Quality Management Systems

Clinical Research vs Manufacturing

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Agenda

- Examine the aspects of a robust QMS and a Quality Assurance Program.
- Review the QMS regulatory requirements and pharma industry standards as it pertains to clinical research vs manufacturing.
- Deep dive into the experiences and results of implementing a QMS and developing a quality culture in different types of pharma service environments.

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What Is a Quality Management System?

- Structured Approach

- Includes:
  - All processes
  - Metrics
  - Management review
  - Continuous Improvement Activities

- Change management program and Annual quality plans

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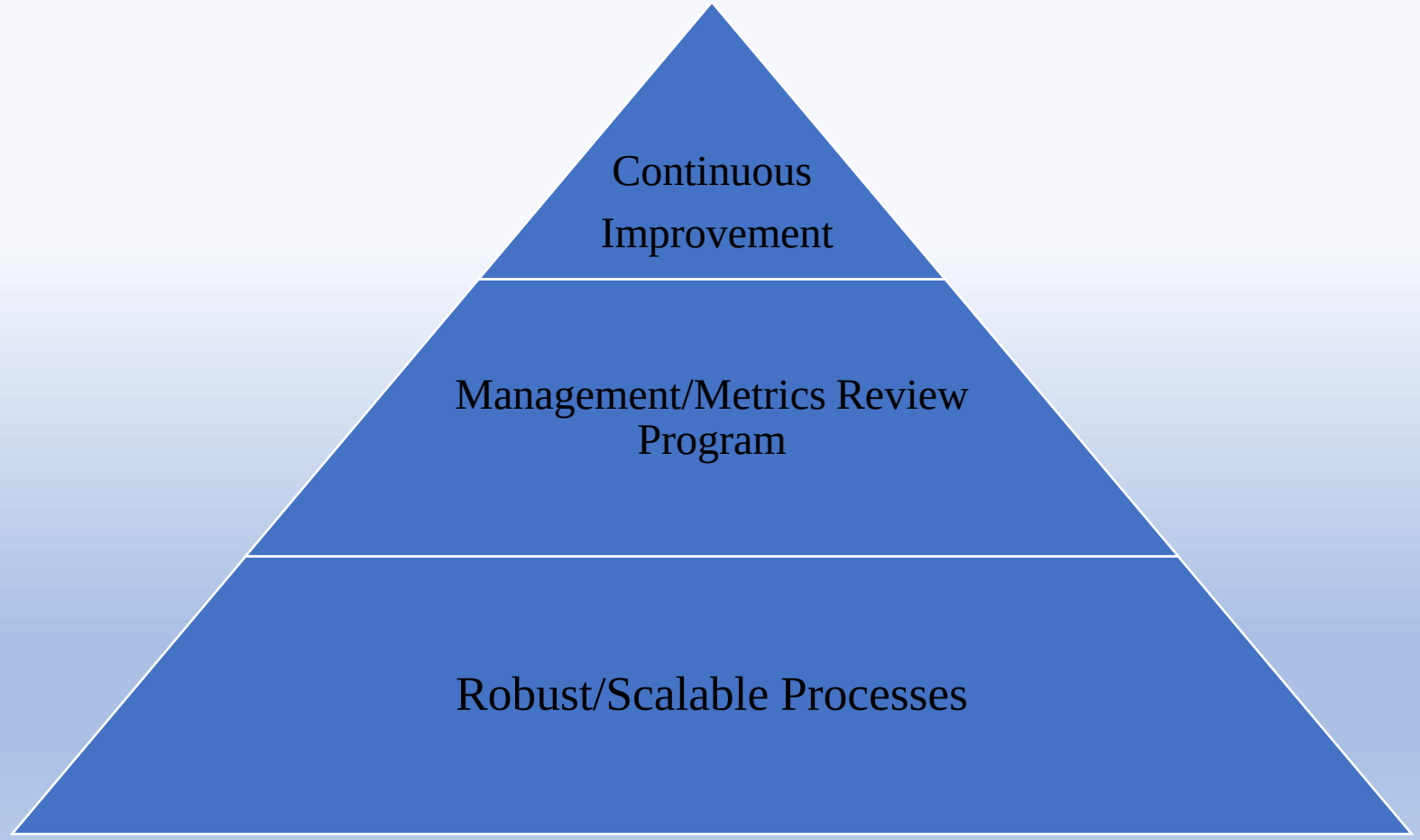
Quality Management System Hierarchy



