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

Application of ICH Q12 Tools and Enablers

Post-Approval Lifecycle Management Protocols

Outline

- **Introduction:** evolution of PACMP concept
- **Expanded (multi-site, multi-product) change management protocols** (*Roche, presenter: Wassim Nashabeh*)
- **Risk-based (step-2) Variation classification in case of changes for biological products in accordance with an approved Post Approval Change Management Protocol** (*J&J/ Janssen, presenter: Ronald Imhoff*)

Introduction: ICH Q12 – evolution of PACMP concept

- Current Q12 draft GL contains evolving concepts regarding PACMPs that warrant a further discussion based on examples:

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587 2. Broader protocols
588 ○ A single PACMP can outline one or more groups of changes for a particular
589 product, or one or more changes that would be implemented across multiple
590 products (e.g., change in stopper across multiple products) and/or at multiple
591 sites (e.g., change in analytical method across multiple sites, change in
592 manufacturing site(s) across multiple products) where the same risk
593 management plan and proposed studies/ tests would be applicable across all
594 impacted products.

2

513 A PACMP typically involves two steps:
514 1. Step 1: Submission of a written protocol that describes the proposed change, its
515 rationale, risk management as well as proposed studies and acceptance criteria to
516 assess the impact of the change(s); This protocol is approved by the regulatory
517 authorities in advance of the implementation of the proposed change(s).
518 2. Step 2: Submission of the actual results/data based on the approved protocol by the
519 regulatory authorities according to the agreed categorization (classification). In certain
520 cases (e.g., non-critical changes, repetitive changes), an approval of the second step
521 may not be required, as it will be managed within the applicant's pharmaceutical quality
522 system.

Example 1: Roche/Genentech

- Site Transfers under an "Expanded Change Management Protocol": multi-site/ multi-product approach (*presenter: Wassim Nashabeh*)
- Key Question: **what needs to be in ICH Q12 to enable such expanded approaches in all regions?**

Expanded Protocols - Outline

- Introduction/ background
- Case Study: Considerations for expanded post-approval change management protocol (ePACMP) for Site Transfer:
  - Scope
  - Quality Risk Management (QRM)
  - Inspection Management/ PQS
  - Comparability
  - Validation
- Summary

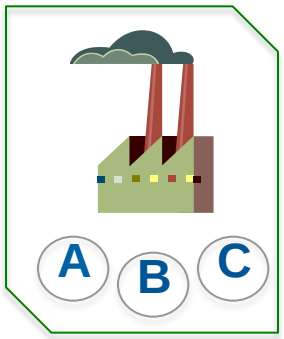
Site Transfers are required to support network mobility and mitigate risk post-approval

- To meet world-wide demand for the drug
  - Manufacturing plant capacity is often limited and must be balanced across a broad network of facilities and products
- To mitigate risk associated with single sourcing to ensure supply to patients
  - Reduce Risk for out of stock situations
  - Safety backup / risk mitigation, in case one site cannot produce material for various reasons
    - Natural disasters
    - Loss by fire
    - Equipment break-down
    - Flexibility to supply all markets

Site Transfer of Product A to Site Y Leveraging ‘traditional’ protocol in the US & EU

Defined business need

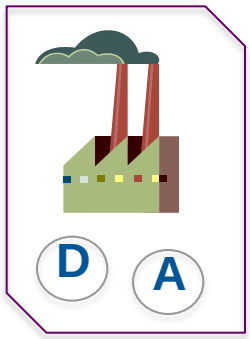
Submit protocol describing site transfer acceptance criteria for product-site combination



