Designing and Developing Products to Meet Patient Needs

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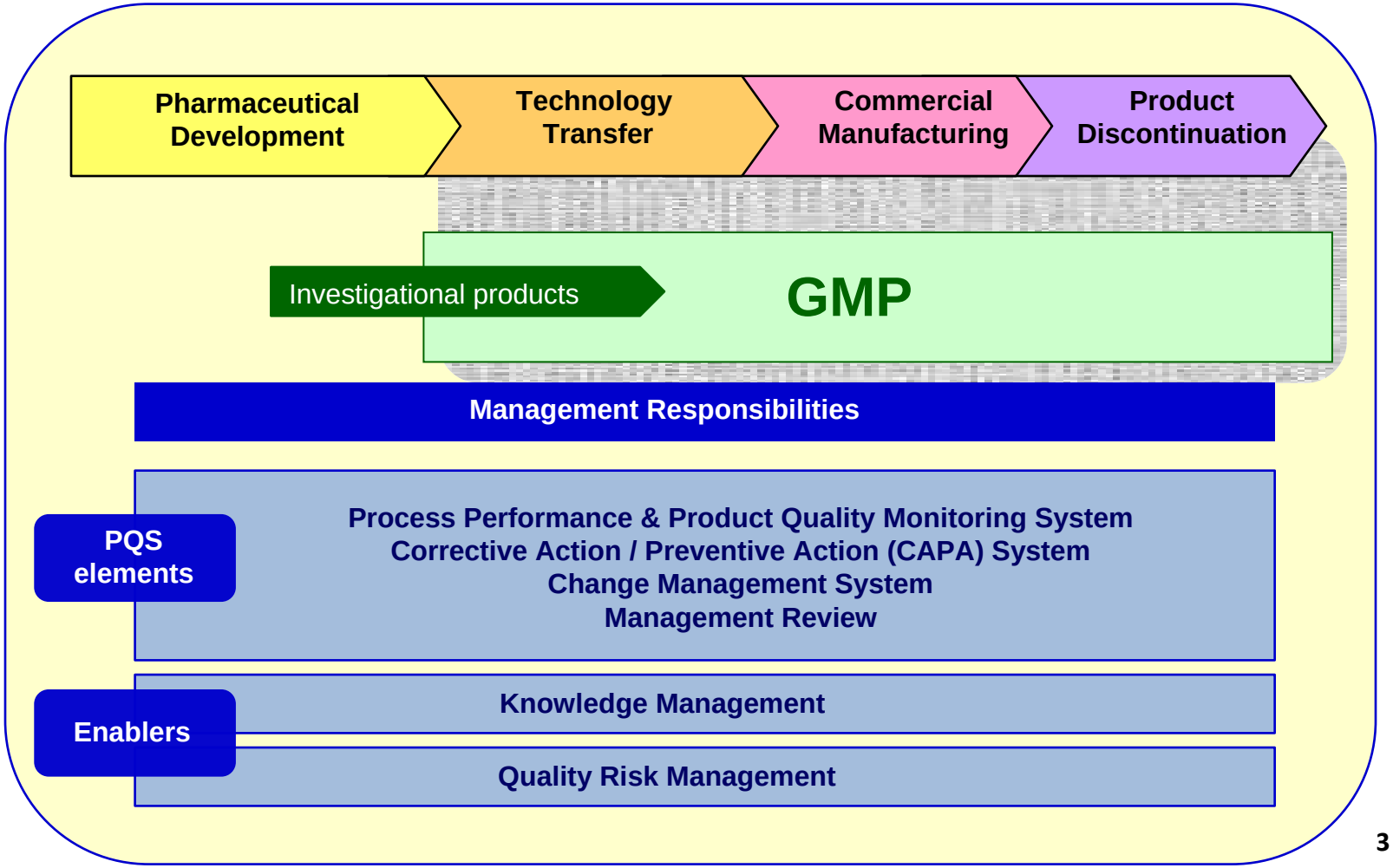
Outline

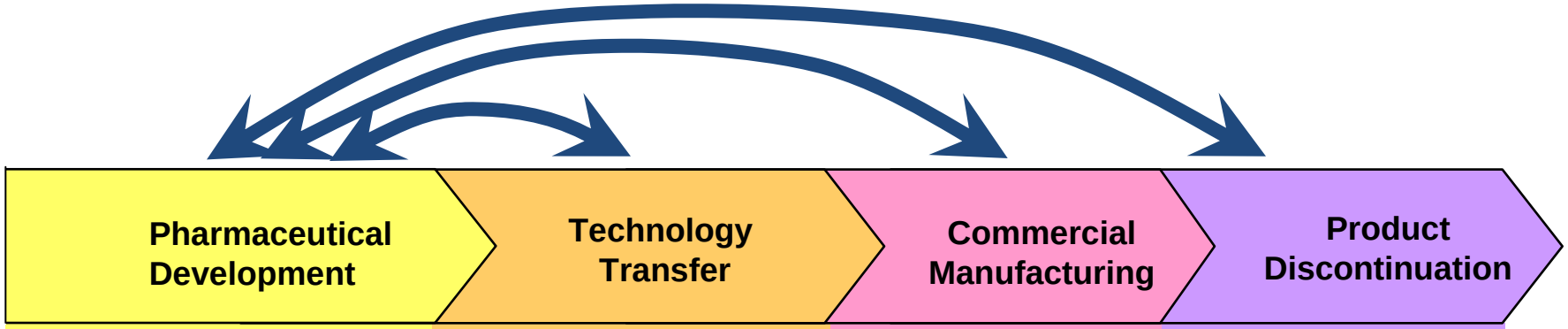
- How does pharmaceutical development fit into the Q10 paradigm?
- How do ICH Q8, Q9 and Q10 work together to ensure products that meet patient needs?
- What are elements of successful implementation?
- Concluding thoughts