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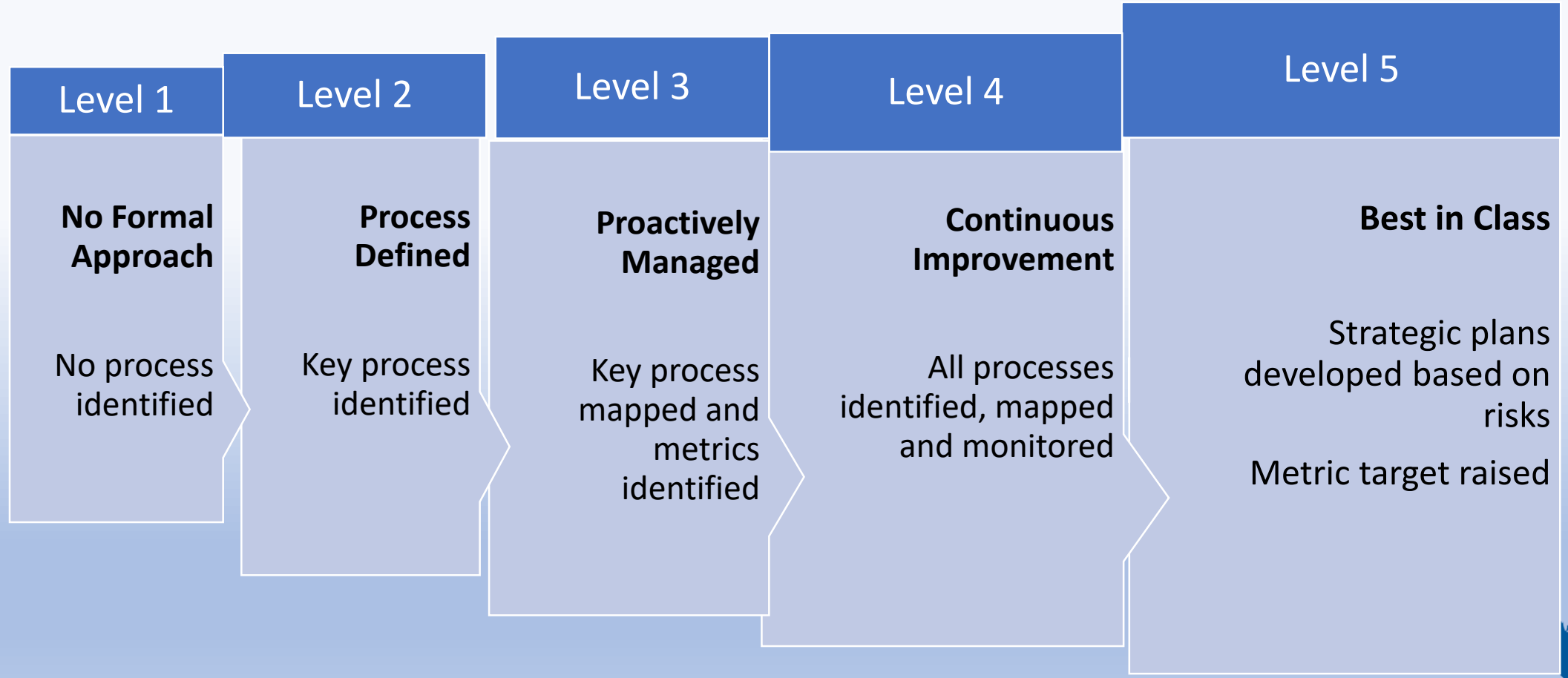
Quality System Maturity Model



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Developing Robust Quality Systems for Clinical Trials

Patient Safety and Data Integrity

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Quality in Clinical Research

