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ICH Q12 - Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Training Material - Module 6

- Pharmaceutical Quality System (PQS) and Change Management
- Relationship between Regulatory Assessment and Inspection

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Overview of the Training Material Chapters 6 and 7

- **Role/importance of a Pharmaceutical Quality System (PQS)**
- **Basis for an effective PQS**
- **Responsibility for the maintenance of an effective PQS**
- **Inspection and regional requirements**
- **How is Change Management (Ch Mgt) a critical element of the PQS?**
- **Communication between Regulatory Assessment and Inspection**

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Role/Importance of a PQS

- A Quality System (QS) is defined in ICH Q9 as ***"The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met"***

- To complement ICH Q9, Q10 defines the PQS as the ***"Management system to direct and control a pharmaceutical company with regard to quality."***

- From ICH Q7 ***"Quality Assurance (QA): The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained."***

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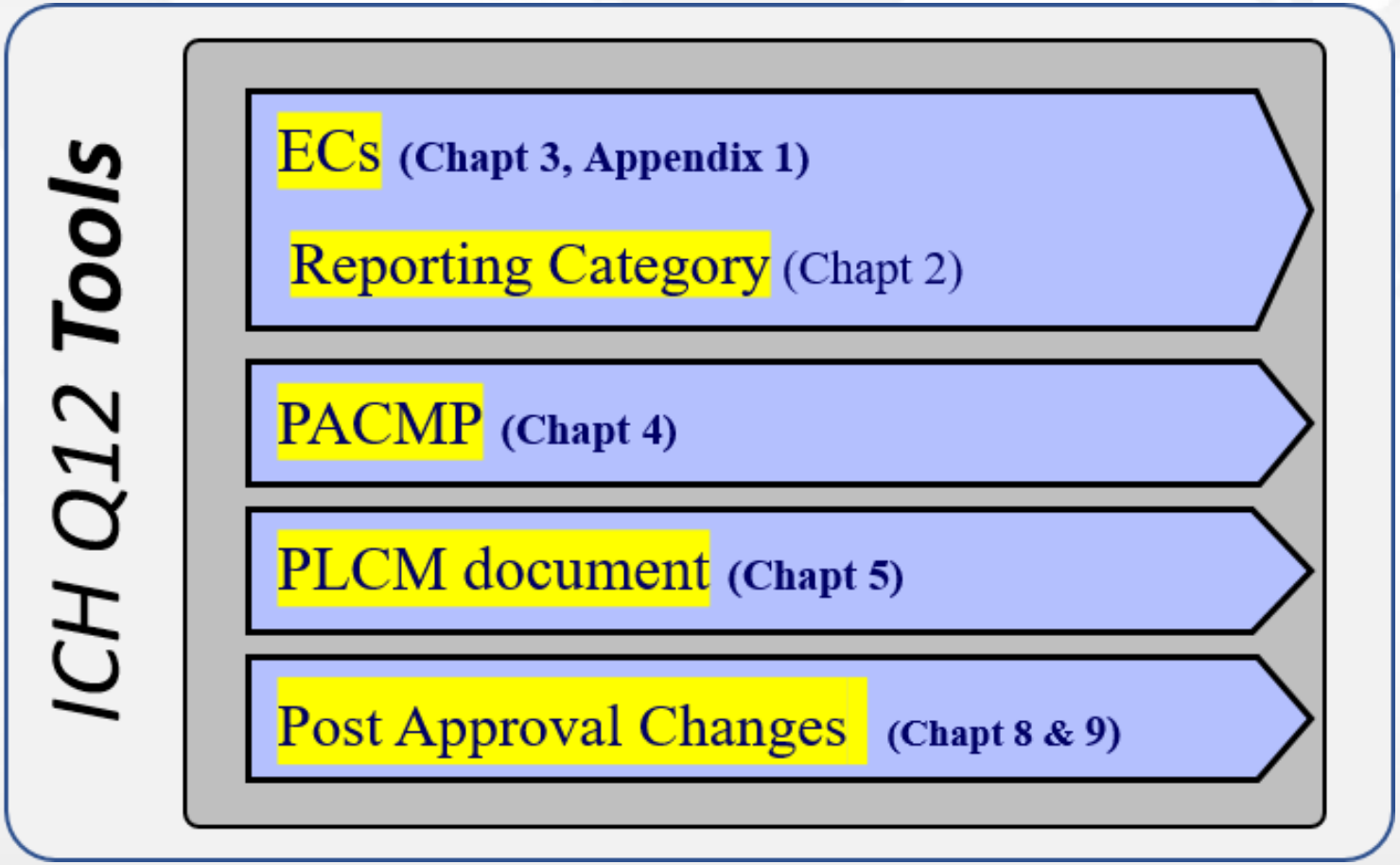
Role/importance of a PQS

An effective PQS is the foundation for implementation



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What aspects of the PQS should be considered to support the use of Q12 tools?