ICH Q10 – Pharmaceutical Quality Systems



ICH Q10 – Pharmaceutical Quality Systems

Knowledge Management & Quality Risk Management



Pharmaceutical Development

- Drug substance development
- Formulation development
- Manufacture of investigational products
- Delivery system development
- Manufacturing process development & scale-up
- Analytical Method development

Technology Transfer

- New product transfers, Development to Manufacturing
- Marketed product transfers: Change in manufacturing or testing sites

Commercial Manufacturing

- Acquisition and control of materials
- Provision of facilities, utilities, equipment
- Production
- Quality control and assurance
- Release
- Storage
- Distribution

Product Discontinuation

- Retention of documentation
- Sample retention
- Continued product assessment and reporting

Knowledge Management and Quality Risk Management

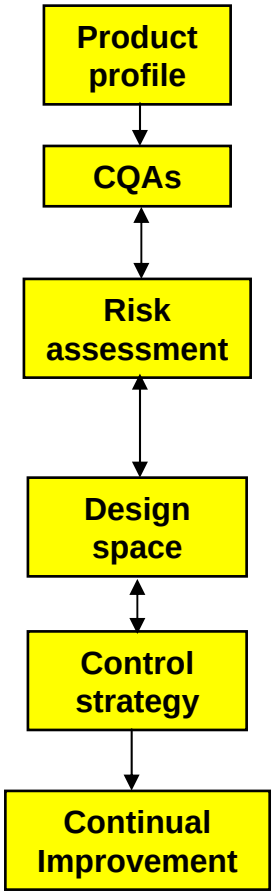
- **Knowledge Management** is "a systematic approach to acquiring, analyzing, storing and disseminating information related to products, manufacturing processes and components" (ICH Q10)
- **Quality Risk Management** is "a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle" (ICH Q9)

People Management

(Effective Integration & Collaboration)

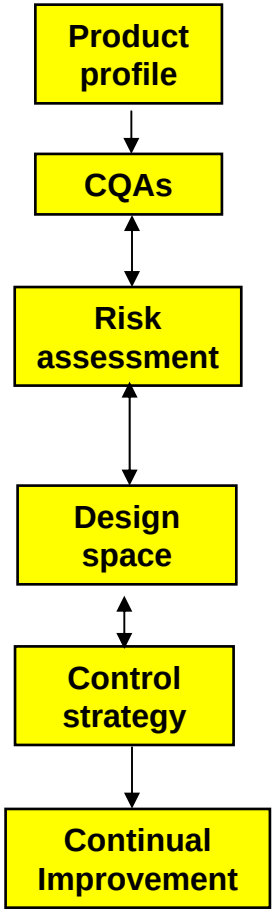
Integration of ICH Q8, Q9 and Q10

Example ICH Q8(R2) Approach



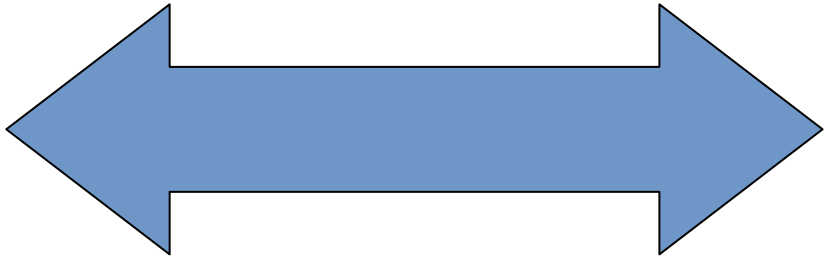
- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

ICH Q8(R2) "Enablers for Success" ICH Q10



Knowledge Management (Q10)

Quality Risk Management (Q9)



Quality Systems Infrastructure (Q10)

