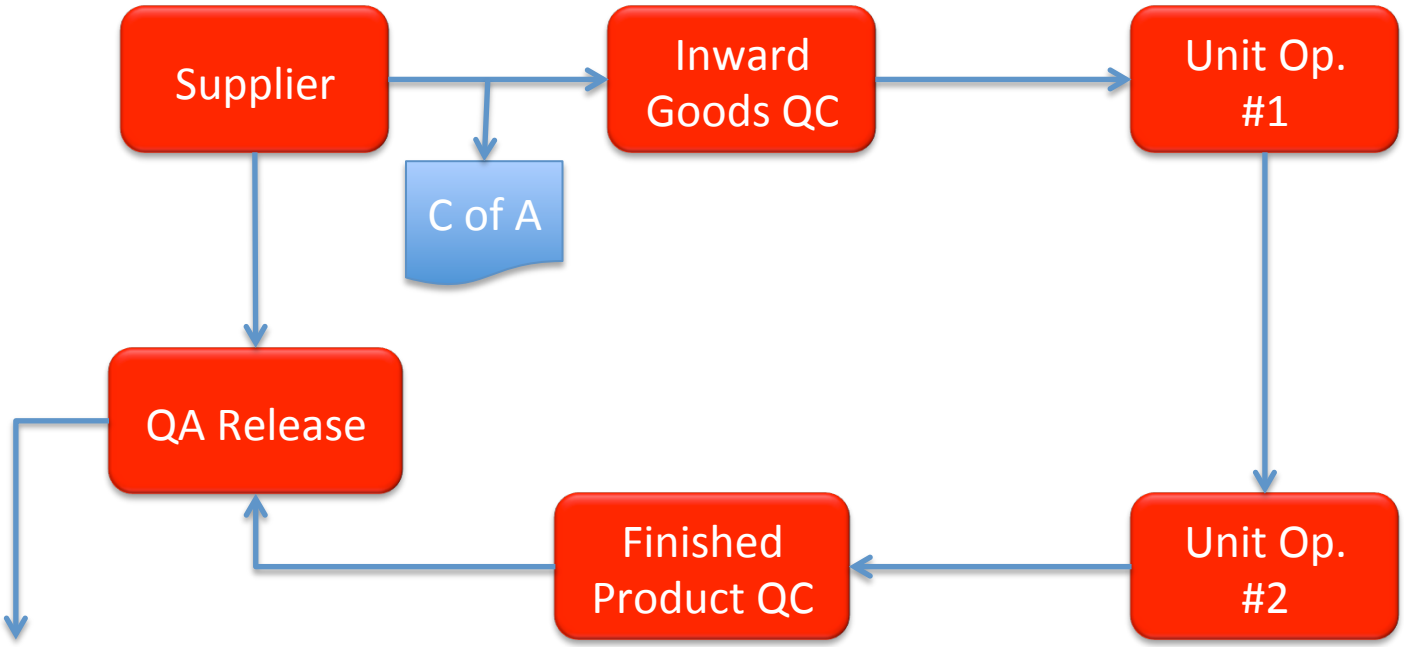
Some Useful Reference Documents

- 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 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