Trial Protocol → Collection & Data Analysis → Trial Report

- Compliance to protocol
- Reliability of data to answer clinical question

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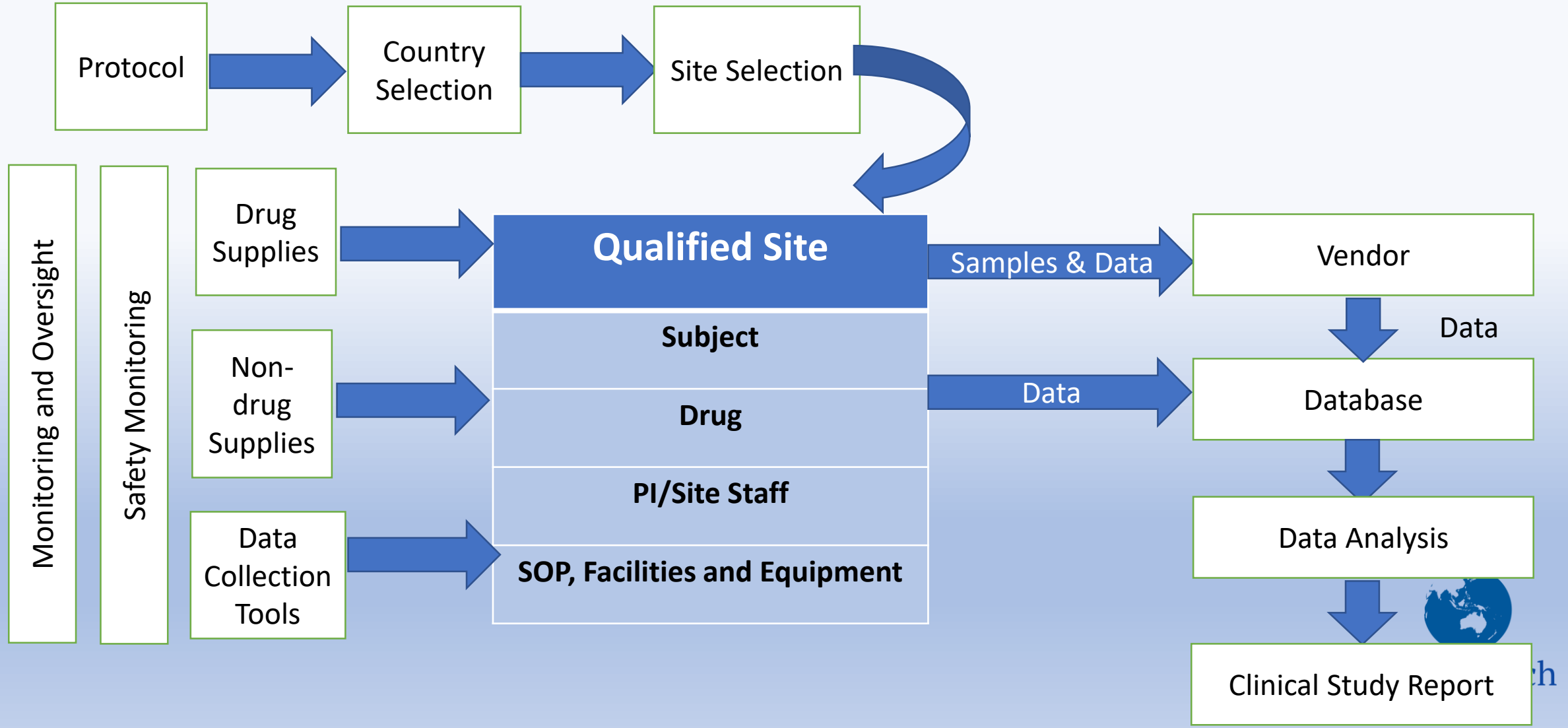
Overview of the Clinical Trial Process



Quality Management Plan

Sponsor develops a quality management plan concurrent to protocol development. Quality drivers are patient safety and data integrity.

- Overall Quality Management Plan
- Clinical Site Quality Plan

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Quality Management Plan

- Study Design/Plan
- Clinical Trial Site Readiness Plan, including Recruitment Plan
- Clinical Trial Lab Readiness Plan
- Monitoring Plan
- QC and QA Plan

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QC Plan

- QC is applied at each stage of data handling to ensure that data is Attributable, Legible, Contemporaneous, Original and Accurate (ALCOA).