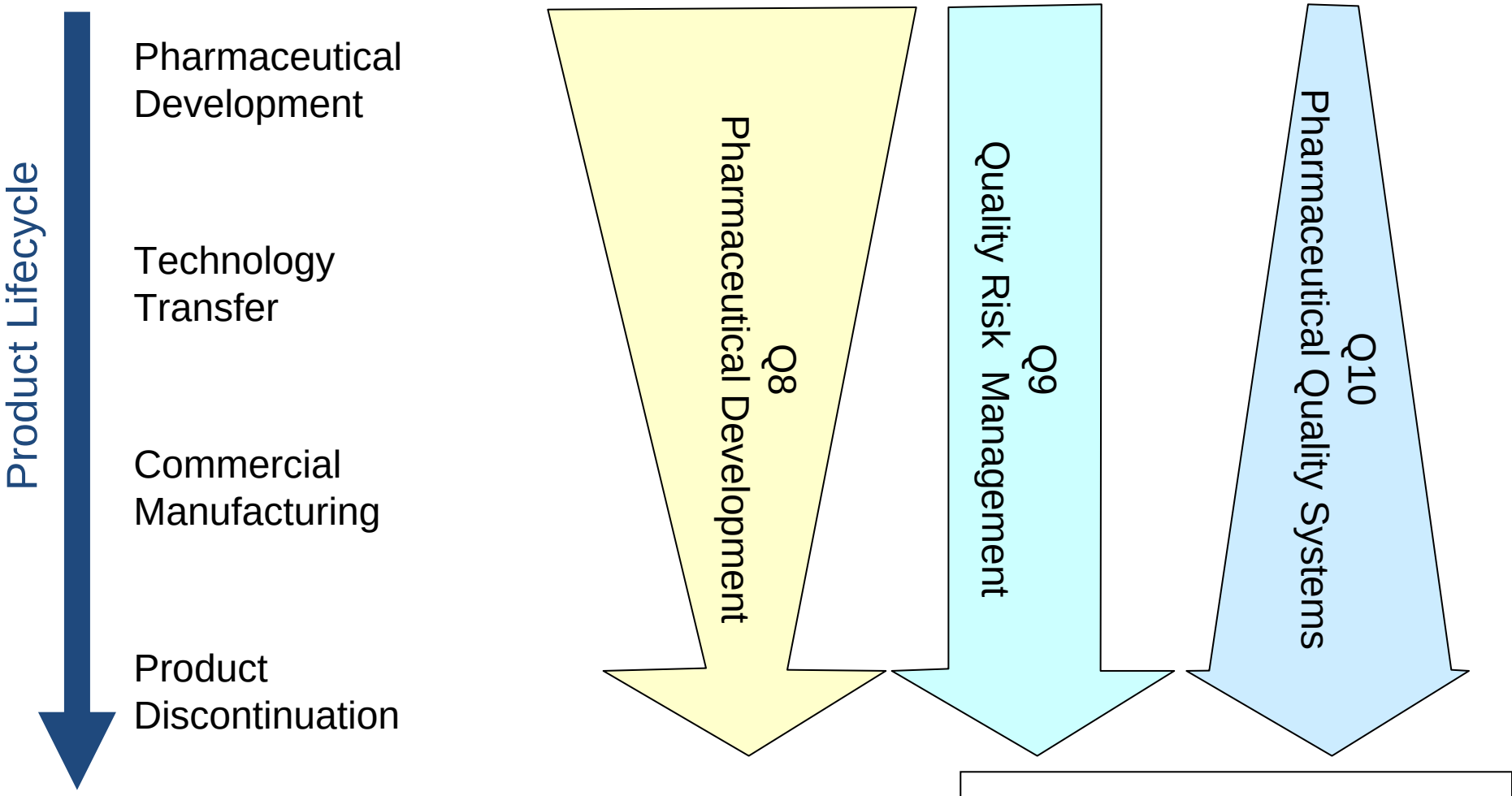
Integrated & Collaborative Working Environment

Product Realization

Establish and Maintain State of Control

Facilitate Continued Improvement

ICH Q8, Q9 and Q10 Working Together



Adapted from: ICH Quality IWG Workshop
Talinn (6/10) and Washington (10/10)

Formulation Development Activities

	ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
Quality Target Product Profile (QTPP)	• Clinical and non-clinical studies on drug substance: bioavailability, PK/PD, and safety	• Informal and/or formal risk assessment to evaluate patient needs and potential medication risks	• Knowledge Management / Prior Knowledge (relevant information to support the understanding, risk assessment, scope of DOE) - Laboratory note book documentation - Development report - Etc…
Pre-Formulation Studies	• Characterization of drug substance (physical properties) • Chemical stability of drug substance, degradation and potential formulation interactions • Development of analytical tests	• Determine failure modes and risk factors for drug substance physical and chemical stability	
Formulation Screening	• Excipient compatibility • Dissolution method development • Screening DOEs	• Determine failure modes and risk factors for excipient interactions	
Formulation Optimization and Selection	• Excipient and drug substance material property & characterization • DOEs for excipient amounts • Stability of drug product and storage conditions • Develop IVIVC relationships	• Opportunities for formal risk assessment	

From: ICH Quality IWG Workshop
Tallinn (6/10) and Washington (10/10)

Process Development Activities

	ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
Process Screening	• Exploration of unit operations • Characterization of process intermediates	• Determine failure modes, risk factors for unit operations and rank risk	• Batch records and operational guidelines for manufacturing • Tech Transfer report • Identification and selection of suppliers that meet raw material needs
Process Development and Optimization (Lab Scale)	• DOEs for process parameters and interactions with material attributes • Development of Design Space • Operational ranges for scale-independent parameters • understanding of critical process operations	• Screening risk assessment to determine potential parameters impacting product quality (e.g., Ishikawa) • Determine critical process steps, process parameters and material attributes (e.g., FMEA) • Potential issues of scale	
Process Development and Optimization (Pilot Scale)	• Pilot to verify lab scale knowledge • DOE and modeling effects of scale • Development of design space • Development of on-line measurement technologies	• Development of control strategy to control risks incl. for scale up	

From: ICH Quality IWG Workshop
Tallinn (6/10) and Washington (10/10)

Technology Transfer

ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
• Gain product and process knowledge • Knowledge supports transfer between development and manufacturing to achieve product realization	• Forms the basis for the manufacturing process • Improves effectiveness of control strategy • Contributes to processes validation and ongoing continual improvement	• Advance understanding through scale-up activities • Provide preliminary indication of process performance and successful integration into manufacturing • Gain knowledge from transfer and scale up activities to enhance the basis for the control strategy

From: ICH Quality IWG Workshop
Tallinn (6/10) and Washington (10/10)