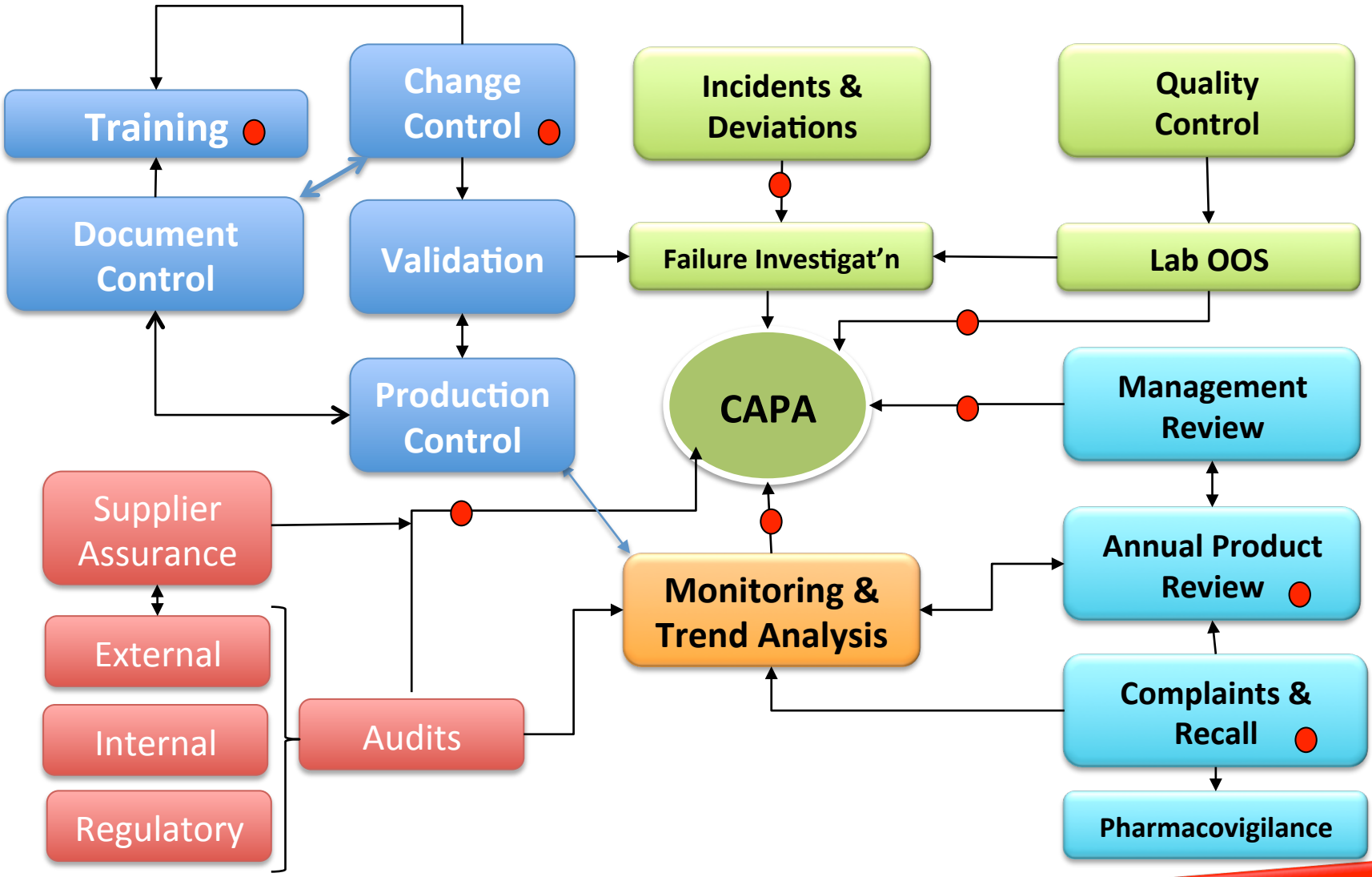
PQS/Compliance Gap Analysis

- 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

