Joint BWP/QWP/GMDP IWG – Industry
European Workshop on Lifecycle Management

PQS & Assessment-Inspection Interaction

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Q12 and PQS : Consideration and objectives

Life Cycle Management

- Considering dynamic change in order to
  - Take advantage of well conduct development (QbD)
  - Endorsing learning from post approval Knowledge
  - Improving quality and adjusting quality oversight
- By a better process understanding and by improving robustness of the quality oversight
  - Getting flexibility in the way to operate
  - Facilitate continual improvement

Q12 and PQS

PQS & Assessment-Inspection Interaction

Life Cycle Management

- How PQS could facilitate the LCM
- Consequences for the review by regulators
- Question related to R&R of Assessor and Inspector
- A key PQS Element : Change Management

Q12 and PQS

Questions raised

- PQS & Change Management
  - Presented by Ursula Busse

- Content of eCP: considerations for ePACMP
- Expanded Change Management Protocol
  - Presented by Wassim Nashabeh

PQS and Change Management

Presented by Ursula Busse

How are changes managed under the PQS?

Initiation
- Compulsory triggers (compliance, supply critical, HA request)
- Continuous improvement triggers
- Open Change request

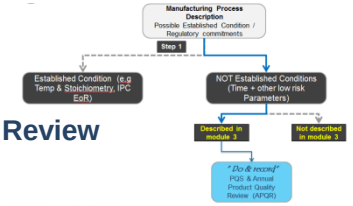
Evaluation and approval
- Risk based
- Impact on product/process, GxP, HSE, supply, other products etc.
- Regulatory evaluation
- Overall change strategy

Planning / Preparation
- Detailed project planning (studies, acceptance criteria)
- Technical phase (data generation)
- Submission preparation if needed, fillings

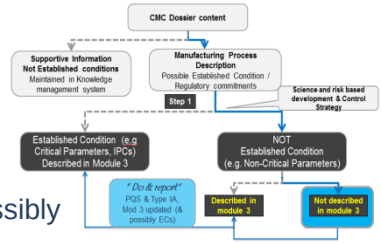
Implementation
- Change implementation according to plan
- Related activities (e.g. stock piling; managing variants)

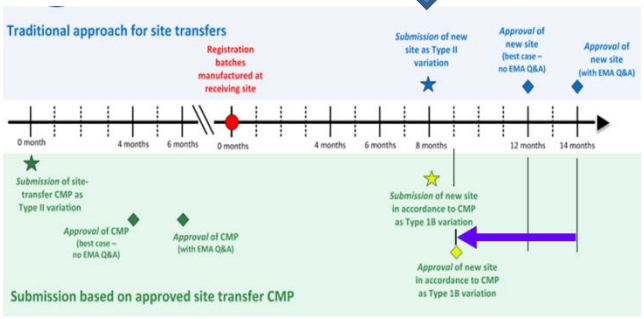
Closure
- Verify effectiveness of change
- Review implementation
- Close change request

" Do & record"
PQS & **Product Quality Review** (PQR)

