ICH Q12: Post Approval Change Management Protocol (PACMP)

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Disclaimer

- This presentation reflects the views of the speaker and should not be construed to represent the views or policies of FDA or ICH.

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Main Document:

1. Introduction
2. Categorization of Post-Approval CMC Changes
3. Established Conditions (ECs)
4. Post-Approval Change Management Protocol (PACMP)
5. Product Lifecycle Management (PLCM)
6. Pharmaceutical Quality System (PQS) and Change Management
7. Relationship Between Regulatory Assessment and Inspection
8. Post-Approval Changes for Marketed Products
9. Glossary
10. References

Appendix 1: CTD Sections That Contain ECs

Appendix 2: Principles of Change Management

Annex:

1. Identification of ECs for chemical and biological products
2. PACMP
3. PLCM

PACMP applicability to ICH Q12

- Development approaches and timelines may not always allow for further science and risk based definition of ECs and reporting categories beyond those established by regional regulation and guidance

- Q12 concepts should create opportunities for broader implementation beyond new products, or one product at a time approaches

PACMP

- A PACMP is a regulatory tool that provides predictability and transparency in terms of the requirements and studies needed to implement a change
- Provides opportunity for lower reporting category when implementing changes
- Chapter Sections
  - Definition
  - Application – Step 1 & Step 2
  - Elements
  - Modification
  - Types

PACMP

- Part of the Q12 ‘suite’ of tools that allow continued opportunities for streamlined change implementation
- Highly aligned with FDA draft guidance on Comparability Protocols (2016)
- Can be included with original application, or with post approval supplement

Benefits

- Prospective agreement between applicant and regulator on:
  - Change to be implemented
  - Studies and acceptance criteria
  - Implementation reporting category
- Allows for predictable change approaches that reduce ambiguity surrounding implementation
- Allows for shorter review clocks for change implementation, when appropriate

Steps

Step 1

- Submission of a written protocol including:
  - Description of the proposed change(s) with rationale(s)
  - risk management activities
  - proposed studies and acceptance criteria to assess the impact of the change(s)
  - other conditions to be met
  - the proposed reporting category
  - any other supportive information

- Approved by regulator in advance of execution of the protocol

Steps

Step 2

- Carry out tests and studies outlined in the protocol
  - If results/data generated meet the acceptance criteria and any other conditions
    - submit this information to the regulatory authority according to the category in the approved protocol
  - If results/data generated do not meet the acceptance criteria and any other conditions
    - reduced reporting category is no longer valid
    - default to existing regional regulation or guidance regarding change implementation
- Depending on the reporting category, approval by the regulatory authority may or may not be required prior to implementation of the change.

Elements

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- Description and rationale for the change
- Supporting information and analysis
- Specific tests, studies, analytical procedures, and acceptance criteria
- Discussion regarding the suitability of the approved control strategy
- Any other conditions to be met (e.g. selected PPQ activities)
- Proposed reporting category for step 2
- Confirmation that ongoing verification will be performed under the PQS.

FDA draft guidance

- Overall summary
- Description and rationale for the change
- Supporting information and analysis
- Specific tests, studies, analytical procedures, and acceptance criteria
- Proposed reporting category for step 2
- Other information (single or multi use protocol)