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

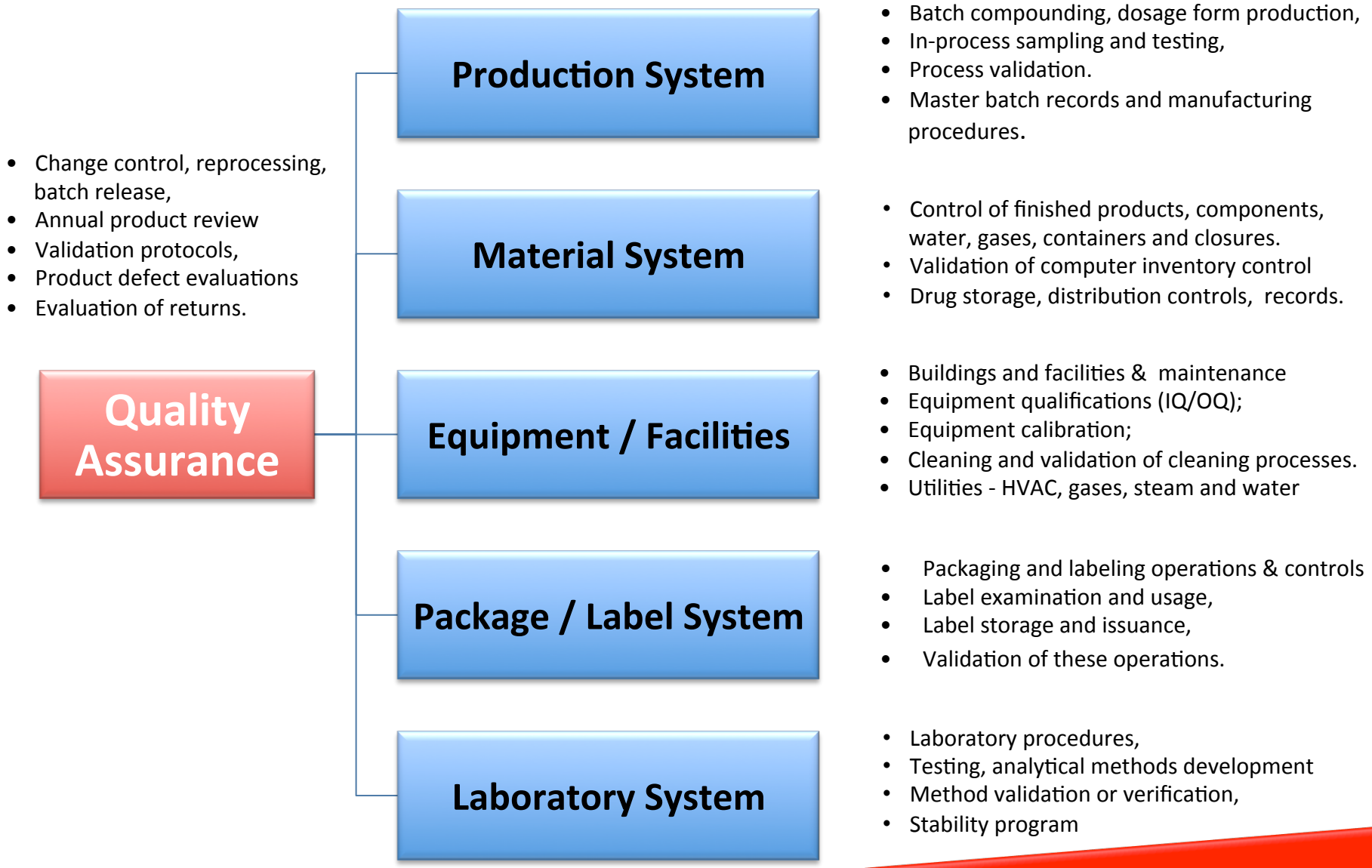
How does a Quality System Fit Together ?