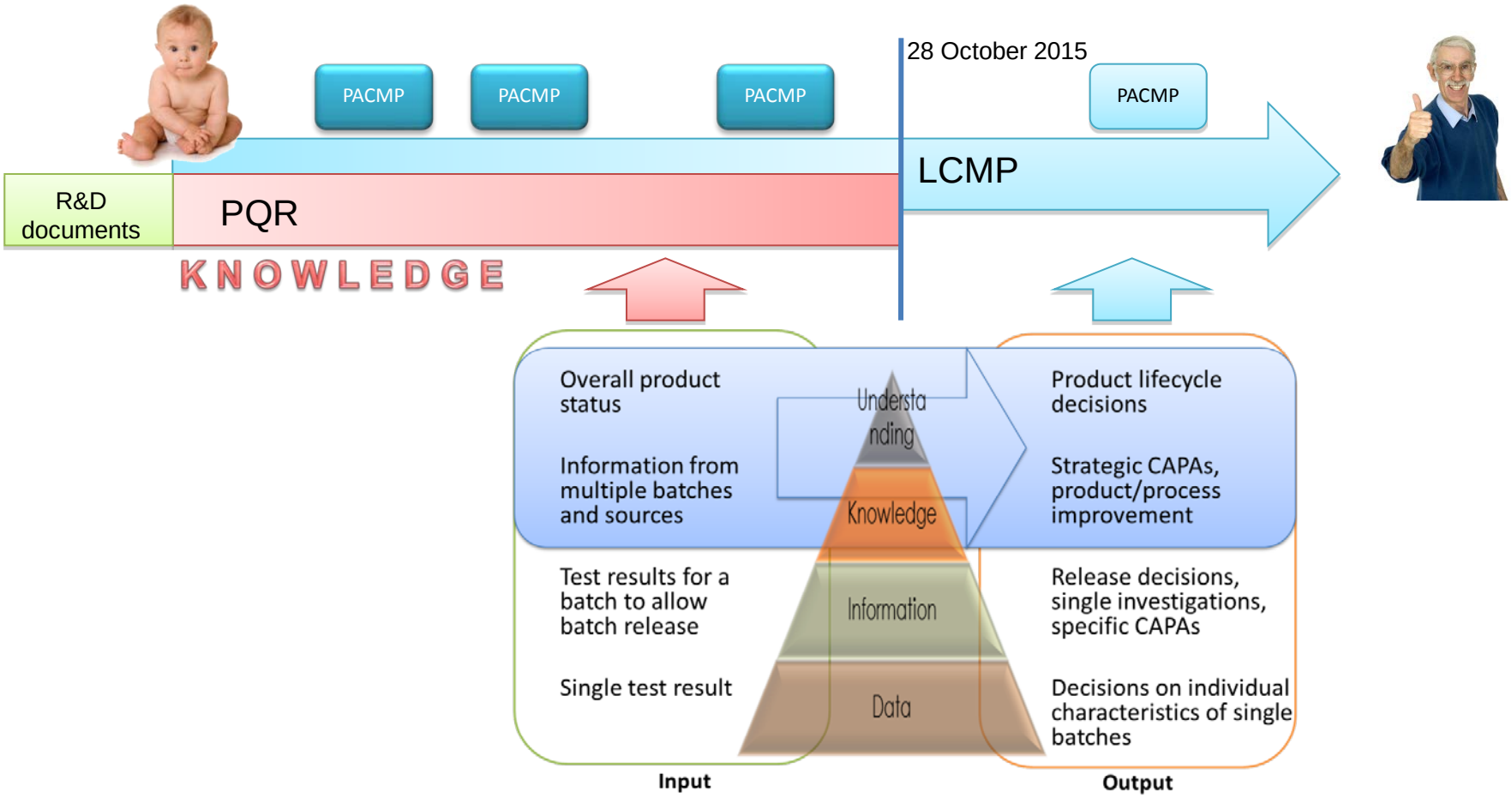


" Do & report"
PQS & Type IA, Mod 3 updated (& possibly ECs)





How do all these documents relate?



PQR and LCMP as knowledge management tools?

Change Management - Challenges

Manufacturing sites
Global functions
Countries

Manufacturing

Manufacturing

Governance

Information

Technology

Process

Commercial

Quality

Development

Regulatory

Contract Manufacturer

Products are the sum of their physical SKUs and all related information

Patients

Health Authority

Inspectors
Assessors

Change Management – Critical elements

- People
  - Right skills (e.g. project management), trained on change management
- Process
  - Clear R&Rs of all involved functions (site, global, country)
  - Clear process governance (review board, change ownership, QA / management oversight at defined check points)
  - Validity of the evaluation phase / risk assessment
    - Involve the right experts (and the right knowledge)
    - Document all the differences (not only the obvious ones), assess all potential impacts
    - Risk assessment free of unconscious bias
  - Proper planning & implementation
  - Quality of the post-implementation verification
- Knowledge
  - Lessons learned are done, documented and used to improve
    - Technical (product/process/platform) knowledge, PQS knowledge
- Tools
  - Holistic IT system (end-to-end process support, access to information)

Should Q12 incorporate critical elements of change management or is Q10 already adequate?