- **Effectiveness and Compliance?**
  - PQS should be effective, as described in **Q10**
  - PQS should be in compliance with ***regional GMP requirements*** where the application is filed
- **Across the entire Supply chain?**
  - Including the effective PQS of the stakeholders
- **Across the product life cycle?**
  - Ch Mgt across supply chain and product lifecycle
  - Effective Ch Mgt: step-by-step description
  - Use of Knowledge Management in Ch Mgt
  - Management review to be considered for an effective Ch Mgt

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Responsibility for the maintenance of an effective PQS and associated inspection

- **PQS maintenance is the responsibility of the company – this includes:**
  - Manufacturing sites and/or
    - Corporate Quality Management
    - MAH where relevant
- **Inspections will continue as foreseen by regional regulatory requirements**
  - **No intent** to require a specific inspection assessing the state of the PQS before the company can use the principles and tools in ICH Q12
  - A manufacturing site can be considered to be in general GMP compliance while resolving deficiencies that do not require regulatory action. In the event that such deficiency has an impact on the ***effectiveness of the change management in the PQS,*** may there be a restriction on the ability to utilise flexibility in this guideline.

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Change Management Across the Supply Chain

Company has to manage communication of information and interactions of PQSs across multiple entities (Internal and External).

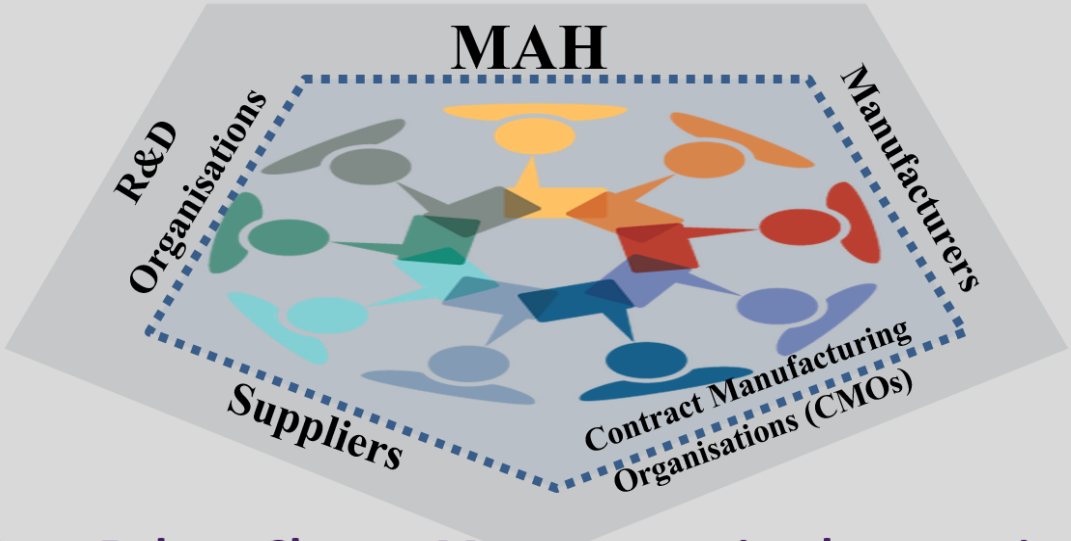
Implementation of robust change management across multiple sites (outsourced or not) is necessary.

The change management activities should be considered to support the approaches defined in the guideline.