Drug Substance
Donor Site X

Product A

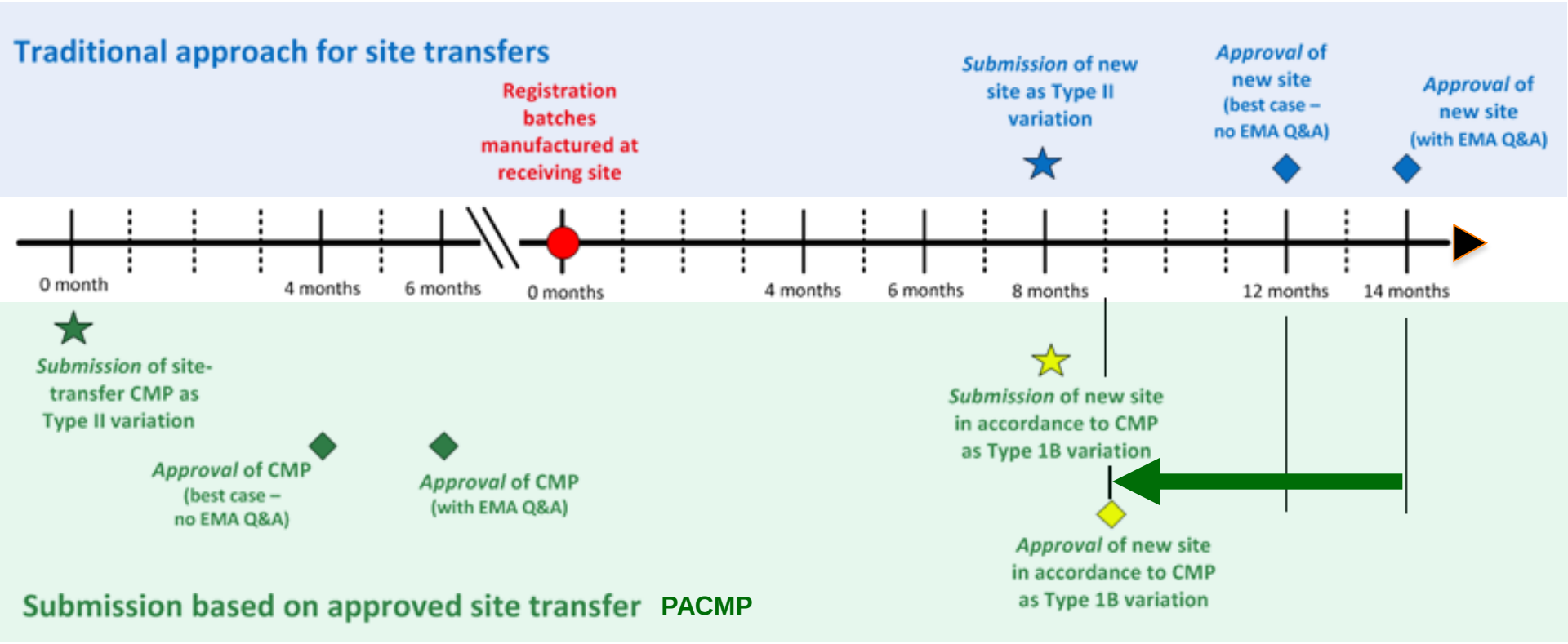
Execute transfer per defined requirements in protocol



Drug Substance
Receiving Site Y

Supplement/ variation with data demonstrating acceptance criteria met

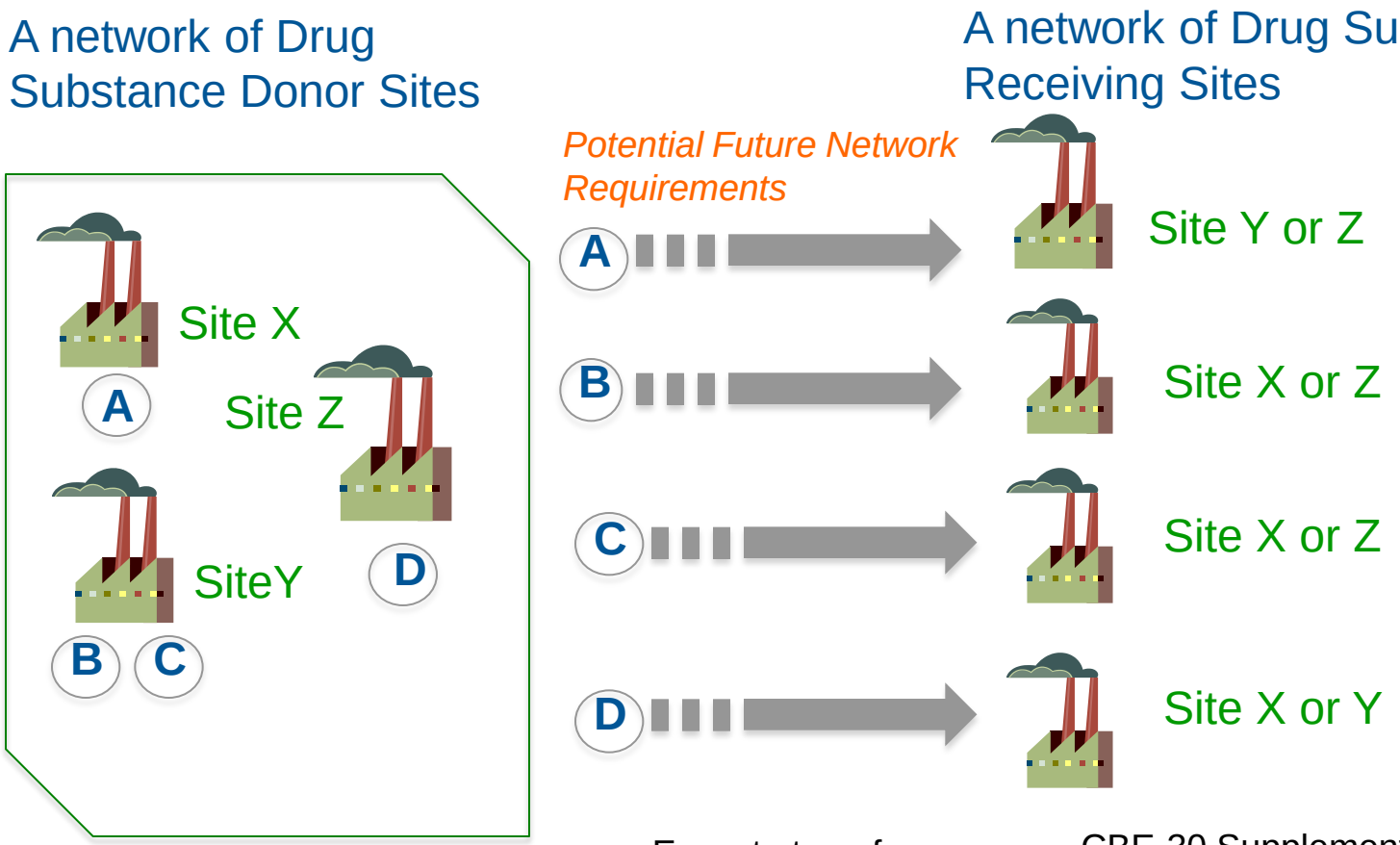
Example (EU): Biologics DS manufacturing site transfer - Benefit of PACMP Approach vs. „Traditional“ Approach*