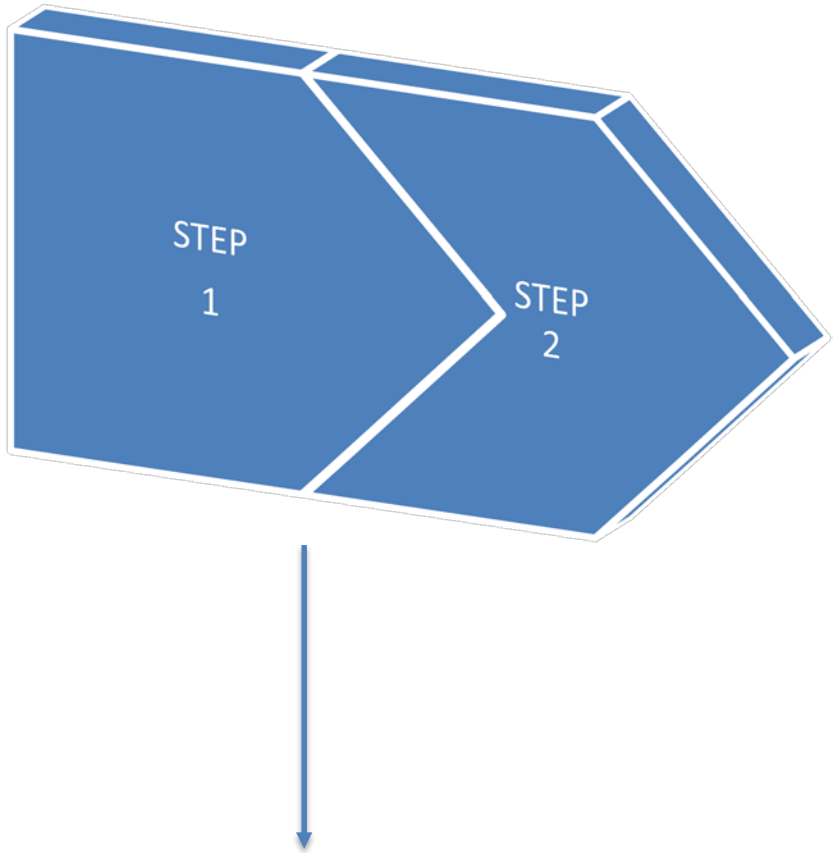
Types

- One or more change(s) to a single product

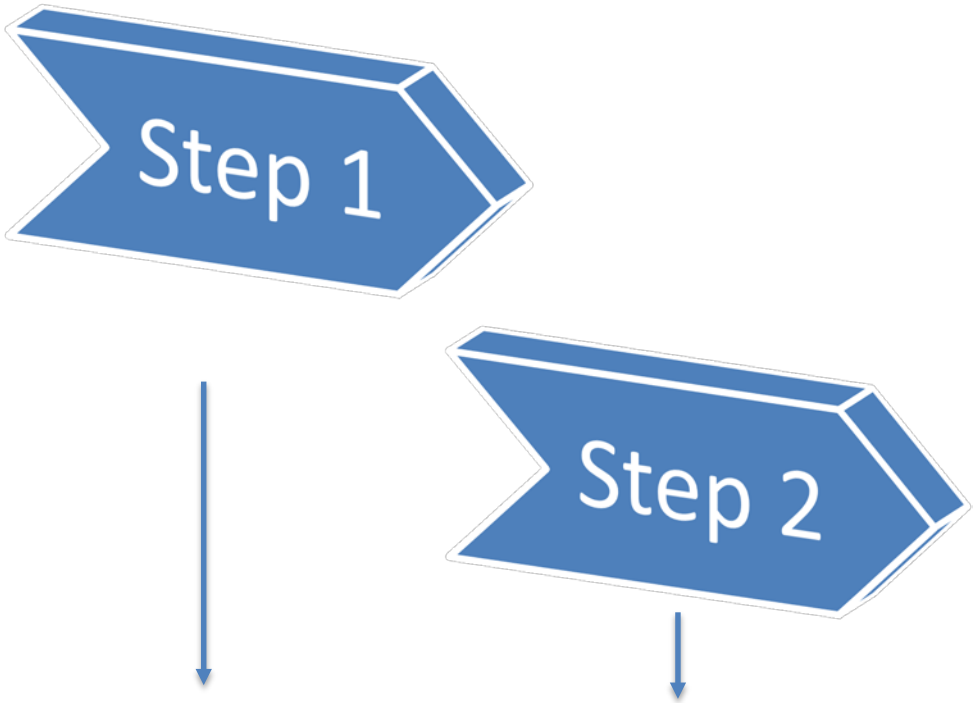
- One or more changes to be implemented across multiple products
  - E.g., change in stopper across multiple products that use the same container closure system

- One or more changes to be implemented across multiple products and at multiple sites
  - E.g., change in analytical method across multiple sites, change in manufacturing site(s) across multiple products

Impact



PAS



PAS

CBE, Annual Report

Modifications

- After approval of step 1, modifications made to the PACMP may require a supplement depending on the impact on the ability to assess product quality under the change

  - Replacement or revision of protocol elements that result in the same or increased rigor is generally a lower impact:
    - Tightened acceptance criteria
    - Changes to comply with compendial requirements

  - Modifications that significantly alter protocol content are generally higher impact:
    - Adding additional applications to a broad protocol
    - Changes to studies, methods, etc…

Expectations

- No change in a PACMP should introduce additional risks to safety, efficacy, or product quality
  - PACMP is generally not suitable for quality changes that require supporting safety or efficacy data

- Periodic re-evaluation and confirmation of validity prior to execution or implementation
  - MAH should follow existing guidance for change notification if an increased level of risk associated with the change is observed

Expectations

- Appropriate defaulting to regional reporting requirements if:
  - Risk of implementing the change has increased
  - Failure to meet acceptance criteria

- Changes are designed, implemented, and monitored under an effective PQS
  - PQS expectations (chapter 6)
  - Change management principles (appendix 2)

Product Lifecycle Management Document (PLCM)

- Serves as a central repository of key elements to provide transparency and facilitate:
  - Strategic approaches to lifecycle management
  - Lifecycle regulatory assessment and inspection
- Maintenance
  - Updated list should be submitted in post approval submissions for CMC changes
  - ECs should be updated based on knowledge gained during the lifecycle

CTD Section	Section Title	Established Conditions Note that identification and justification of EC is presented in the relevant section of CTD	Reporting Category when making a change to the Established Condition	PACMP or Post-approval CMC Commitment, if applicable
		Equipment Type Diffusion blender (V-blender)	Notification Moderate	
		Scale 200kg	Notification Low	PACMP included in the MAA for expanded range for scale to be submitted as a Notification Low
		Blend speed 10-20rpm	Notification Low	
		Blend time 15-25 minutes	Notification Low	CMC commitment to monitor dissolution performance for 10 batches manufactured at upper end of blend time range due to potential over lubrication at the proposed commercial scale (200kg).

Conclusion

- Broad alignment in ICH regions on the value of this tool to implement ICH Q12

- Up front alignment allows for:
  - Predictable change implementation
  - Better global product lifecycle management
  - Enhanced transparency between regulator and MAH regarding approach to risk assessment and control

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