“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



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

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

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

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

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

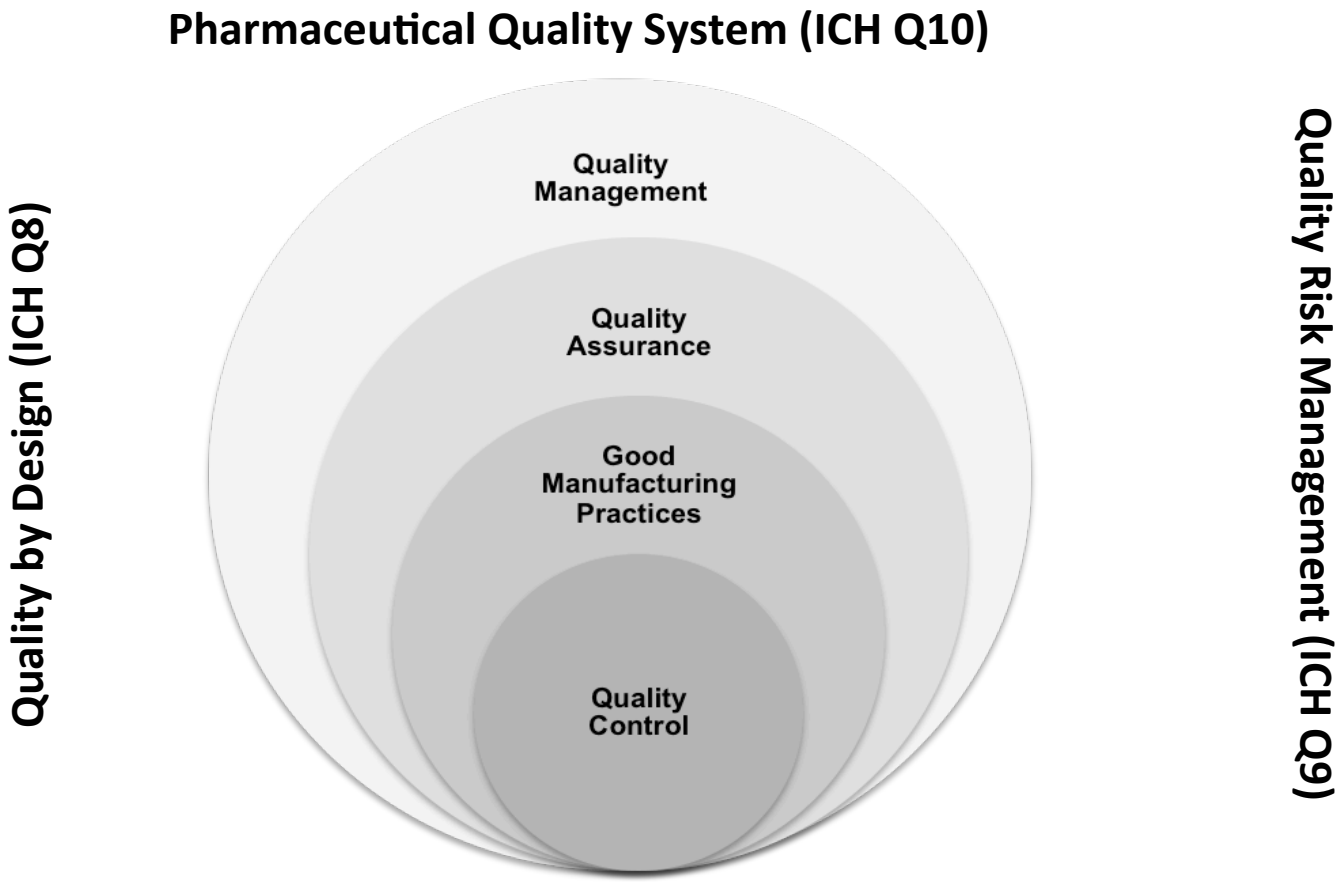
- Laboratory procedures,
- Testing, analytical methods development
- Method validation or verification,
- Stability program

