aqpa
Austrian Qualified Person Association

ICH – Q12
Life Cycle Management

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Overview

„Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management“

- ICH: Draft version endorsed on 16 November 2017
- EMA: Start of Consultation: 18 December 2017
- EMA: End of Consultation: 18 December 2018

- Guideline: 27 Seiten
- Annex: 18 Seiten
- Kommentare durch Unternehmen anwesender QPs?
- Kommentare durch AQPA erforderlich?

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/12/WC500240552.pdf

Introduction

- „increased knowledge can contribute to reduction in number of regulatory submissions“
- „enhance management of post-approval changes, and transparency between industry and regulatory authorities“
- „Effective PQS and compliance with GMPs are necessary“

Categorisation of Post-Approval CMC Changes

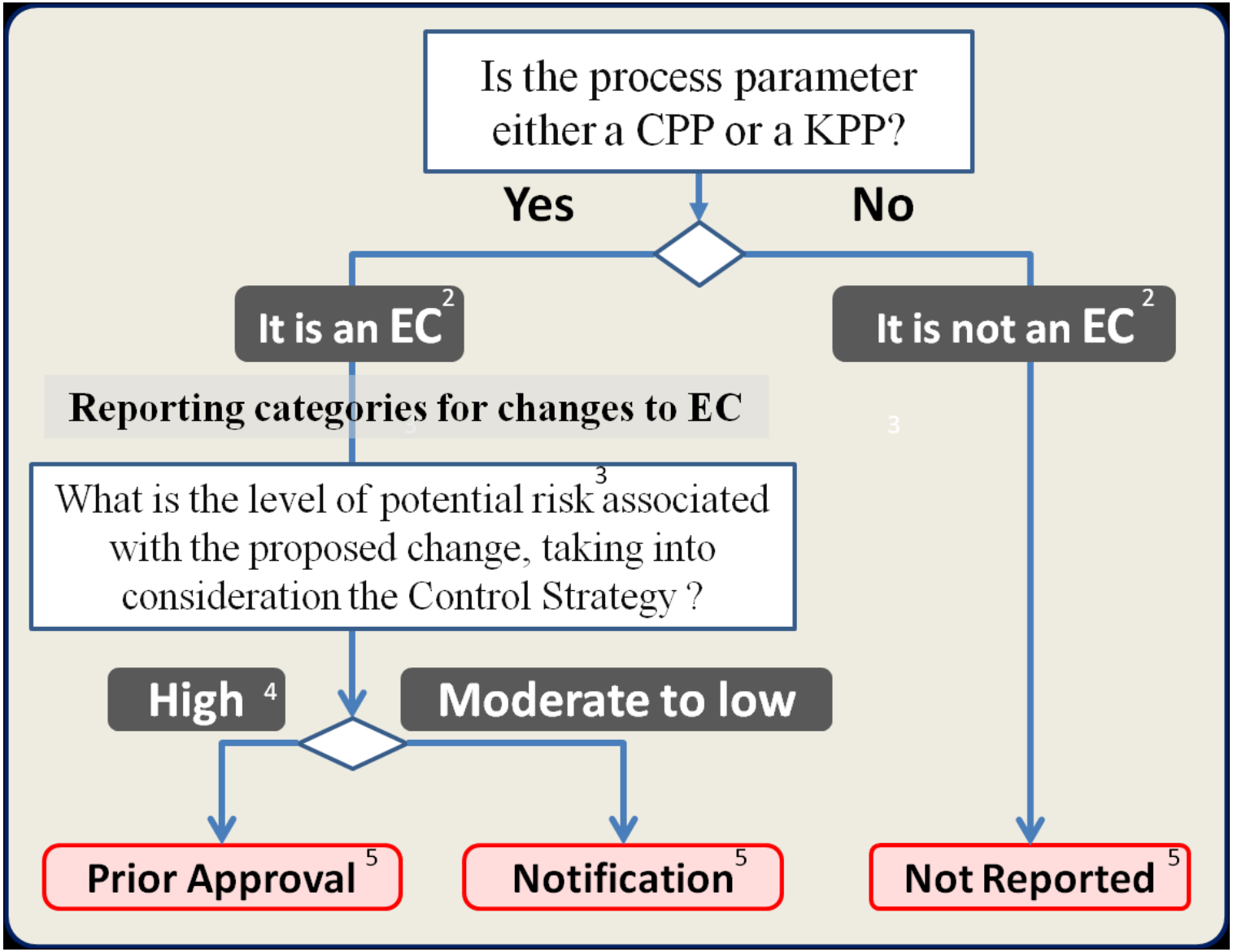
- Classified with regard to potential to have adverse effect on product quality of drug product
- Prior-approval: sufficient risk, inspection may be associated
- Notification: moderate to low risk, formal communication within defined time period before or after implementation (timely awareness of change by the regulator necessary)
- Not-reportable: lowest risk, verified on routine inspection
- Risk based categorisation:
  - Use of tools and enablers
  - Use of lower category (if certain criteria met and relevant documentation is provided)
  - Need for inspection may preclude ability to use lower category

Established Conditions (ECs)

- Legally binding information necessary to assure product quality. Any change necessitates regulatory submission
- What information can be designated as supportive information that would not require regulatory submission, if changed
- MAH may propose reporting categories for changes to ECs
- Supportive information not considered to be ECs
- Implicit ECs: derived from regulation or guidance
- Explicit ECs: identified and proposed by MAH
- MAH should provide rationales for ECs and reporting category
- Appendix 1: sections of MA containing ECs

