Lifecycle CMC Management: ICH Q12 Progress to date

BWP/QWP/GMDP IWG Industry
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Please take note

- The following slides represent the current status of Q12 (October 2015)
- Still discussion needed but some main principles and concepts or approaches identified
- Please note that the document (version 2.01) sent on October 22, 2015 is an unedited draft of the Q12 Technical Document for use by the EMA Lifecycle Management Workshop delegates only

  (for information only!!)

Workshop Objective

- Gathering input from European stakeholders with invited observers, including EWG members, on the
  - core expectations for the ICH Q12 guideline,
  - design of the proposed ICH Q12 tools and enablers,
  - application to typical post-approval changes.
- Don’t expect all the answers.
- ICH Q12 experts will listen.
- The output from the workshop will be used to progress on the development of the ICH Q12 Technical Document
- Participants are the drivers of this workshop

Overview Q12

- Reminder
- Reasons and expectations
- Scope
- Key elements/Enablers/Tools
- Other topics for discussion
- Challenges
- Conclusions

New Paradigm in Pharmaceutical Quality

- Described mainly in ICH Q8, Q9, Q10 and Q11
- Combines science (technological understanding), risk management, quality system over lifecycle of product and process
- Opportunities:
  - Manufacturing process improvements and potential opportunities like design space, real time release testing…..
  - Risk-based regulatory decisions (reviews and inspections)
  - *Reduction of post-approval submissions*
    - *Fully implemented?*
    - *Full benefit achieved?*

Current Status

extract from concept paper

- Lack of strategic and proactive planning by industry
- Regulatory processes are complex and not always risk-based, leading to unnecessary delays in manufacturing improvements and intensive use of resources
- Lack of incentive for proactive implementation of manufacturing improvement
- Inefficient use of industry and regulatory resources addressing less important issues
- QbD and recent ICH Guidelines have not fully produced the expected benefits and operational flexibility
- Challenges in lifecycle management can, for example, lead to disruption in supply chain and drug shortage

ICH Q12: Scope and Objectives

- "….to facilitate the management of post approval changes in CMC *in a more* ***transparent, predictable and efficient*** *manner* across the product lifecycle"

- Addresses: pharmaceutical products (chemicals, biologicals) including already marketed products
- Optimization of resources for assessment and inspection
- Support innovation and continual improvement and help to assure drug product supply

- *What is needed to make Q12 a success?*

Expectations from Q12

- Clarify important parameters for manufacture and control based on risk, product type, development approaches, manufacturing experience, GMP status
- Provide harmonized tools to facilitate prospective changes over the product lifecycle
- Exemplify ICH expectations of assessment and implementation of frequent manufacturing changes
- Promote development of proactive product lifecycle strategy

ICH Guidelines with LCM Elements

- Q10: Pharmaceutical Quality System
- Q11: Development/Manufacturing APIs
- Q3D: Residual elements
- M7: Genotoxic impurities
- ICH Pts to consider Q8, 9, 10: Control Strategy (3.1)
- ICH Pts to consider Q8, 9, 10: Design Space (6.4)

Raising awareness of importance of monitoring product and process during lifecycle but no concrete or practical implementation guidance

Q12 Guiding Principles

Key Elements – Enablers – Tools

- Pharmaceutical Quality System
  - Change management
  - Knowledge Management
- Established conditions
  (for manufacture and control)
- Post Approval Management Protocols
  - Lifecycle strategy

Pharmaceutical Quality System (PQS)

- **Basis: ICH Q10**
- Quality manual (Q10): should reflect company's (manufacturer , MAH) policy towards LCM
- Further issues needing discussion incl.:
  - Outsourcing:
    - Relation/influence QS supplier – MAH
      (chapter 2.7.: Management of Outsourced Activities and Purchased Materials)
  - Need to identify a mechanism to demonstrate (Industry), to assess and verify (Regulators) if a company/ manufacturer/ MAH's PQS supports full implementation of Q12 and its potential benefits?
  - What is about changes in the "health" of the quality system at a facility over time?
  - Others?