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

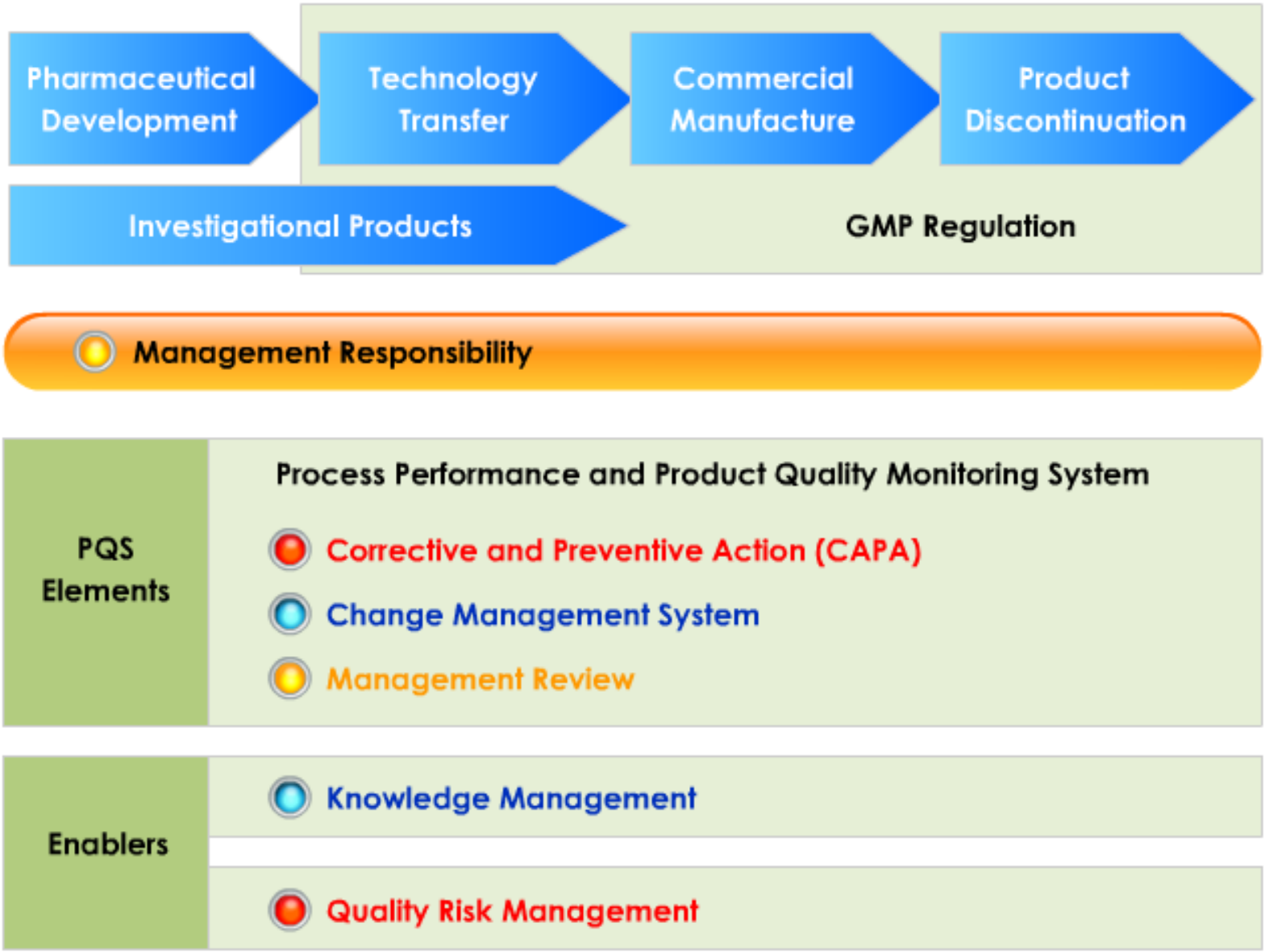


ICH Q10 - Some Important Principles

- 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.