Identification of ECs

- Critical Process Parameters (CPPs): ICH Q8(R2)
- Key Process Parameters (KPPs): not directly linked to CQA (critical quality attributes) but need tight control to assure process consistency
- Appropriate justification to support identification of ECs
- Parameter based approach (limited process understanding): large number of inputs along with outputs (incl. IPC)
- Enhanced approach (increased understanding of interaction between inputs and product CQAs): focus on most important input parameters and associated outputs
- Performance based approach (data-rich environment): focus on control of output rather than inputs (e.g. in-line continuous monitoring, PAT, etc.), monitoring of all parameters with potential impact on product quality
- Suitably detailed description important to provide clear understanding of what is and is not necessary to assure product quality



1 This diagram does not apply as is for the performance-based approach.
2 Appropriate justification is expected for ECs and non-ECs
3 Assessment of risk to quality using tools and concepts found in ICH Q9
4 In some cases, moderate risk changes may require prior approval.
5 See Chapter 2 for further guidance on reporting categories and see Chapter 3.3., regarding roles and responsibilities related to managing changes and maintaining an approved application.

Identification of ECs

- Criticality and risk should be evaluated periodically and updated based on acquired knowledge
- MAH should consider impact of concurrent changes when assessing appropriate reporting category
- ECs related to analytical procedures should include elements which assure performance of the procedure (based on method complexity, development and control approaches)
- Use of this guideline should not lead to providing a less detailed description of analytical procedures in the MAA

Revision of ECs

Change of approved ECs may be necessary as result of knowledge gained during Life Cycle

- Post-approval regulatory submission (validation data, batch analyses)
- PACMP (Post Approval Change Management Protocol)
- Approved post-approval regulatory commitment
- Describe justification for change and its reporting category
- Management of all changes to and maintenance of approved MA is responsibility of the MAH
- Holder of a referenced submission (e.g. DMF) has responsibility to report changes to the MAH
- Approval of ECs and subsequent changes is responsibility of the regulatory authorities

Post-Approval Change Management Protocol (PACMP)

- Protocol (commercial phase) how change would be prepared and verified (impact and suggested reporting category)
- Requires approval by regulatory authority
- Specific conditions and acceptance criteria must be met
- If review of initial risk assessment indicates increased risk, previously approved reporting category is no longer appropriate -> consultation with regulatory authority!

PACMP

Two steps:

- 1: Submission of written protocol (approval by regulatory authority in advance of execution)
- 2. Tests and studies performed and submitted to regulatory authority
  - If results meet criteria approval may not be required (depending on reporting category)
  - If criteria are not met, change should follow existing guidance
- Significant changes not anticipated in step 1 cannot be implementented as part of step 2
- However, minor unanticipated modifications normally considered within scope (if appropriately justified)
- No change should introduce additional risk to product quality or patient safety
- Change requiring supportive efficacy, safety (clinical or non-clinical), or human PK/PD data is generally not suitable for a PACMP

Elements of a PACMP

- Detailed description (including rationale)
- List of specific tests and studies based on initial risk assessment (proposed acceptance criteria)
- Suitability of approved control strategy or any changes needed
- Any other conditions before implementation (e.g. certain qualification steps)
- Supportive data from previous experience (where applicable)
- Proposed reporting category
- Ongoing verification under the PQS
- Demonstrate suitable scientific knowledge and understanding

Modification to an PACMP

- Modification to an approved PACMP should provide the same or greater capability to assess effect on product quality
- Requires notification/communication with regulatory authority
- May require
  - Approval of amendment, or
  - Submission of new protocol

Types of PACMP

- One or more changes to a single product
  - Add justification how changes are related and that inclusion in a single protocol is appropriate
- Broader protocols; additional considerations e.g.
  - Same risk mitigation strategy across all products and/or sites

Product Lifecycle Management (PLCM)

- Outlines specific plan, proposed by MAH
- Includes
  - Key elements of control strategy
  - The ECs
  - Proposed reporting categories for changes to ECs
  - PACMPs (if used)
  - Any post-approval CMC commitments
- Updates throughout product lifecycle as needed
- Submitted with original MAA or with a variation
- Updated PLCM included in submissions for CMC-changes
- Located in CTD module 1, 2, or 3
- Revision history for PLCM document
- Tabular format recommended -> examples in Annex III

PQS and Change Management

- If PQS is found not to be compliant, it may result in restrictions to use flexibility of Q12
- Robust change management across multiple sites is necessary
- Changes to ECs should be communicated in timely fashion between MAH and regulators, between MAH and manufacturing chain, and vice versa
- Process knowledge and continual improvement are drivers fo change
- Organisation responsible for batch release should be aware of all relevant changes and involved in decision making
- Communication mechanism (MAA changes and GMP issues) should be defined, including CMO-contracts

Annex

- Ilustrative examples:
  - ECs
  - PACMP
  - PLCM document

EFPIA

- 23.3.2018: Meeting mit EU-Kommission
  - Delegated regulation on variations needs to be revised
  - EFPIA/EBE/Vaccines Europe to develop position paper:
    - All issues with variations regulation
    - Arguments why revision is beneficial (public health and regulatory point of view, not only industry)
  - Wunschdatum (position paper): Ende Juni 2018

EFPIA: European Federation of Pharmaceutical Industries and Associations
EBE: European Biopharmaceutical Enterprises