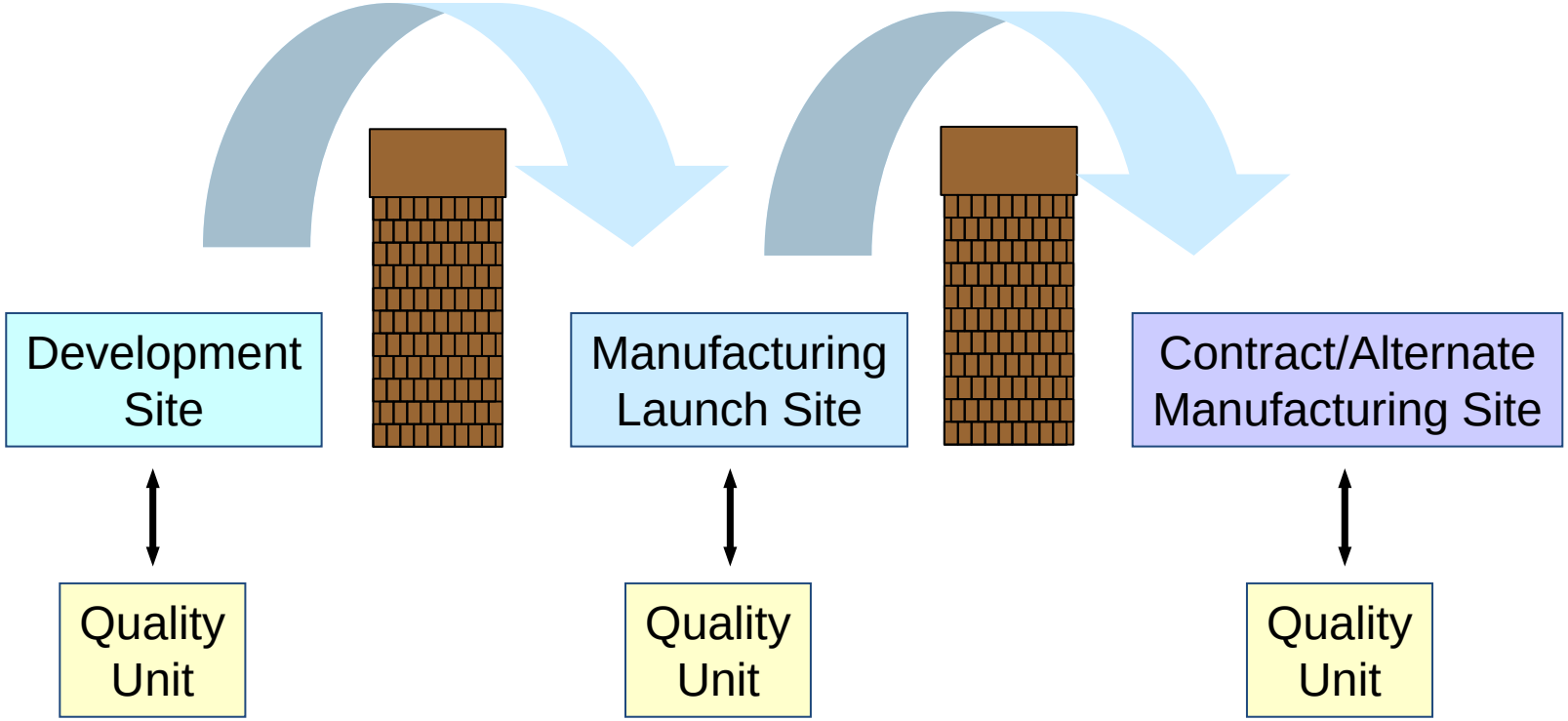
Commercial Manufacturing Activities

	ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
Commercial Scale Manufacturing for Drug Product	• Definition of commercial process design • Commercial scale runs to verify process design, with additional sampling to verify understanding • Implementation of on-line measurement technologies	• Development of a control strategy for commercial manufacturing, including in-process controls, end-product testing, raw material controls and change control • Check procedures in the PQS regarding risk from Process specific procedure (e.g., sampling plans, design space and model verification, change control for movement within design space)	• Process-specific operating procedures (e.g. sampling plans, design space etc.) • Documentation to support on-line testing methods • Validation to demonstrate process and analytical method reproducibility • Storage of development reports, risk assessments
Continual Process Verification and Continual Improvement	• On-going analysis and trending process data (MVA, SPC, etc.) • Evaluation of process changes and associated effect on intermediates and products	• Manage risks of process or material attribute change (including changes within or outside of design space) • Review risks in audits/inspections and implement risk-based CAPAs	• Procedures on process monitoring and action limits • Change control procedures including how and when to do risk assessment for process changes and evaluation of the change • Maintenance and update of knowledge management

From: ICH Quality IWG Workshop
Tallinn (6/10) and Washington (10/10)