Change Management - Effectiveness Checks

- PQS pre-requisite ('robust' PQS), must cover
  - Process for managing PAC end-to-end
  - Established Target Product Profile, Critical Quality Attributes for products
  - Well developed deviation and change control PQS elements
- Change (post implementation) verification
  - Monitor deviations and process/analytical trends (especially step changes) for potentially caused by PAC
  - Longer term trending of stability, deviations, OOS, technical / medical complaints, inspection/audit outcomes
- Change Management System (PQS) verification
  - Metrics (product quality, compliance, productivity; issues/achievements)
  - Management review
  - Internal audit by corporate function

What does effectiveness look like to authorities?
Should Q12 incorporate effectiveness criteria?

Role of the Qualified Person

- Change Management & PQS
  - Ensures impact of changes have been evaluated; additional tests/checks are complete
  - Ensures self-inspection programme is active and current
- Unplanned changes (deviations)
  - May consider confirming compliance or certifying a batch where an unexpected deviation occurred
    - E.g. deviations from non-EC / no impact on quality but 'non-compliance' to MA
- Conformance to the MA
  - Ensures batches are manufactured in accordance with the MA, also for outsourced activities
    - The QP needs to account for changes in non-EC parameters that are not necessarily reflected yet in the MA

Re-define what 'in accordance to MA' means?
E.g. in accordance to ECs?

Potential Inspection Issues

- Non conformance to MA for non-EC parameters
  - Non-EC changes are maintained in the Company quality system and therefore always available for inspection
  - Differences between the approved modules and manufacturing site documentation will be observed during inspection for non-EC parameters that have not been updated in the MA yet
- EC listed in dossier should be very clear and unambiguous to avoid any misinterpretation

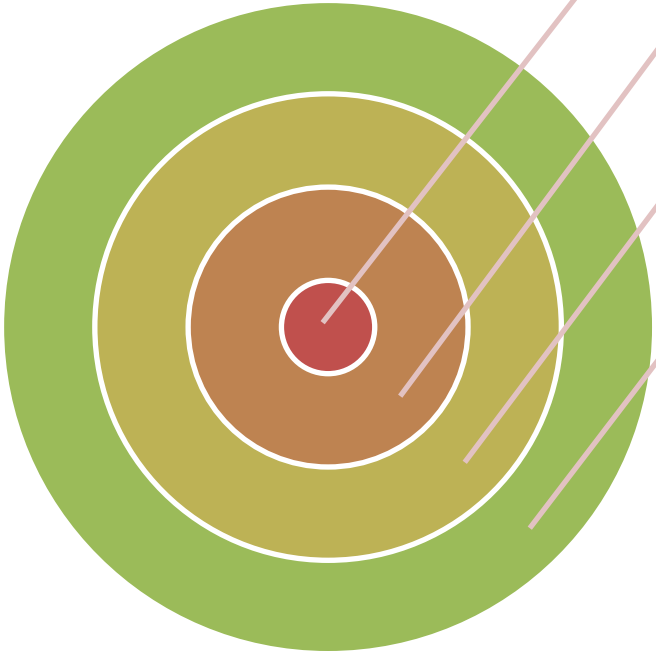
Re-define what ‘non-conformance to MA’ means?
E.g. non-conformance to ECs?

Potential Inspection Issues

- Variability of certain EC parameters
  - ECs are binding but some may be subject to inherent variability
  - Typical example: batch formulae or batch size
    - EU guidance 'Manufacture of the finished dosage' (1996) allows 10% variability of the nominal excipient quantity.
  - Flexibility that is currently allowed should be available to a site who can justify and document any variations within their PQS

Allow flexibility for EC parameters for specific batch(es) when supported and/or documented internally by the company and therefore available for inspection?

PQS vs Regulatory Filing



Change

Medicinal Product

Assessors (EU variations regulations)

Manufacturing site(s)

Company/ies (PQS)

Inspectors (EU GMPs)

Where there is more "Do and Tell", Assessor – Inspector interaction is required:

What do Inspectors need that they do not currently have?