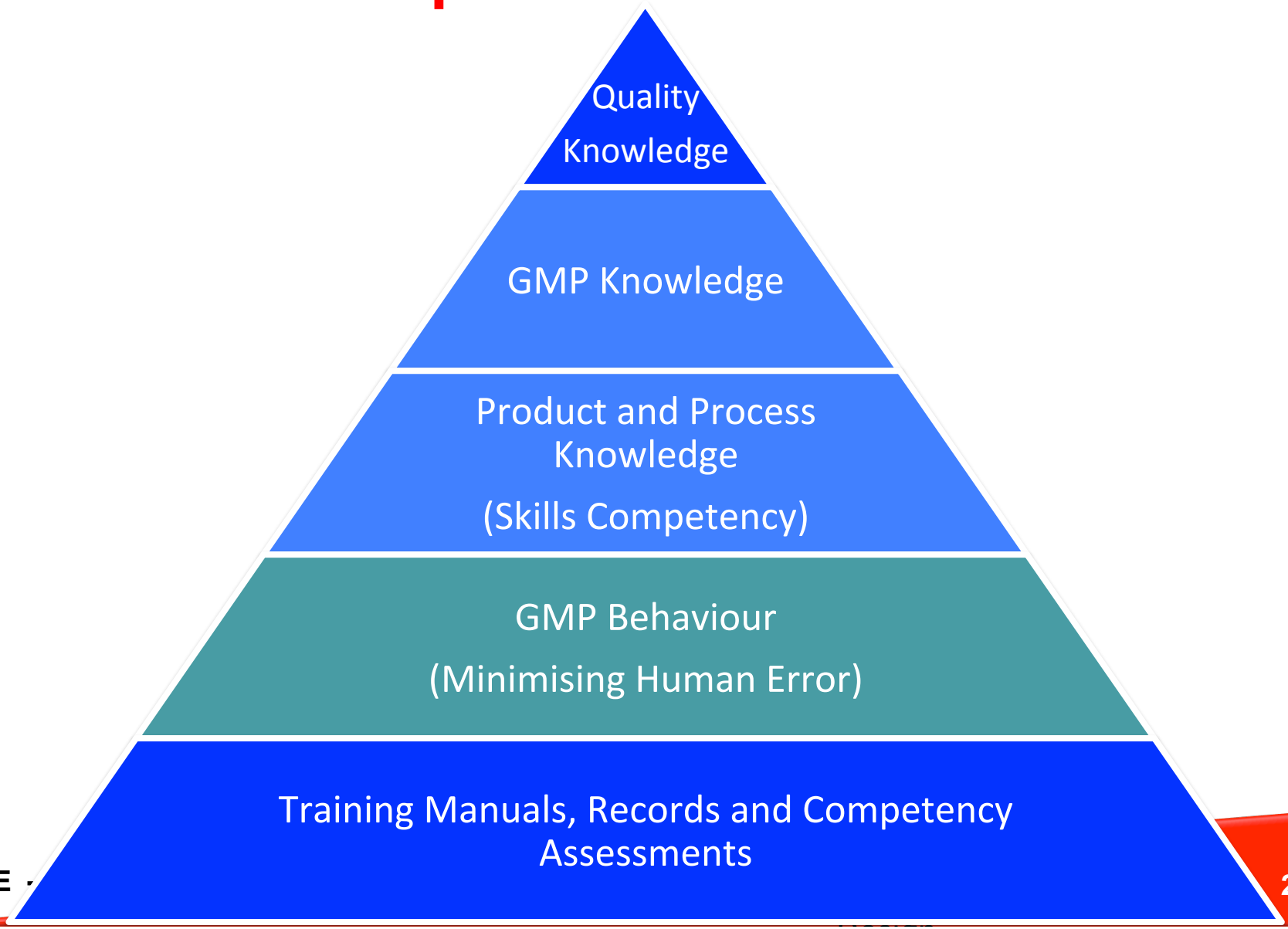
- While some aspects of the pharmaceutical quality system can be company-wide and others site-specific, the effectiveness of the implementation of the pharmaceutical quality system is normally demonstrated at the site level.