Change Management ICH Q10

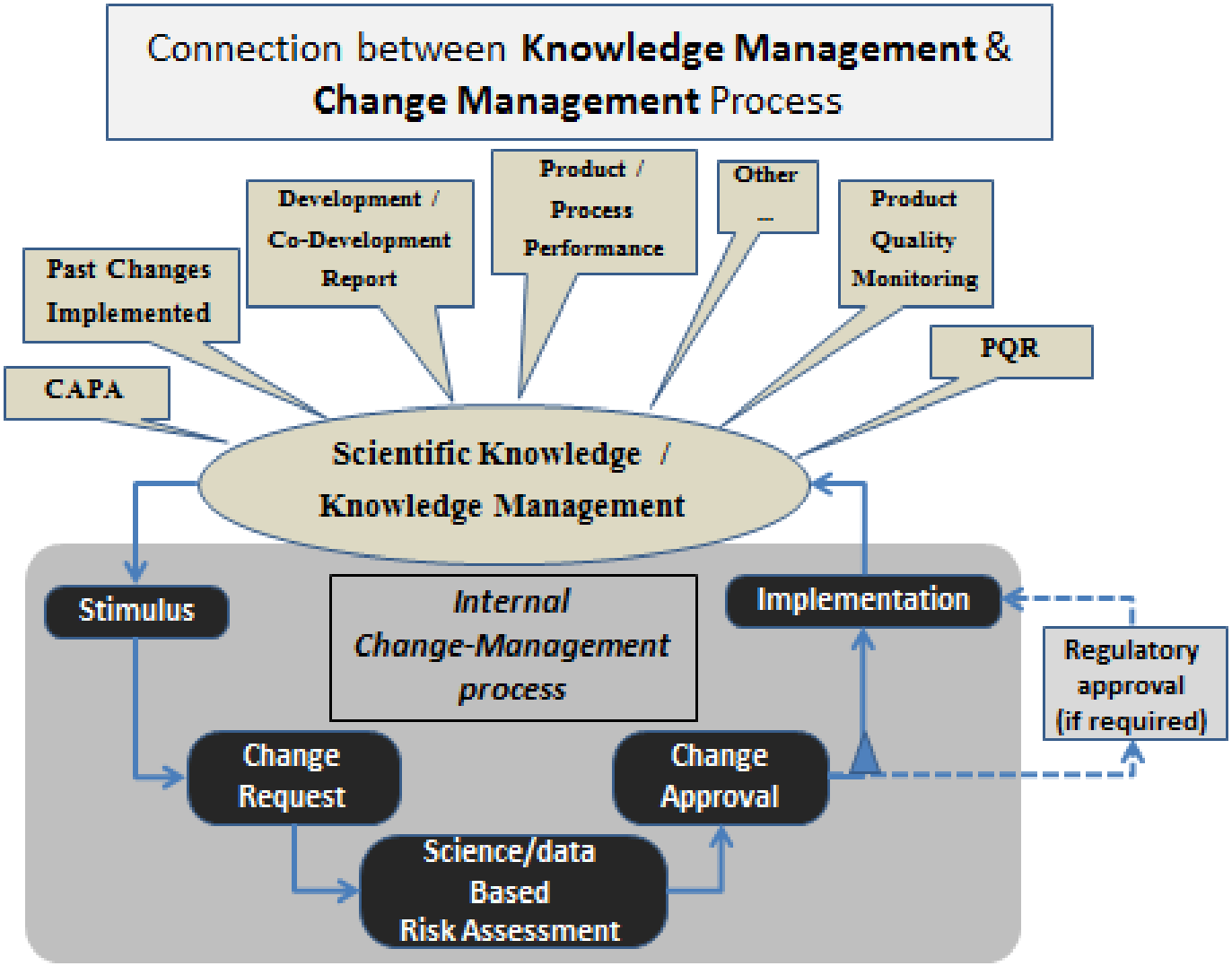
- Definition:
  A systematic approach to proposing, evaluating, approving, implementing and reviewing changes

- Changes handled solely under GMP
- Changes subject to a regulatory submission to the competent authorities (are also handled under GMP)

Knowledge: Basis for a Change

- Defined as in Q10
- Implementation of changes has to rely on company's product and process understanding
- Knowledge
  - At time of submission
    - In principle shared with Regulators
  - During commercialisation
    - What to do with the gained knowledge if any….?
    - How to share and communicate inside/outside?
    - Knowledge from suppliers?! (Outsourcing)