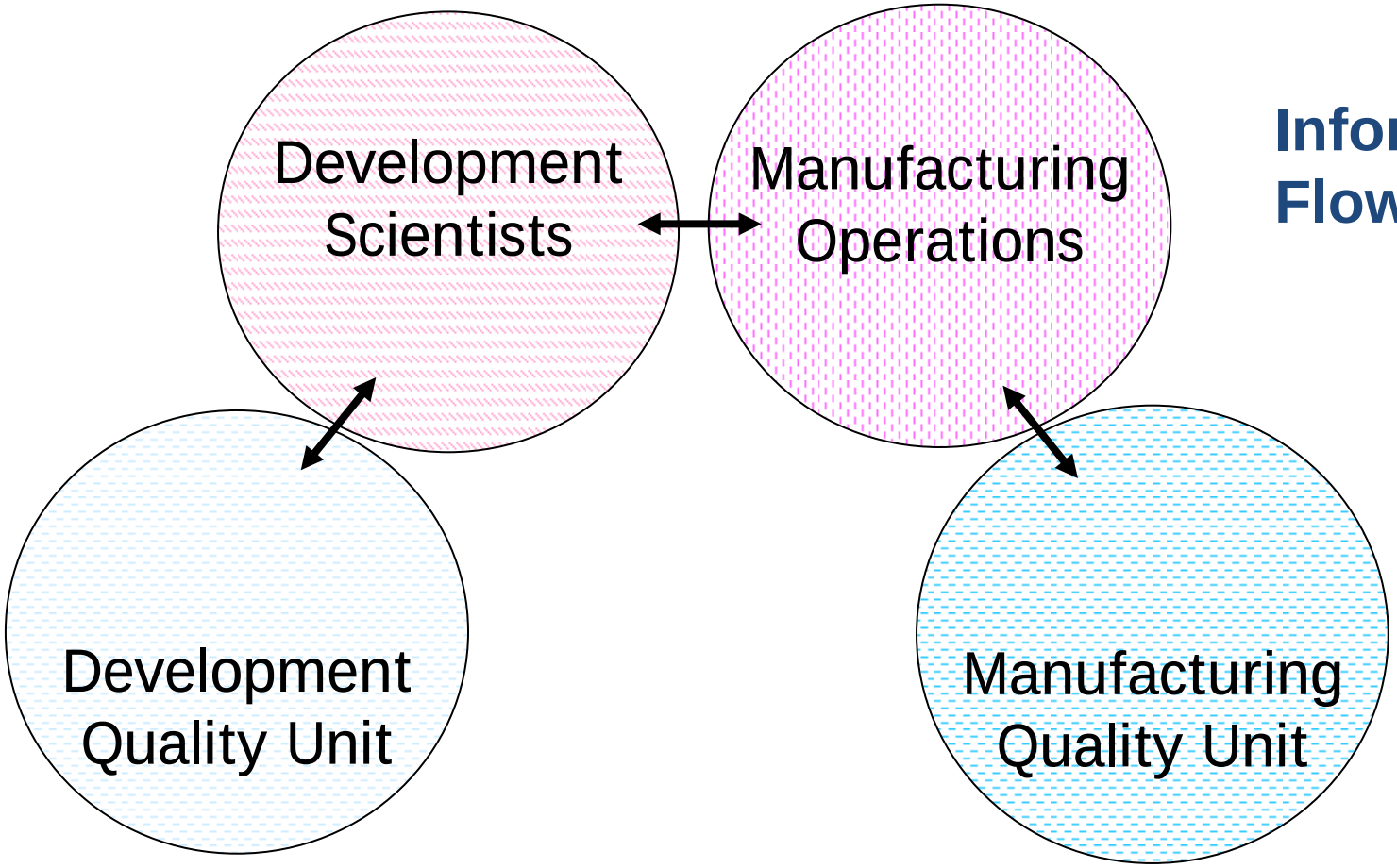
Integration and Collaboration to Assure Pharmaceutical Quality (Industry and Regulators)

Pharmaceutical Lifecycle – Traditional Approach