- Systemic checks on compliance of trial process and the reliability and integrity of data

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QA Plan

Training and Document Management

- Staff on GCP, protocols, other documents and applicable regulations
- Management of documents and SOP

Vendor Management

- Qualified vendors & service providers for GXP activities
- Develop Quality Agreement
- Monitor Vendors

Auditing

- Develop strategic audit plans for sites
- Site audit (investigational sites, testing sites, data retention facility)
- For each site, rank each risk and adjust auditing plan

Quality Metric: Tracking of KPI and Continuous Improvement

Clinical Site Quality Plan

- Developed for each clinical research site for each study
- Managed by site coordinator and approved by principal investigator
- Identify and document on-going processes and activities
- Includes tools, checklists and templates for Quality Management
- Living document and is modified based on deviations
- Includes daily, quarterly and annual activities

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View of Regulators

Janet Woodcock's vision for Manufacturing Quality Systems:

"a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."

Similar quality system approach for clinical trials with full integration of quality and quality improvement

- Quality by Design (ICHQ8)
- Risk Management (ICHQ9)
- Quality Systems (ICHQ10)
- Data Integrity

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Building Quality into Clinical Trials

- **Say what you do:** Senior management develops policies, procedures, standards and protocols
- **Do what you say:** Communicate to affected staff, training, auditing
- **Prove it:** Risk based monitoring, risk-based auditing and trend analysis/ metrics from monitoring/auditing to ensure procedures/plans are followed
- **Improve it:**
  - Prioritize risks: (low, medium and high) based on patient safety and data integrity impact.
  - Implement holistic CAPA to broadly evaluate the issues and improve

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QbD and Risk Management

- FDA Guidance for Industry: Oversight of Clinical Investigations- A risk-based approach to monitoring (2013)
- EMA reflection paper on “Risk-based Quality Management”
- ICH Q8: QbD
- ICH Q9: Quality Risk Management
- ICH Q10: Quality Systems

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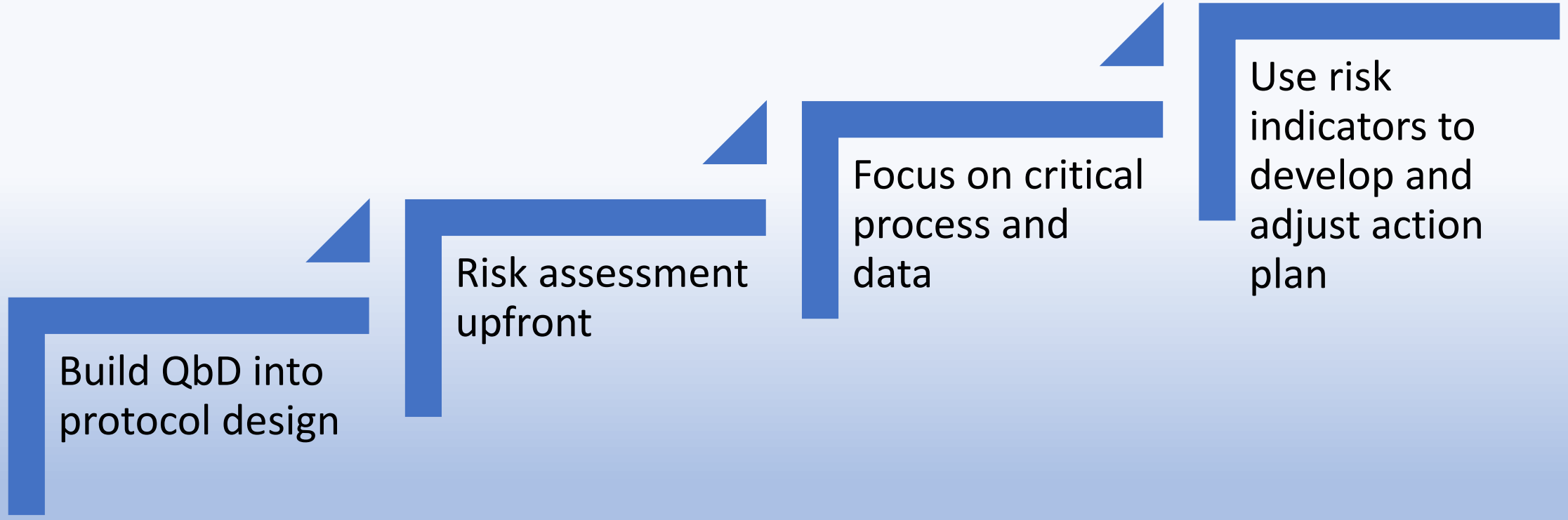
QbD and Risk Management