No intention to provide guidance how to manage

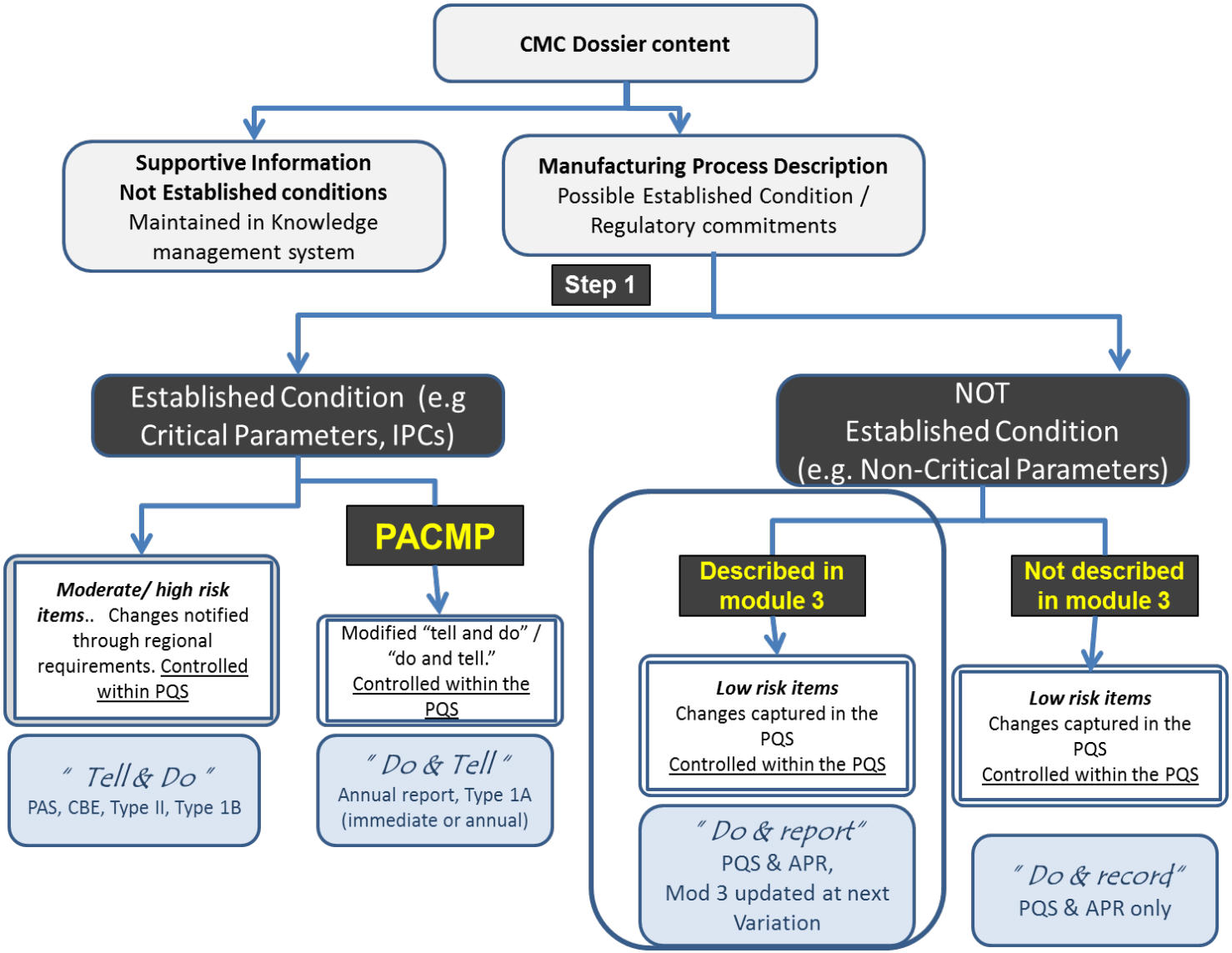

Connection between **Knowledge Management** & **Change Management** Process
Past Changes Implemented
Development / Co-Development Report
Product / Process Performance
Other ...
Product Quality Monitoring
PQR
CAPA
Scientific Knowledge / Knowledge Management
Stimulus
Internal Change-Management process
Implementation
Regulatory approval (if required)
Change Request
Change Approval
Science/data Based Risk Assessment

Established conditions
(current draft definition)

- Established Conditions for Manufacture and Control (EC) are certain binding information or elements concerning the manufacture and control of a pharmaceutical product, including description of the product, elements of the manufacturing process, facilities and certain equipment, specifications [i.e., test, method and criteria] and other elements of the associated control strategy (e.g. storage conditions or shelf-life), found in a submission, that assure process performance and desired quality of an approved/licensed product.

Established conditions (2)

- Proposed by applicant – approved by Reg. Auth.
- Advantage: more transparency
- Further issues needing discussion incl.:
  - Update of file: should reflect actual status
  - Specific location in CTD?
  - To define in a general way or product specific or a combination of both?