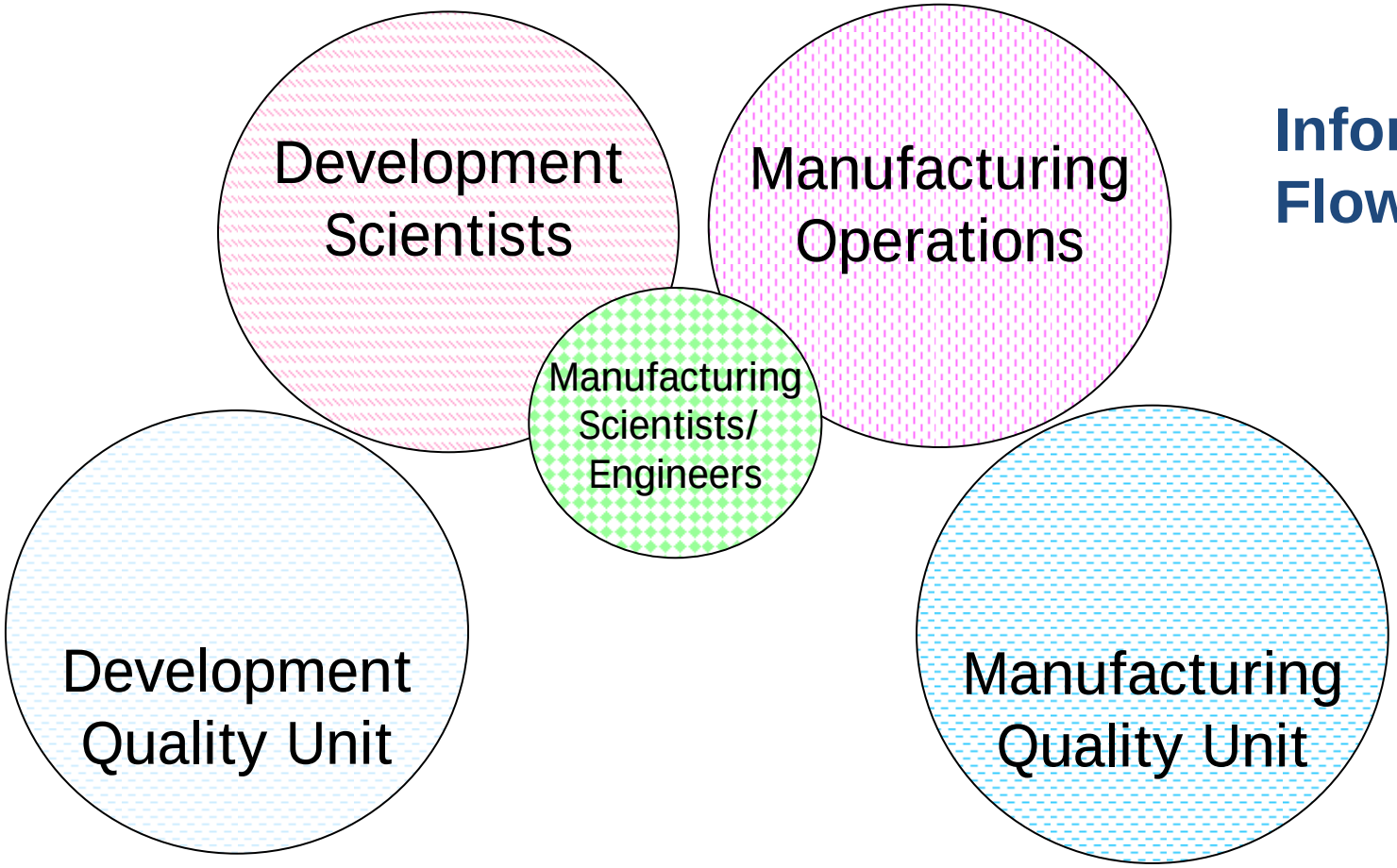
- Traditionally, little integrated communication between organizations
- Different goals in different organizations (timelines, budgets, priorities - process robustness vs. yield)