Change Management across Supply Chain

Supply chains multiple Stakeholders

Effective interaction to effectively utilize knowledge



For a Robust Change Management implementation

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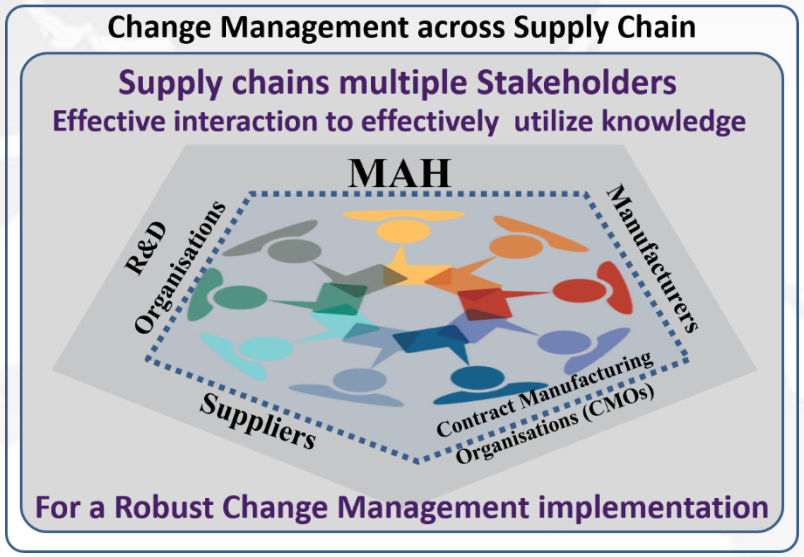
Change Management Across the Supply Chain

Change management activities to be considered:

- **Change to ECs**: Communicated in a timely manner
  - Between MAH and the regulatory authority
  - Between MAH and the manufacturing chain
- **Timeliness of communication**:
  - Driven by the impact of any change related to **ECs**
  - Targeting the relevant entities in the supply chain



- **Drivers for change : Process knowledge, Continual improvement**, **QRM outcome**
  - Example: CMO proposing process improvements (Control and product consistency). Data generated to be used to revise **ECs** and associated **PLCM documents** if necessary
- **Communication mechanisms related to MAA changes and GMP issues**
  - Should be defined in relevant documentation (including contracts with CMOs, e.g., Quality Agreement) and all communications should be available for management review (see ICHQ10)
- **Critical failure in PQS anywhere in the supply chain may impact the ability to use the tools in the guidelines**
  - Should communicate such failures to affected regulatory authorities

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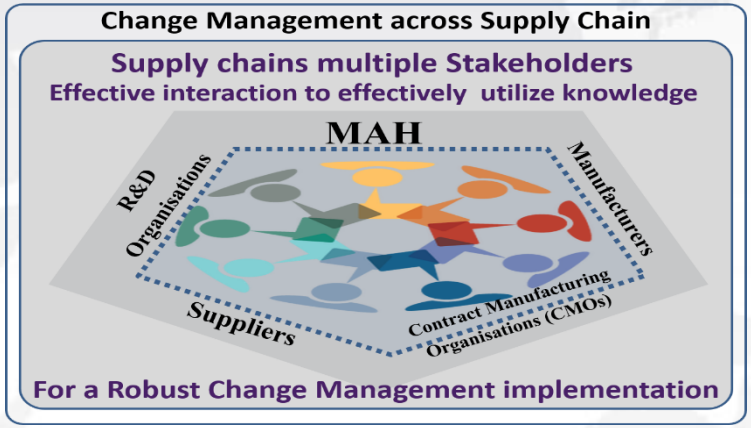
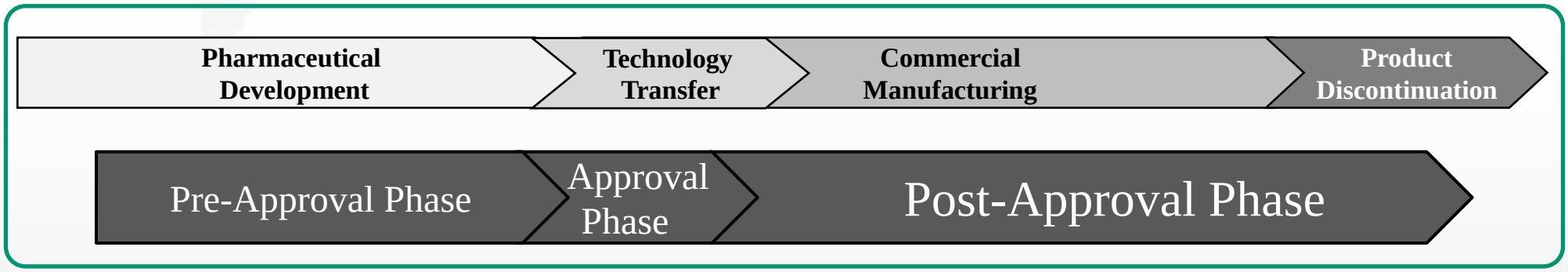
Change Management across the supply chain