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Data Integrity in Clinical Trials

- Conduct data integrity risk assessment during protocol design
- Identify most appropriate approach for ensuring data integrity
- Review of audit trail for computer-controlled equipment

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Manufacturing vs Clinical Research Quality Systems

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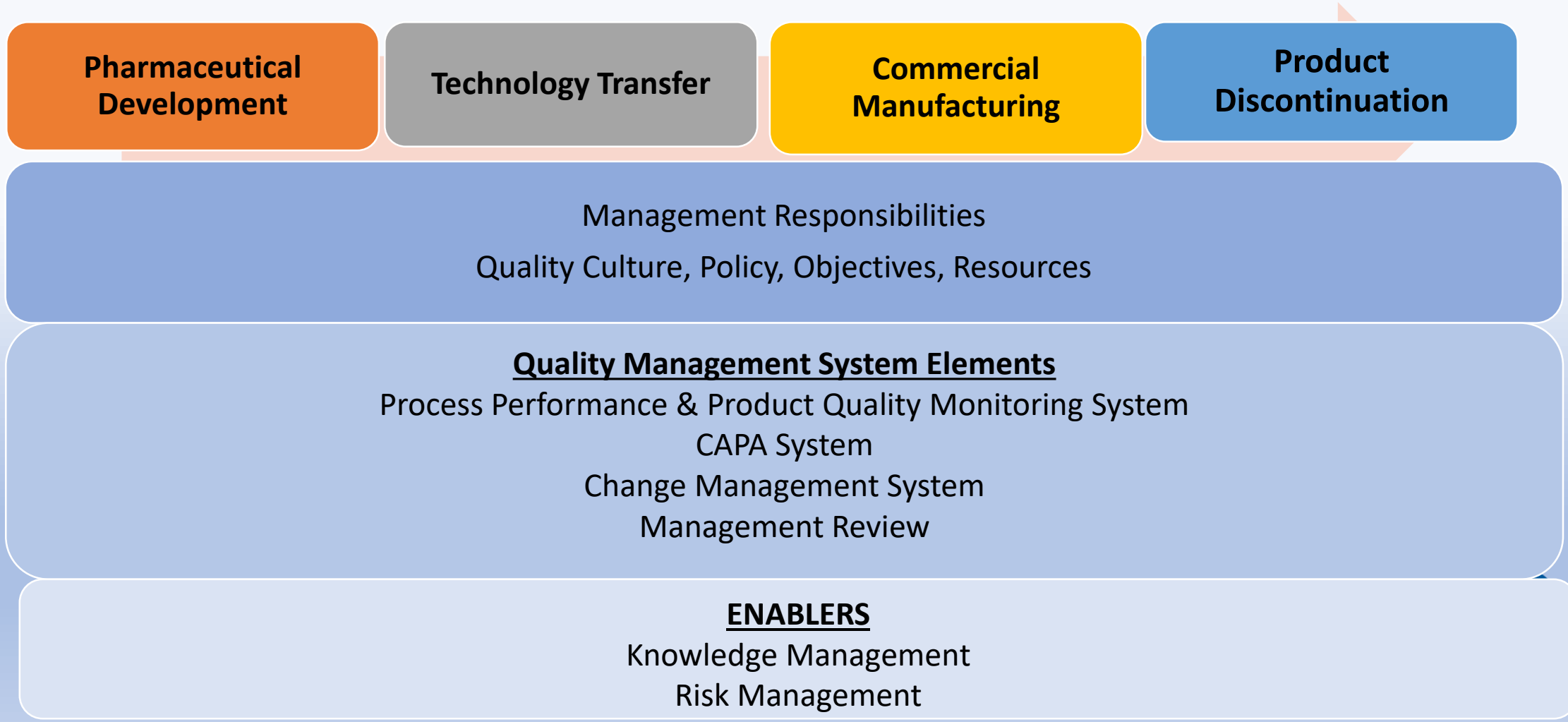
Pharmaceutical Quality System Model for Product Manufacturing Lifecycle