ICH Q10 - Pharmaceutical Quality System

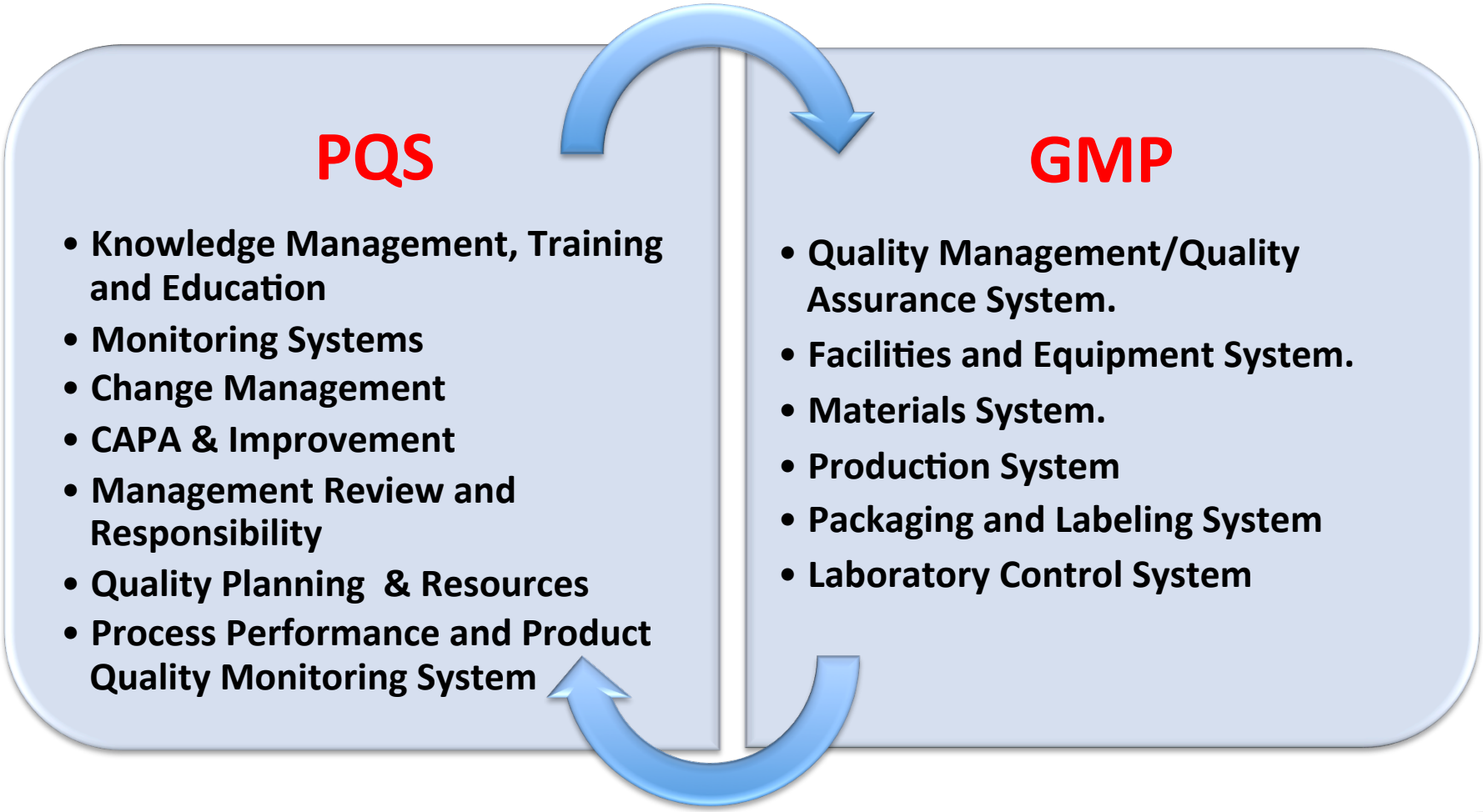


A Hierarchy QMS/GMP Documentation

Expectation of Skills and Knowledge Development of Personnel



Integration of PQS and GMP Elements in the Quality 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