And all along the product life cycle

Change Management all along product lifecycle



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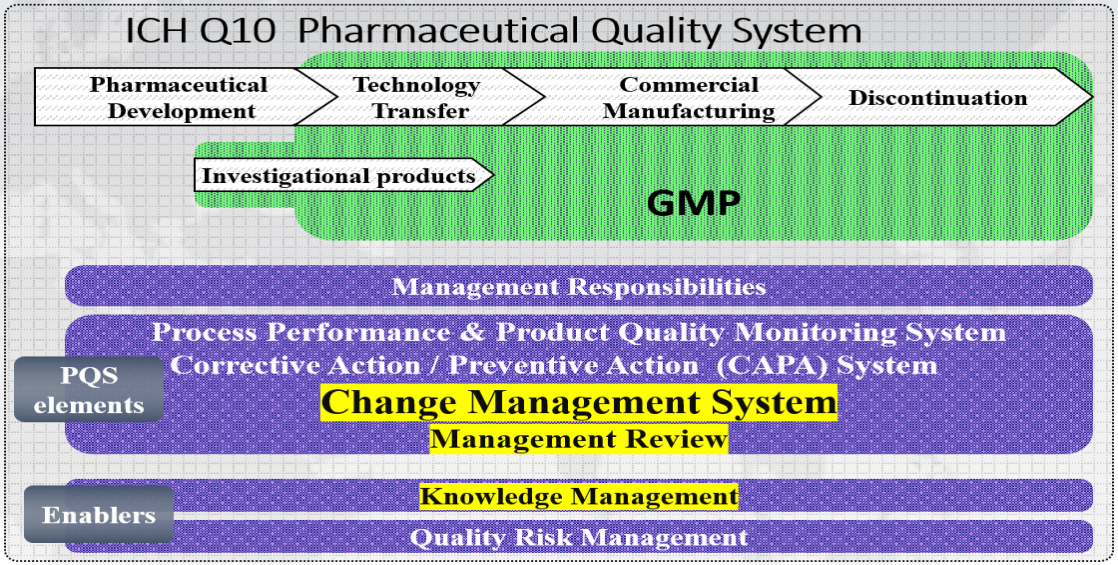

How is Change Management a critical element of the PQS?

As described in Q10, an effective PQS is necessary

- Among the PQS elements, ***Change Management*** is critical to control post-approval changes
- ***Knowledge*** Management is a key enabler to provide the signals for making changes
- The appropriate ***Management Review*** is needed to secure the effectiveness of the change management process
- An Effective Change Management Process is illustrated step by step in the following slides (Ref. Appendix 2)

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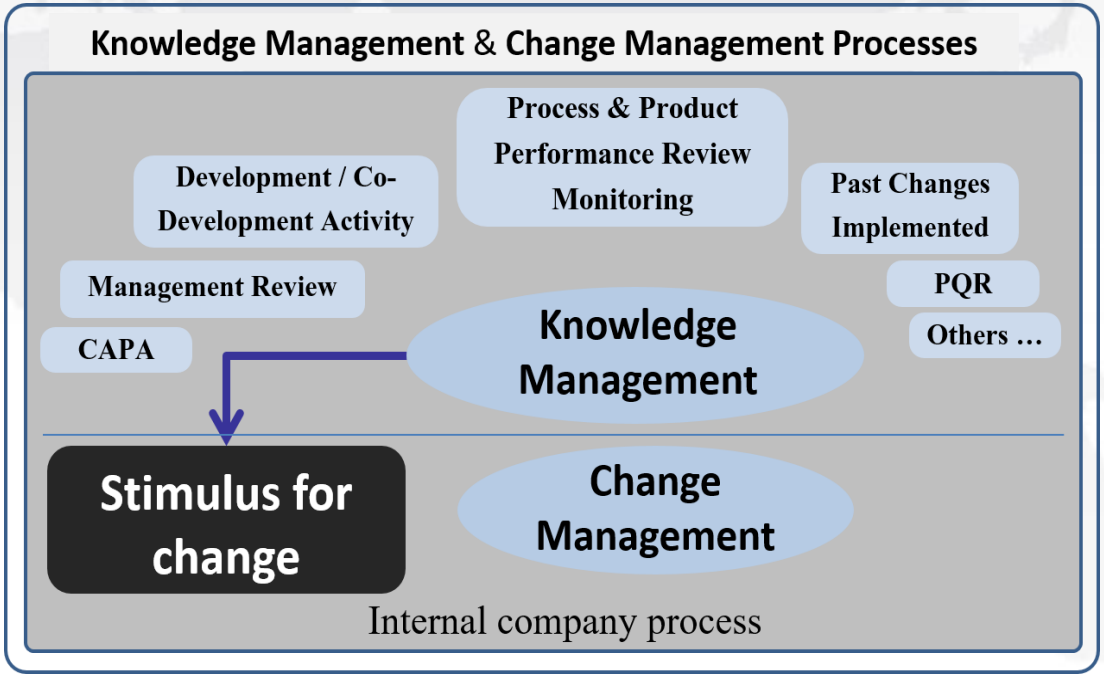
Change Management: Stimulus for Change