What do Assessors need?

Do communication barriers exist?

PQS vs Regulatory Filing

- “Regulators will assess the maturity of the PQS during on-site inspections... Confidence in self-governance will allow more changes to be managed solely under the PQS..”

Company A
Immature PQS

Company B
Mature PQS

- Incentive for companies to ‘upgrade’ their PQS

How will regulators account for different levels of PQS maturity?
Or changes to PQS effectiveness over time?

Additional Discussion Points

Impact of “Do and tell”	• What practical effect would more use of “Do and Tell” have on inspection practice?
Suggestion to include some PQS information in the MAA (as non-EC)	• When would this be appropriate and why?
Effective Lifecycle Management through the PQS depends on Manufacturer and MAH	• How are regulators assured of the adequacy of the latter’s PQS?

PQS – elements requiring emphasis when used for 'down-graded' changes

- SOP for managing PAC in the PQS
  - Describing PQS and business process for handling PAC
  - Decision tree and company approach to science and risk based assessment of PAC in terms of reporting level
  - Documentation requirements for assessment, implementation and follow-up (including effectiveness check of the PQS) on PACs
- Change Control System Element
  - PACMP & HA assessments documentation
  - Change request for the change itself
  - Results including any deviations observed
  - Assessment of results obtained against the PACMP and the HA assessment requirements/acceptance criteria
  - Global and local implementation plan
  - Inventory of PACs covered in the PQS
- Deviation System Element
  - Assessment of unintended consequences of PAC (effectiveness check)
- Annual Product Quality Report
  - Inventory of all PAC including reporting level