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

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**

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**

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

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

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

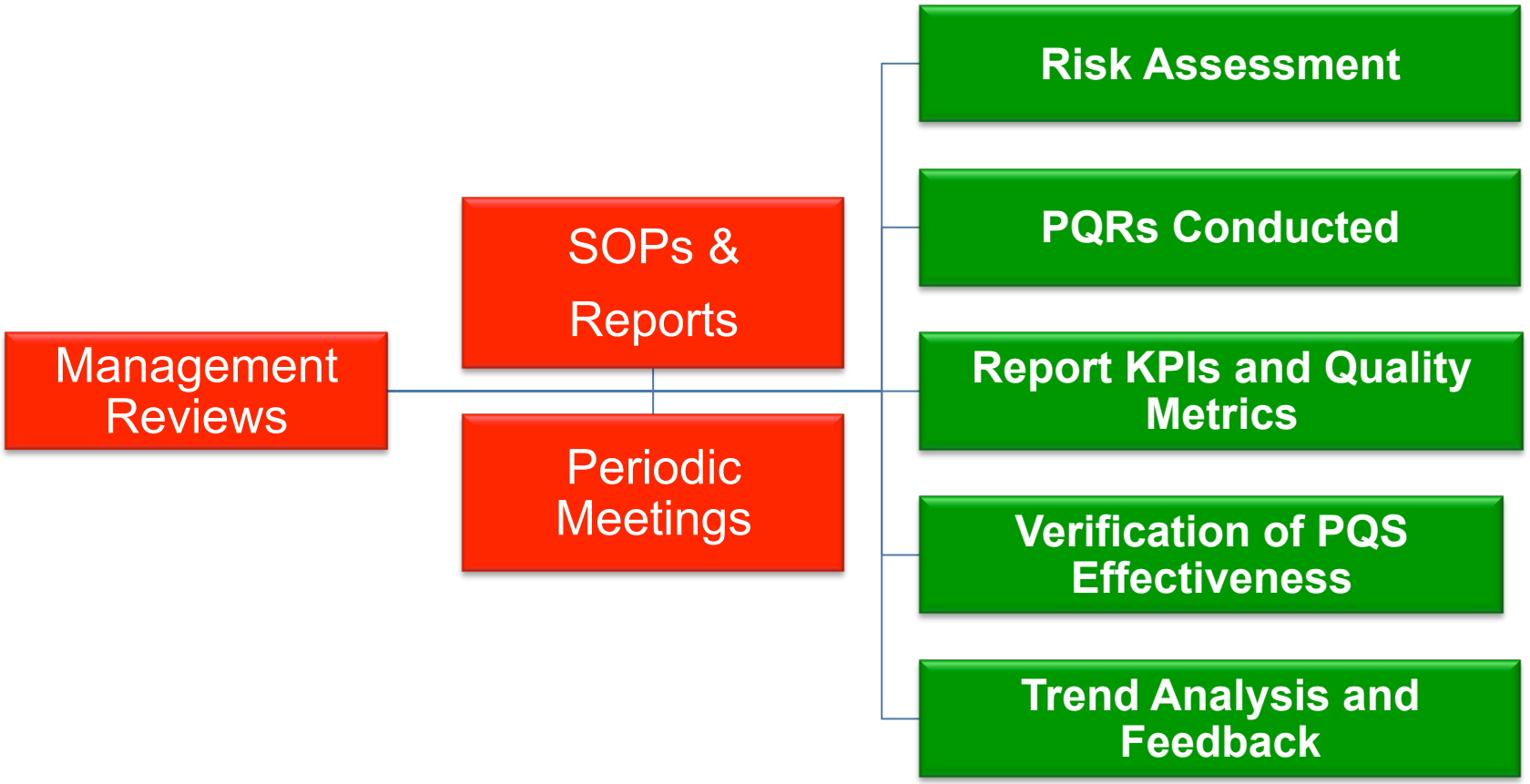
PQS, Compliance and Quality Organisation

- 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



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

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