1. **Capture stimuli for change**

   Effective PQS is capable of capturing stimuli for post-approval changes (PAC), e.g., product performance and process robustness.

2. **Ensure full understanding of the scope of the change and its implications for all aspects of the process and control strategy**

   Including:

   - ***The impact on ECs***
   - ***Aspects that are not ECs in affected marketing authorisations***

3. **Leverages existing process performance and product quality knowledge**

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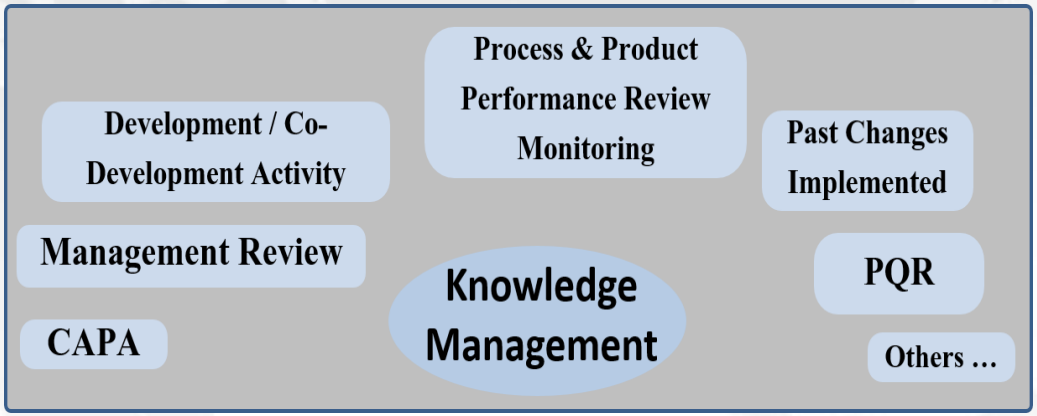
Change Management: Use of Knowledge Management & Management Review



- **Active Knowledge Management is part of an effective change management**
- **Information from multiple sources is integrated**, including & not limited to:
  - Developmental studies
  - Process understanding documents
  - Product or process trending
  - Product-specific CAPA outcome
- **Active sharing of knowledge (between MAH & relevant manufacturing Stakeholders)**
  - Developmental studies
  - Process understanding documents
  - Product or process trending
  - Product-specific CAPA outcome
- **Management Review**
  - Monitoring the timelines of Change Management & the performance of the change
  - Ensuring that the post-implementation verification occurs and reviewing the results as a measure of Change Management effectiveness