- **Up to 5 months faster approval of the site change using a PACMP (time benefit similar in US)**

**Note: approval timelines for type II variation in this scheme include positive CHMP opinion and Commission Decision*

Site Transfer Leveraging expanded Comparability Protocol (eCP) – a reflection of the experience with US-FDA

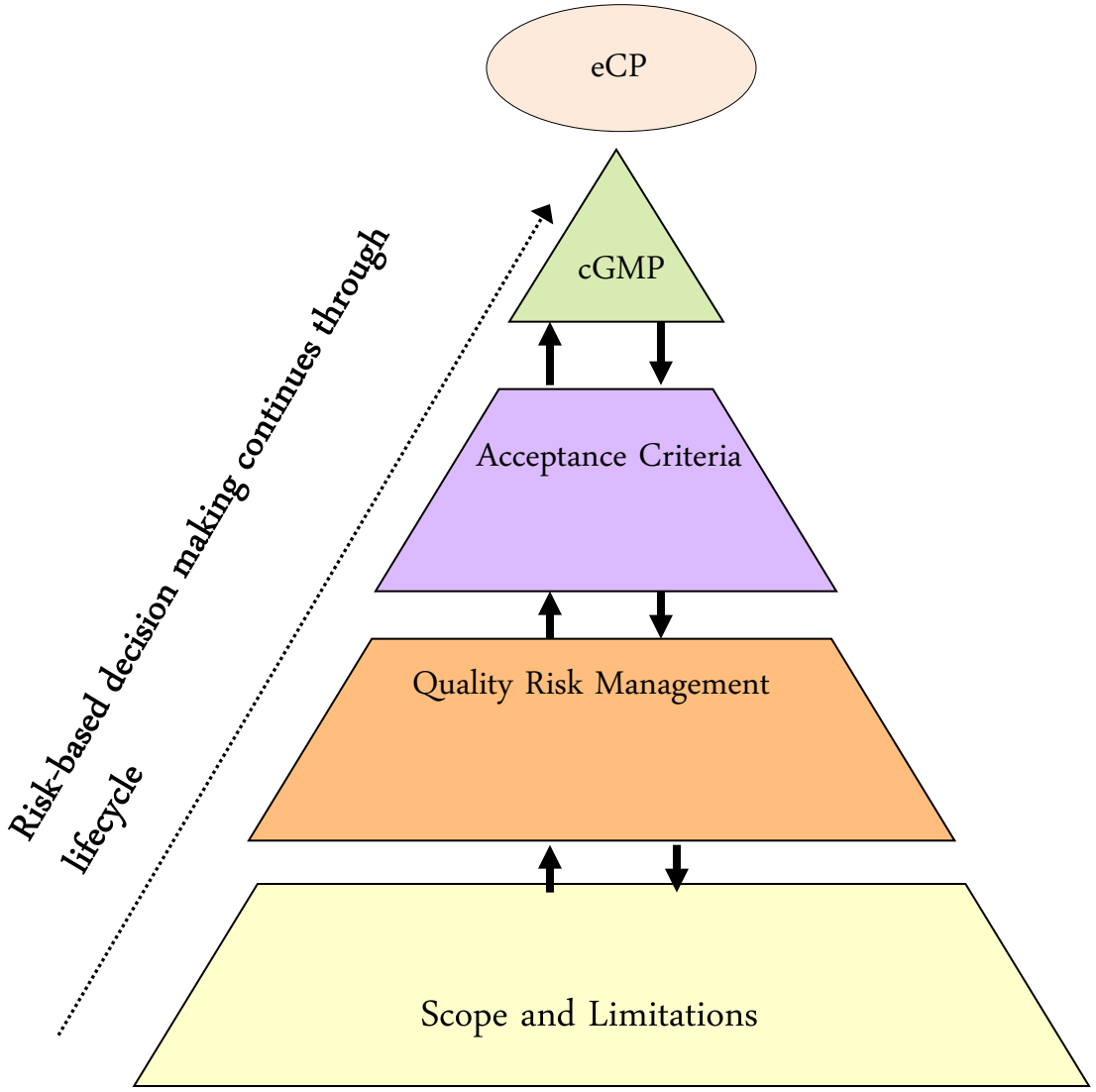


Submit eCP describing site transfer acceptance criteria broadly for both Site and Product

Execute transfer per defined requirements in eCP

CBE-30 Supplement with data demonstrating acceptance criteria met

eCP Site Transfer General Strategic Framework



Strategy & Scope of the Site Transfer eCP

- **The primary objective of the Site Transfer eCP is to support the mobility across drug substance manufacturing sites, i.e. transfer from one donor site to one or more recipient site(s)**:
  - Several monoclonal antibodies
  - Several sites, incl. CMOs (*sites already licensed with appropriate inspection record)*
  - **Reduces the number of regulatory submissions of similar content and drives consistency**
  - Effectively leverages concepts of Quality Risk Management and ICH Q9
  - Builds upon company's experience with site transfers across products and sites
- Scope excludes opportunistic significant process changes; typical process adaptions linked to scale and equipment differences in scope

Site Transfer Risk Assessment Considerations

- **Performed for each site transfer**
- **Identifies, scores, and documents** the potential hazard and harm associated with each unit operation and process change, as well as the prevention and detection controls
- **Accounts for known elements of the process**
  - Robustness
  - Existing controls
  - Potential impact to product quality
- **Considers the subjectivity of risk assessment**
  - Team
  - Facilitator
  - Training
  - Consistency and calibration of risks
  - Severity, Occurrence, Detection scoring definitions

Site Transfer Risk Assessment Example

Failure modes prospectively identified and assessed by team of experts