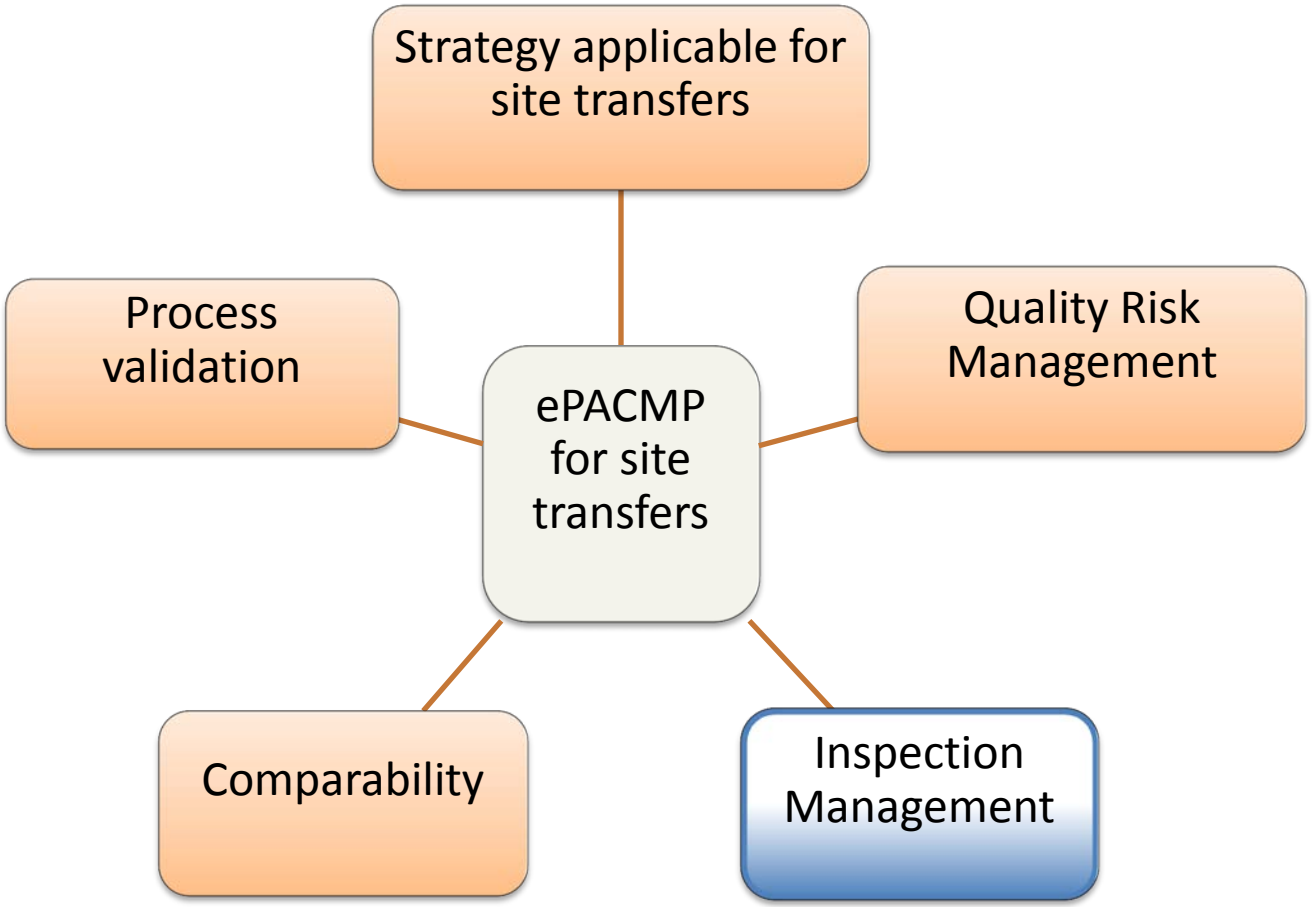
For Discussion

- Should Q12 incorporate critical elements of change management or is Q10 already adequate?
- What does effectiveness look like to authorities?
  - Should Q12 incorporate effectiveness criteria?
  - Re-define what 'in accordance to MA' means?
  - E.g. in accordance to ECs?#
- Allow flexibility for EC parameters for specific batch(es) when supported and/or documented internally by the company and therefore available for inspection?
- Where there is more "Do and Tell", Assessor – Inspector interaction is required:
  - What do Inspectors need that they do not currently have?
  - What do Assessors need?
  - Do communication barriers exist?
- How will regulators account for different levels of PQS maturity? Or changes to PQS effectiveness over time?
- What practical effect would more use of "Do and Tell" have on inspection practice?
- Suggestion to include some PQS information in the MAA (as non-EC) . When would this be appropriate and why?
- Effective Lifecycle Management through the PQS depends on Manufacturer and MAH. How are regulators assured of the adequacy of the latter's PQS?

PQS and Change Management

Presented by Wassim Nashabeh

Content of eCP: considerations for ePACMP



Should an Inspection Management strategy be included in ePACMP?

Expanded Change Management Protocol: *Inspection Management*

Site Inspection Assessment:

- **Risk-ranking tool** provides a generic approach to assess site and process risks for technical transfers, incl. CMOs
- Will help to understand the level of overall inspectional risk at the recipient site
- Will serve as an evaluation of the GMP compliance status of the recipient site
- **Highlights the importance of assessor-inspector collaboration**

What value would the regulators find in a sponsor generated site risk assessment protocol?

Expanded Change Management Protocol: *Site inspection assessment - risk ranking tool*

Risk factors	
Facility	CMO vs. internal network Facility experience Inspection history etc.
Product	Raw materials used Tech. Transfer experience Product knowledge etc.
Process	Similarity to existing process Process knowledge Manufacturing complexity etc.
Experience	Workforce experience Quality system Technology competence etc.

Risk level	Submission requirements
low	In scope of protocol, moderate change submission (CBE-30, Ib var.); stress stability data only
medium	In scope of protocol, moderate change submission (CBE-30, Ib var.), incl. 6-month real-time stability data
high	Outside of scope of protocol, i.e. major change submission

Are these the right risk factors to consider? Should submission requirements be linked to risk level?

For Discussion

- Should an Inspection Management strategy be included in ePACMP?
- What value would the regulators find in a sponsor generated site risk assessment protocol?
- Are these the right risk factors to consider? Should submission requirements be linked to risk level?