Traditional Approach for Industry



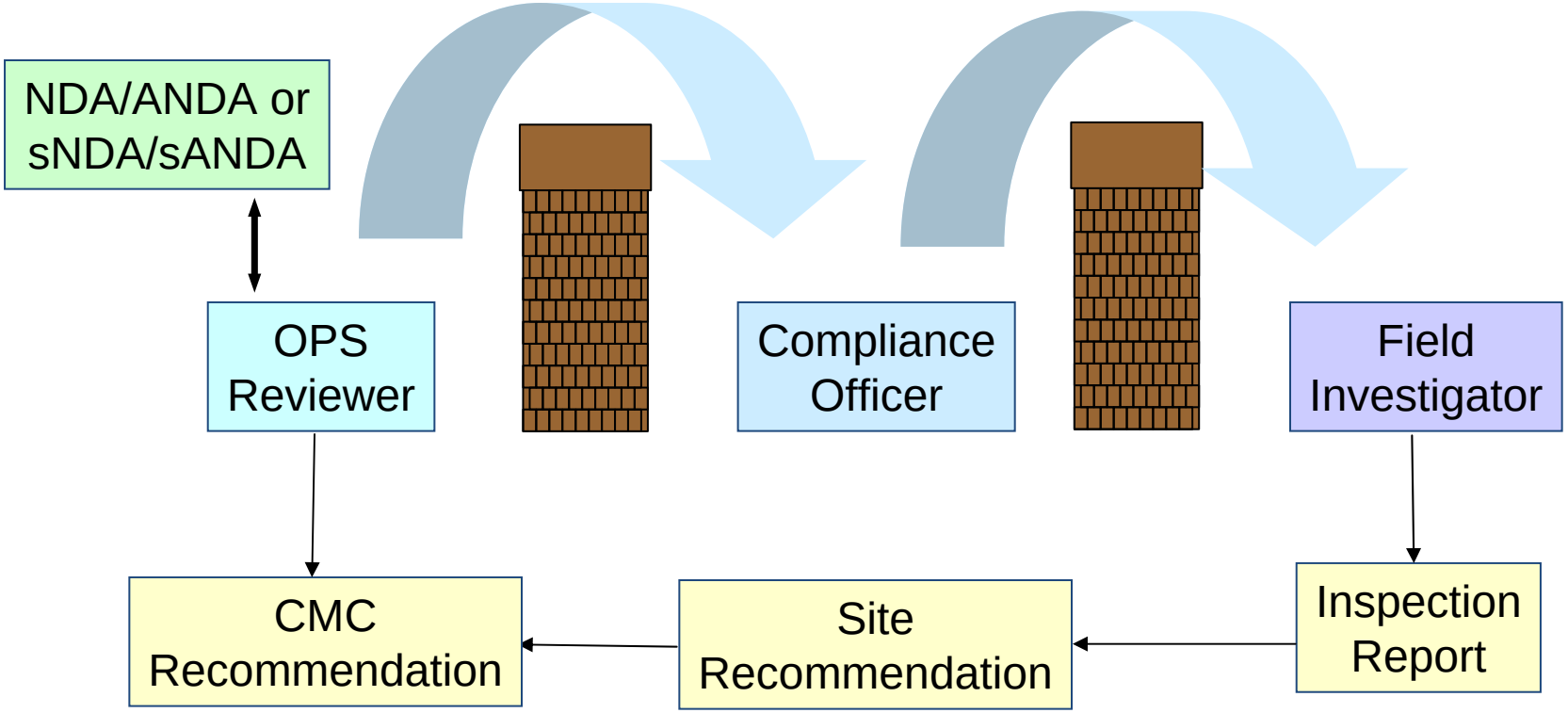
Information Flow

Integrated Approach for Industry



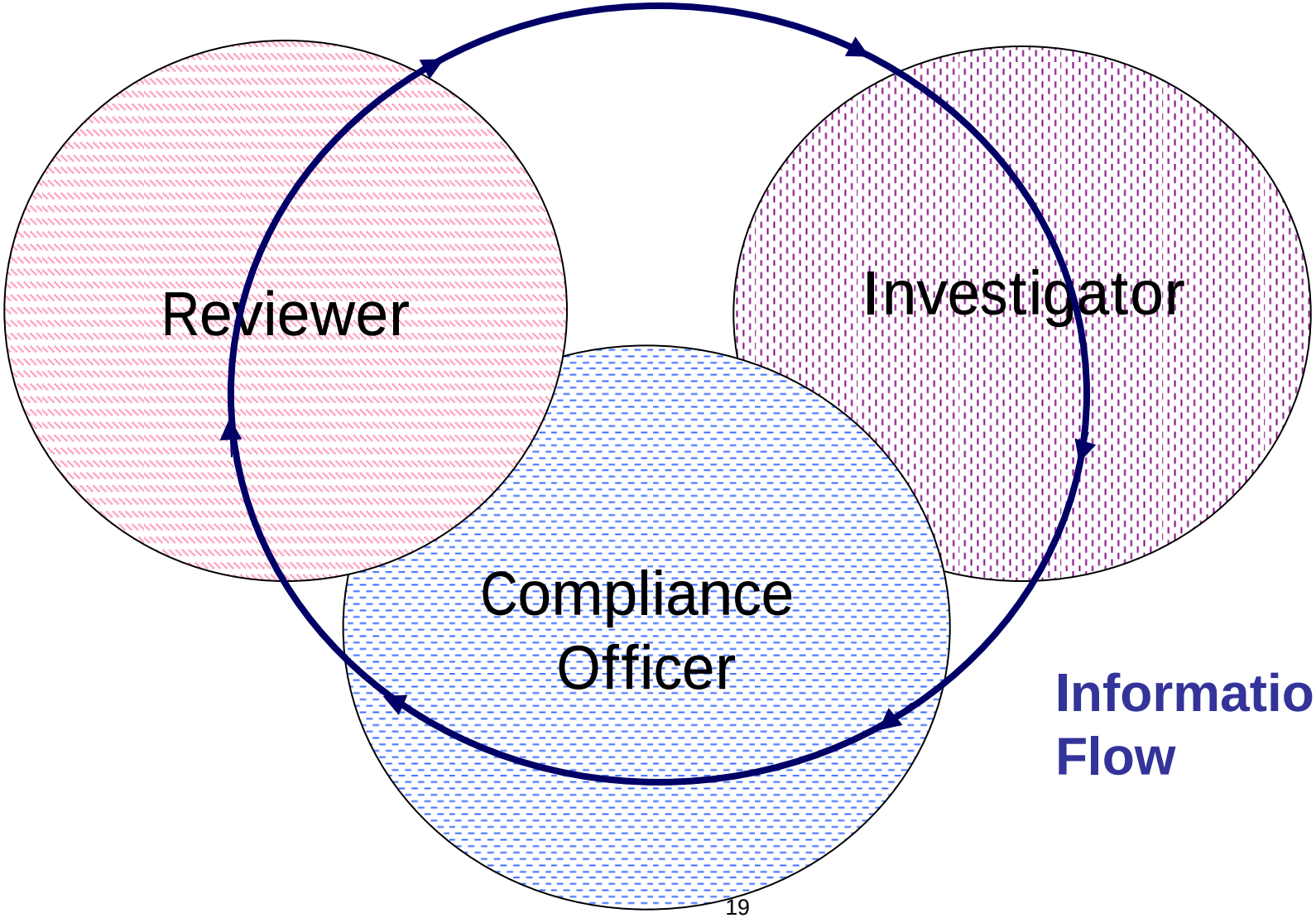
Information Flow

Application – FDA Traditional Approach



- Traditionally, little integrated communication between organizations
- Different goals in different organizations (timelines, priorities)

Integrated Approach for Regulators (FDA)



Information Flow

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Collaborative Working Environment