Framework for Manufacturing QMS

Management Controls

- Quality Policy & Quality Manual
- Metrics & Performance Dashboard
- Quality Management Review

Quality Systems

- Internal Auditing
- Regulatory Submission, Notification and Communication Process (BPD)
- Document Control
- Change Control
- Training
- Deviation Management
- CAPA

Quality Systems

- Risk Management
- Internal Auditing
- Product Release
- Process Data Monitoring and Improvement
- Supplier Management
- Production
- Facilities and Equipment Controls
- Materials Controls
- Packaging and Labeling
- Laboratory Controls

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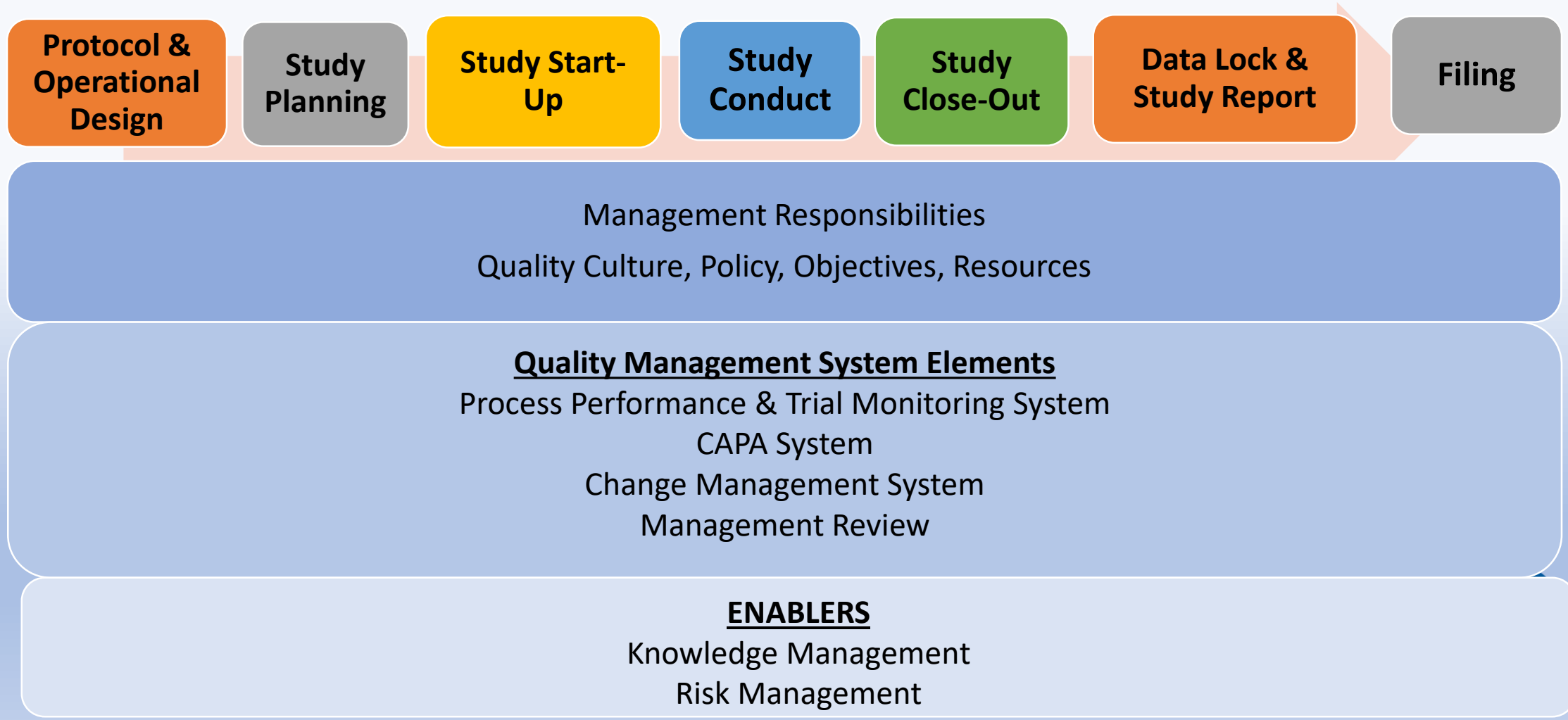
Pharmaceutical Quality System Model for Clinical Trial Lifecycle (GCP)