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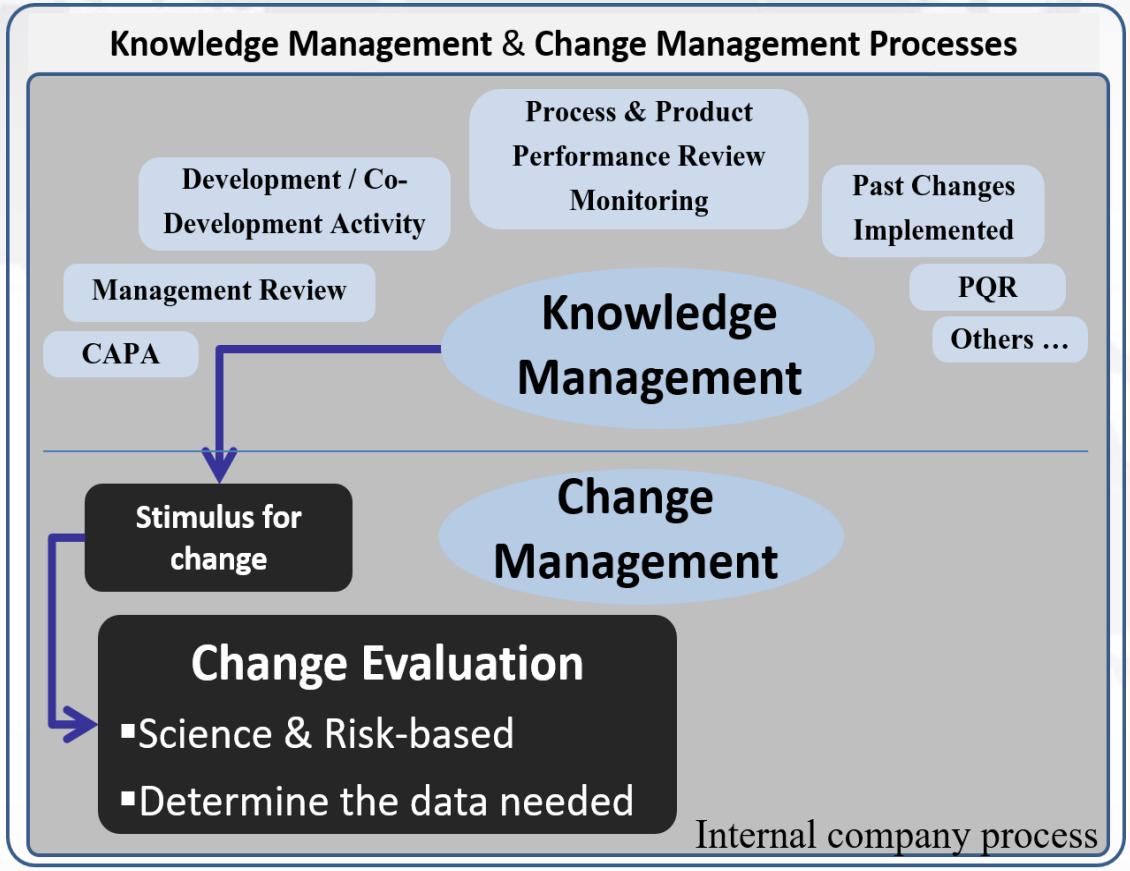
Change Management: Change Evaluation

4. **Assess and manage potential risks** for the change based on science and prior knowledge and considers the potential impact if the intended change is not implemented.



5. **Determine data** (existing and/or to be newly generated) needed to support the change

   Accordingly develops study protocols describing the methods, acceptance criteria and post-implementation monitoring

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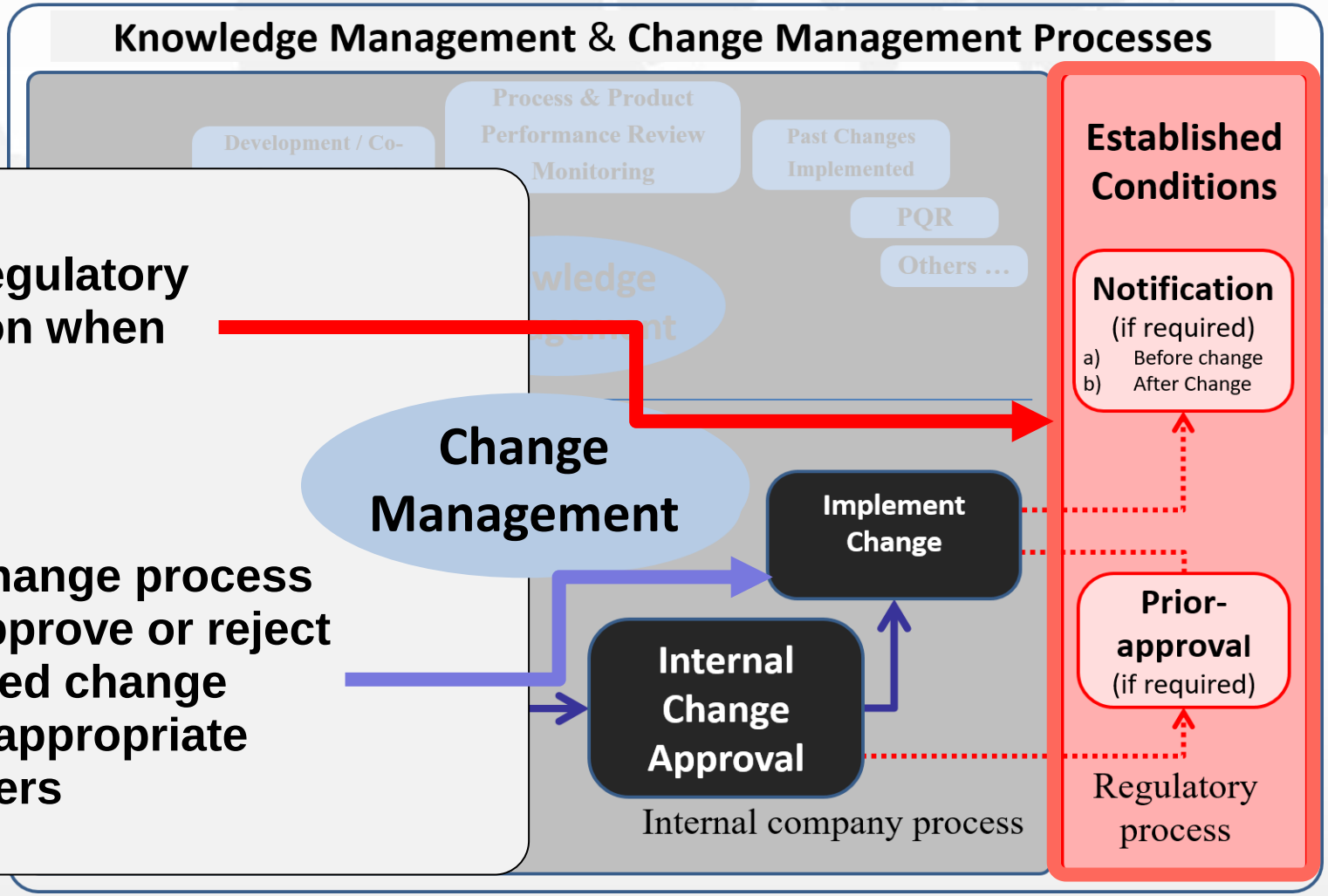
Change Management: Internal Change Approval