No silos

No gatekeepers

Open Information Sharing and Teamwork

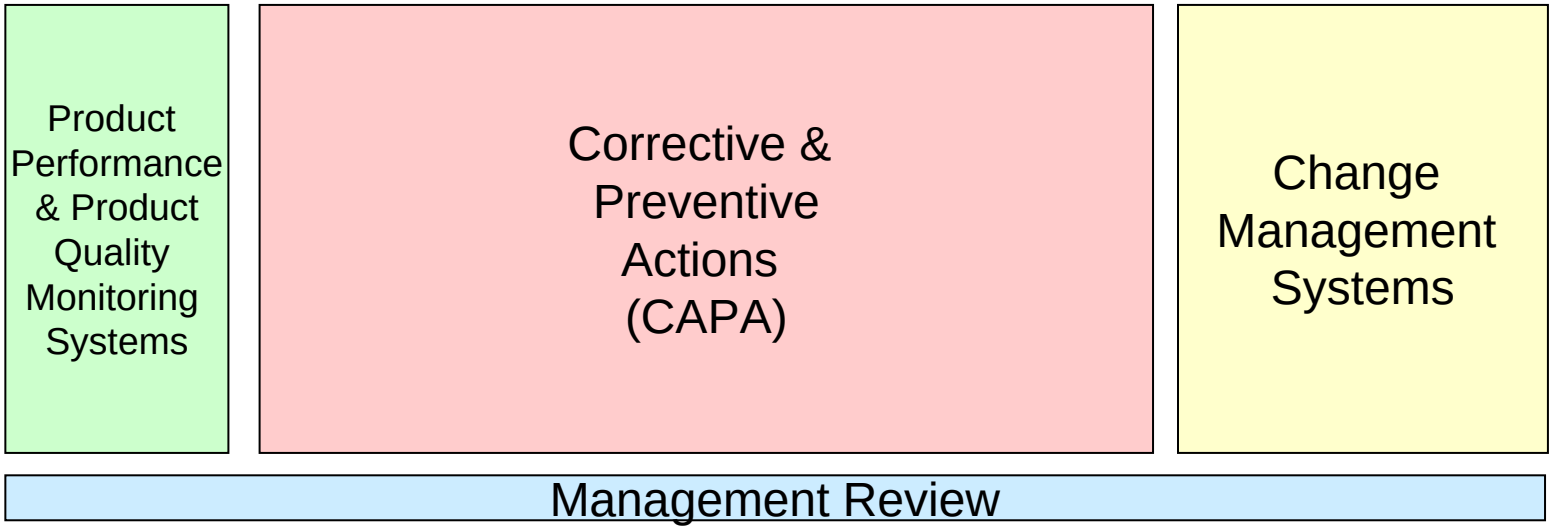
Applies to both Industry and Regulators

Collaborative Working Environment to Support Pharmaceutical Quality

- Understand and respect the roles and needs of colleagues
- Engage in open and early communication
- Collaboratively develop risk assessment and management plans
- Develop, maintain and utilize a system for knowledge retention
- Anticipate and plan for problems
- Develop a “Culture of Quality”

Pharmaceutical Quality System Elements (Q10)

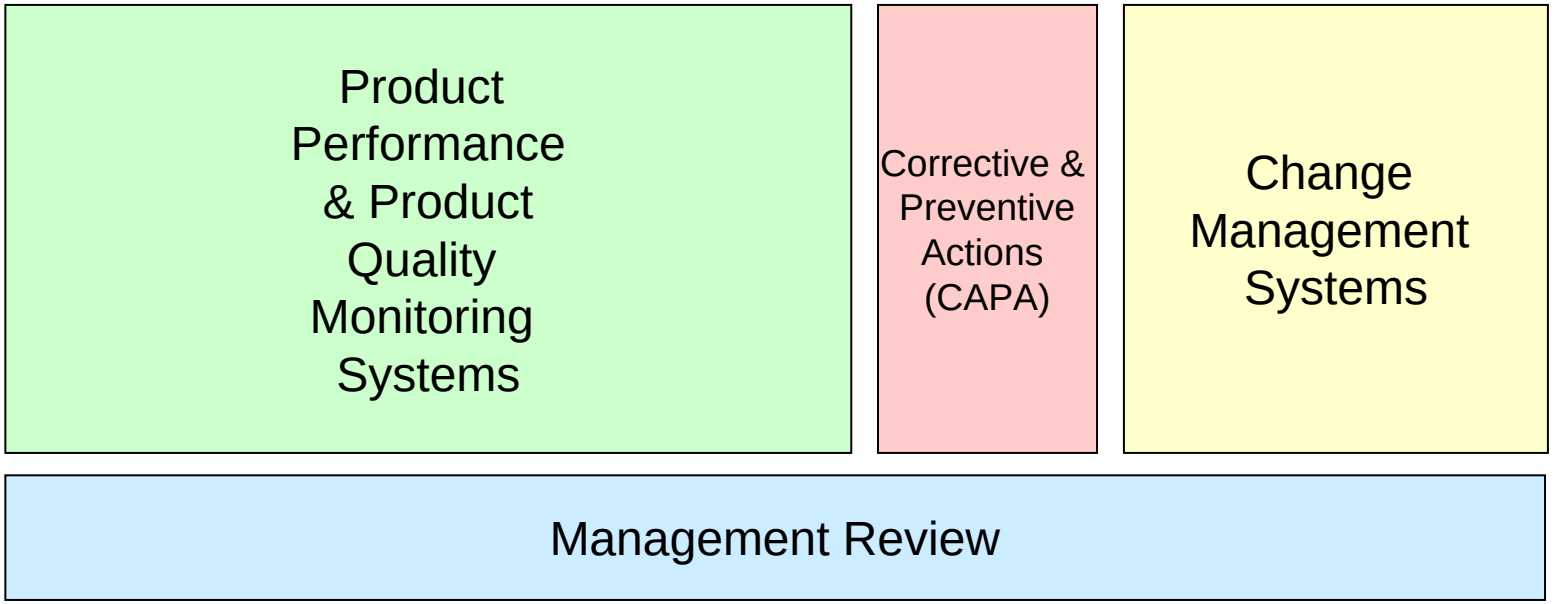
Traditional Approach



Reactive Approach

Pharmaceutical Quality System Elements (Q10)

Q10 Approach



Proactive Approach

Benefits of Integration - Regulators

- More risk focused inspections
  - Reviewer knowledge shared with investigator to facilitate quick understanding of product and process related risks
  - Compliance knowledge shared with investigator to facilitate understanding of facility related risks
  - Participation of reviewers and/or compliance officers in more inspections
- Better informed review
  - Better understanding by reviewers of how PQS supports product quality
  - Feedback from field related to product quality issues
  - Better ability to understand firm's approaches to changes in supplements

Increased efficiency and effectiveness

Future Directions on FDA Integrated Approach

- CDER is working toward enhancing integration between review, inspection and compliance
- Additionally, CDER is building its quality systems, including those related to inspection
  - Knowledge management
  - Communication
  - Defined procedures
- Joint training programs enhance learning and networking with reviewers, compliance officers and investigators
  - Pharmaceutical Inspectorate Program
    - Classroom training
    - Level 3 Rounds
  - External training (e.g., ICH training)
  - Internal training (e.g., Continuous manufacturing workshop)

Concluding Comments

- ICH Q8, Q9 and Q10 are linked together to provide a systematic, modern risk- and science- based approach to pharmaceutical manufacturing and development
  - Relevant for all drug products throughout product lifecycle (new, legacy and generic drugs)
- Knowledge Management, Quality Risk Management in the PQS and Integration/Collaboration are enablers for delivering products that meet patient needs over the product lifecycle
- Better integration between work units and functions will support enhanced product quality both for Industry and Regulators

Acknowledgments

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