Framework for Clinical Study QMS

Management Controls

- Quality Policy & Quality Manual
- Quality Standards & Quality Culture
- Metrics & Performance Dashboard
- Quality Management Review

Quality Systems

- Supplier Management
- Vendor Qualification and Oversight Program
- GCP QA or Auditing (CRO, vendors, clinical sites)
- Adverse Event Program
- Good Documentation Practices

Quality Systems

- Document Control
- Change Control
- Training
- Deviation Management
- Root Cause Analysis
- CAPA
- Risk Management
- Issue Escalation
- Process Monitoring and Improvement (trends of deviations)
- Facilities and Equipment Validation
- Method Validation

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Manufacturing vs Clinical Research QMS

Manufacturing

- Manufacturing is a production where output is a material product
- Deviation to manufacturing process and testing
- Change to process and testing

Clinical Research

- Clinical research is protocol-based study where output is a study report
- Deviation to trial protocol
- Amendments to the approved protocol

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Comparison of Metrics

Manufacturing

- Deviation closure on time and deviation rate
- CAPA on time and effectiveness
- Customer complaint rate and on-time closure
- Adverse event rate (post-marketing)
- Training complete before task

Clinical Research

- Protocol or SOP deviation rate
- Error rate on informed consent form
- Dropout rate
- Adverse event rate (pre-marketing)
- Percent of subjects randomized that don’t meet inclusion/exclusion criteria
- Training complete before task

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Quality Culture

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What is Quality Culture?

- An environment
- Set of Behaviors
- Quality Culture is about knowledge-based decision-making
- Driven from the top of the organization

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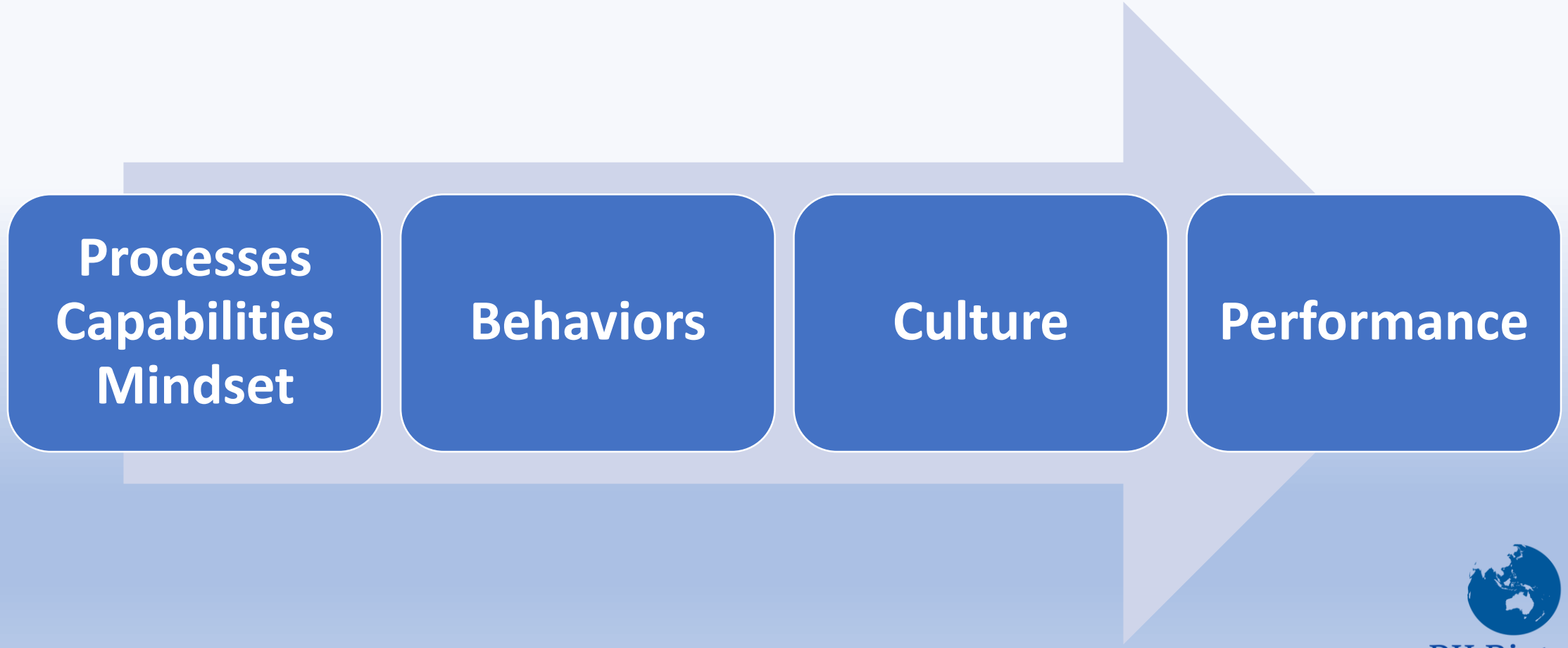
Quality Culture and Performance