6. **Ensure Regulatory submission when required**

7. **Defined change process used to approve or reject the intended change involving appropriate stakeholders**

Steps 6 & 7 are closely linked

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Change Management: Implement Change

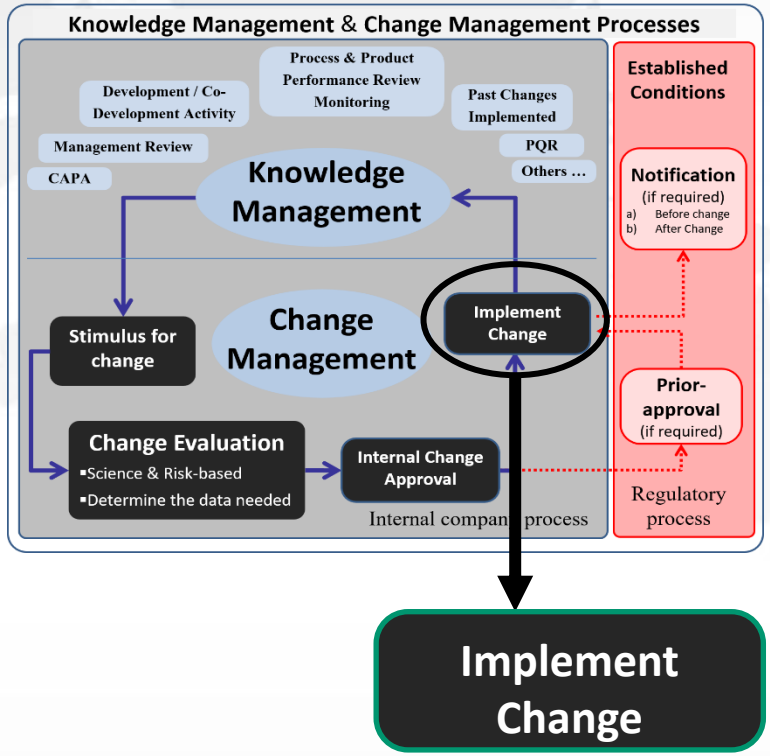
8. Implementation based on:

a) Alignment with study protocols, PLCM document, PACMP (if applicable)

b) Data generated demonstrating objective and acceptance criteria met

9. Risk mitigation developed (if deviations or unanticipated risks)

10. Verify effective outcome, post-implementation (without unintended consequences for product quality)



11. Post implementation

a) Capture product/process knowledge

b) Ensure regulatory filings and PLCM document (if applicable) are updated

c) Ensure change included and assessed in Product Quality Review (where applicable)

12. Availability for review

a) The change management system should be available for review during audit/inspection.