CMC Dossier content
Supportive Information
Not Established conditions
Maintained in Knowledge management system
Manufacturing Process Description
Possible Established Condition / Regulatory commitments
Step 1
Established Condition (e.g Critical Parameters, IPCs)
NOT Established Condition (e.g. Non-Critical Parameters)
PACMP
Moderate/ high risk items.. Changes notified through regional requirements. Controlled within PQS
Modified "tell and do" / "do and tell." Controlled within the PQS
Described in module 3
Not described in module 3
Low risk items Changes captured in the PQS Controlled within the PQS
Low risk items Changes captured in the PQS Controlled within the PQS
" Tell & Do "
PAS, CBE, Type II, Type 1B
" Do & Tell "
Annual report, Type 1A (immediate or annual)
" Do & report"
PQS & APR, Mod 3 updated at next Variation
" Do & record"
PQS & APR only

Post Approval Change Management *Protocol* (PACMP)

- A PACMP describes specific changes that the MAH would like to implement during the lifecycle of the product and how these would be prepared and verified (detailed description)
- Procedure (**tool**) for a faster and predictable implementation of a change.
- Since last revision of variation regulation some experience in EU
- Not to confuse with GMP change management!

Post Approval Change Management *Protocol* (PACMP) (2)

- Types
  - Protocols for specific changes e.g.
    - Analytical method
    - Manufacturing site
  - Broader protocols will enhance utility e.g.
    - More changes across multiple products or sites

PQS Enablers

- Knowledge Management
- Quality Risk Management

Important Supporting Information
- Overall Lifecycle Strategy Story
- Use of Knowledge
- Leverage of Pharmaceutical quality System as Q10

Draft V12

Pharmaceutical Development → **Technology Transfer** → **Commercial Manufacturing** → **Product Discontinuation**

Pre-Approval Phase → Approval Phase → Post-Approval Phase

Industry

Development DS & DP
- Initial gain of knowledge
- Prior knowledge

Submission of MA (and Lifecycle Management Plan – LCMP), incl.:

Ref. to **Regulatory Commitment/ Established cond.:**
- What is **in**, what is **out**
- What is for inspection
- What needs regulatory review
- Define **do & tell** and **tell & do**
- Location in CTD

Post-Approval Change Management Protocol(s) (PACMPs)
- Broad & Specific protocol
- Change Mgt for Regulatory
- Future extrapolation

1. Changes performed as agreed in the LCMP / PACMP(s)
2. Further gain of knowledge based mainly on commercialisation
3. Submission of an updated/new LCMP / PACMP according to gained knowledge
4. Other changes

Regulatory Influence
- Legislation
- Scientific advices
- Guidelines including Q&A and other relevant documentation

Assessment of the application

Approval of
- Regulatory Commitments/ Established Conditions
- PACMPs

1. Regulatory submission as per agreed procedure (incl. no regulatory submission but subject to inspection, if applicable)
2. Not applicable
3. Evaluation of a new LCMP / PACMP
4. Evaluated according to regional legislation

Regulators

Assessment / Inspection

Other Q12 Items

- Interaction Assessors – Inspectors
- Concrete / practical examples
- Glossary
- Location issues

Interaction Assessors - Inspectors

- Location of information: what information goes where?
- Responsibilities
  - Product review and inspection programs must operate in a coordinated and synergistic manner
  - Submission of information about the robustness of the PQS and inform regulator confidence in the PQS's ability to manage changes effectively according to ICH Q10/Q12 principles.
- Communication Inspector – Assessor
- Implementation of a robust PQS supporting Q10 and Q12

Interaction Assessors - Inspectors

- Q12 is not expected to alter the way changes, that can currently be made under GMP without submission to the competent authorities, are managed. Q12, however, aim to clarify expectations with regard to variation or “GMP handling”
- The intention of ICH Q12 is not to increase the workload of both Assessors and/or Inspectors

Practical Examples

- Concrete examples to facilitate implementation:
  - Analytical method changes
  - Process changes
  - Site change

Summary - Challenges

Still some work to do!

- Sufficient guidance: Balance between “What” and “How”
- Practical implementation within Industry and Authorities
- Location in CTD
- Identification of established conditions
  - Update of “established conditions” during Lifecycle
- Application to medical device?
- Global relevance of Q12
- Categorization of changes: based on risk!
- How to deal with legacy products
- Lifecycle strategy

Summary – Challenges (2)

- How to keep track of the regulatory dossier?
- Change in MA application procedures/policy?
- Change to inspection procedures and policy?
- Collaboration Assessors - Inspectors
- Eligibility for Q12:
  - PQS
  - Control strategy in place
  - Global supply chain

- From the Q12 Business Plan:
  - ‘This guideline is not intended to introduce new requirements necessitating changes to the regulations in the regions’

Thank you for your attention!

Discussion

- Is the overall concept understood?
- Is something missing?

- Change of MA application assessment procedures?
- Change of inspection procedures and policy?
- Company eligibility for Q12?
- What needs to be done to ensure use of Q12?

Workshop Sessions

- Established conditions
- Post-approval protocols
- PQS and interaction Assessors - Inspectors
- Strategy
- Final discussion