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Quality Culture

System and Process	Capabilities or Organizational Competency	Mindset
• Robust manufacturing processes • Robust quality system with scientific decision making using QRM/product knowledge • Robust businesses process • Metrics and continuous improvement in place	• Adequate resources ensuring assigned responsibilities and authorities • Do employees have adequate skills, knowledge, experience, education & training?	• Is quality on the agenda? Are goals, objectives and priorities clearly defined? • Do people speak up about risks? Communication of quality issues at each level. • Is the quality mindset built into systems and processes?

Signs of Quality Culture

- Leadership
- Knowledgeable employees
- Robust QMS
- Strategic planning for Quality
- Operational excellence
- Less discussions about Quality and Compliance because it is done naturally

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Quality Culture

- The top issue for FDA observations for drugs has been inadequate procedure, procedures not followed etc.

- Root cause: lack of organizational quality culture

- Culture change in an organization is a journey and the leader's commitment and perseverance is critical to the success

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Quality Culture Transformation: Step by Step

- In-depth “As Is” analysis of the current quality culture.
- Establish “To be” state for quality culture.
- Identify the gaps and root cause analysis.
- Develop culture transformation plan

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PDA Assessment Tool:

5 Categories, 12 Attributes and 24 Sub-Attributes

1. **Leadership Commitment**
   - ***Leadership Commitment to Quality***
     - Accountability and quality planning
   - ***Enabling Capable Resources***
     - Feedback and coaching
     - Training and staff development
     - Rewards and recognition
2. **Communication and Collaboration**
   - ***Quality Communication***
     - Quality Communication
   - ***Collaboration with Auditors***
     - Collaborations
     - Operational readiness & knowledge Behaviors
3. **Employee Ownership**
   - ***Understanding Quality Goals***
     - Impact on product quality
     - Patient Impact
   - ***Safety Culture***
     - EHS Program
     - Targets
4. **Continuous Improvement**
   - ***CAPA Robustness***
     - Root Cause
     - Human Error
   - ***Management Review and Metrics***
     - Management Review
     - Metrics
   - ***Clear Quality Objectives***
     - Continuous Improvement
   - ***Internal Stakeholder Feedback***
     - Internal stakeholder feedback
     - Quality culture survey
5. **Technical Excellence**
   - ***Utilization of New Technologies***
     - Manufacturing Technology
     - New Technology
   - ***Maturity of Systems***
     - QMS processes
     - Maturity Model
     - Responsibilities

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ISPE Culture Excellence Assessment Tool

- 6 Cultural Excellence Dimensions:
  - Leadership and Vision
  - Mindsets and Attitudes
  - Assessment and GEMBA (Real place)
  - Monitoring and Measurement
  - Management Oversight and Reporting
  - Structural Enablers

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Conclusion

- Build robust processes and quality systems
- Identify quality and performance indicators
- Continuous improvement
- Develop quality management plans based on risks

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THANK YOU

QUESTIONS?

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