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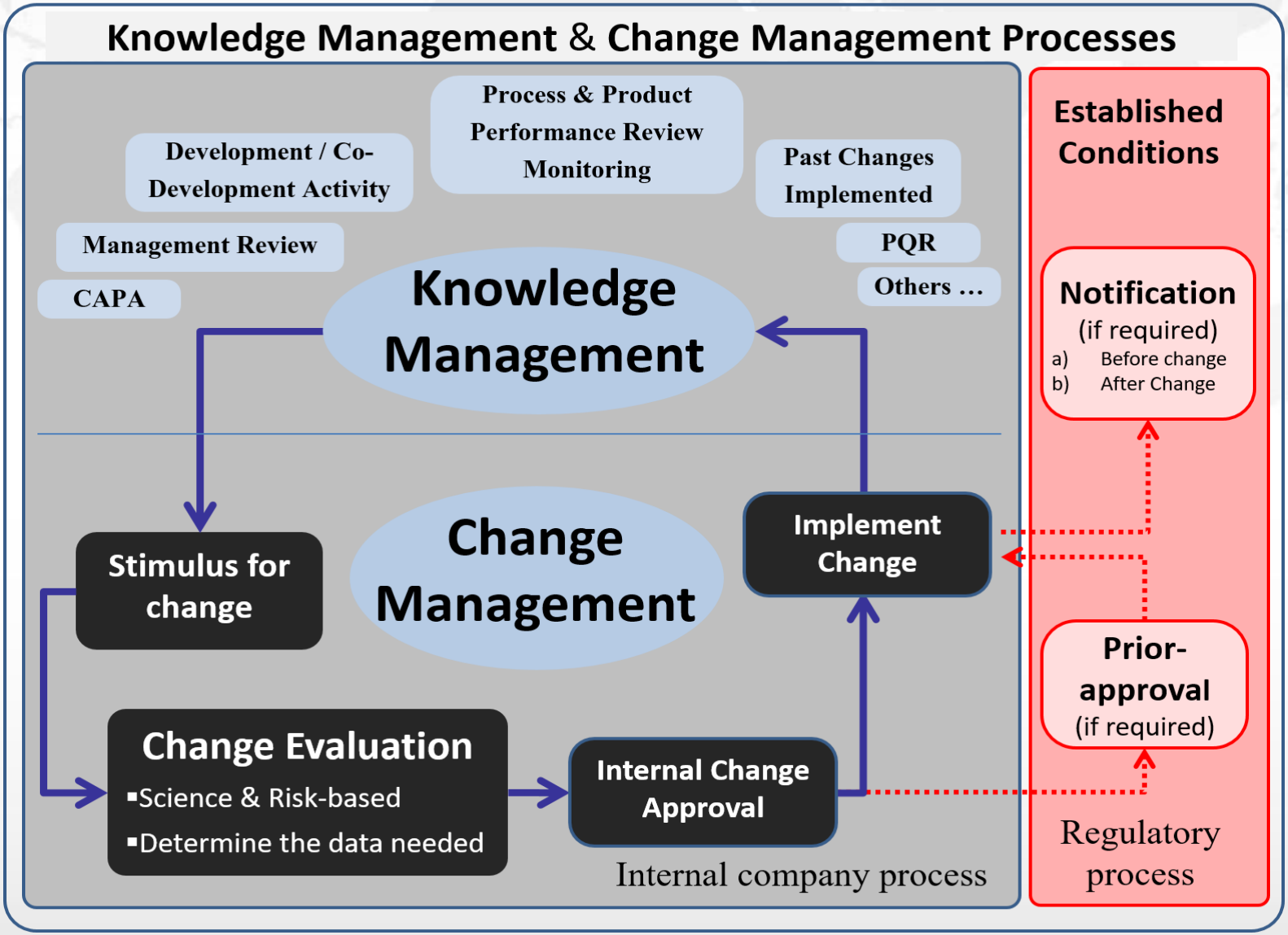
In summary



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Regulatory assessment and inspection relationship and communication

- Regulatory assessment & inspection are complementary activities, and their fundamental roles remain unchanged. Nevertheless, **effective communication** between assessors and inspectors can facilitate regulatory oversight.
  - Appropriate mechanisms to share knowledge and information through respective activities can facilitate access to necessary information and mitigate increased submission burden on the MAH
  - Example:
    - Inspection's conclusion available for assessor to support oversight of product lifecycle management
    - Most recent PLCM document, when applicable, available to inspectors providing awareness of the currently approved status of PLCM elements
- **Communication between regulators across regions is encouraged**