Process Step	Process Change	Hazard	Harm (Hazard Effect)	Severity	Hazardous Situations (Potential Causes of Hazard)	Preventative Controls	Occurrence	Detection Controls	Detection	PRN (SxO)	RPN (SxOxD)	Recommended Action
Chromatography (general)	Pool tank mixers are different	Localized product aggregation	Potential product quality impact (e.g., aggregate formation)	6	Different agitator design, improper controls around mixing	Batch record instructions	4	CofA testing, Batch record verification of mixing controls	4	24	96	Validation of mixing to establish mix times and speeds during Engineering run
Affinity Chromatography	In-line dilution of equil buffer (required due to buffer tank volumes)	Wrong concentration of equil buffer due to in-line dilution loaded on column	Process performance impact (yield loss). Minor shift in process performance/ product characterization. Potential product quality impact.	6	Equipment failure (e.g., conductivity probe, pump motor, flow meter)	Mixing ratio defined in automation, automation limits for conductivity, automation controls around equipment failure, calibration, PM, probe standardization procedures	2	Automation controls for conductivity prior to column going in-line, chromatogram review, pump alarms, equipment failure results in skid hold	2	12	24	

<u>Note:</u> Risk Priority Number (RPN) is the product of the Primary Risk Number (PRN) and the score for probability of detection.

Risk Prioritization Matrix

Identified thresholds of risk acceptability incorporated in overall applicability to Site Transfer eCP

			Probability of Detection				
			2	4	6	8	10
Primary Risk Number (PRN)	100	High Risk	200	***400***	***600***	***800***	***1000***
	80		160	320	***480***	***640***	***800***
	64		128	256	***384***	***512***	***640***
	60		120	240	***360***	***480***	***600***
	48		96	192	288	***384***	***480***
	40		80	160	240	320	***400***
	36	Moderate Risk	72	144	216	288	***360***
	32		64	128	192	256	320
	24		48	96	144	192	240
	20		40	80	120	160	200
	16		32	64	96	128	160
	12	Low Risk	24	48	72	96	120
	8		16	32	48	64	80
	4		8	16	24	32	40

Risk Priority Number (RPN):	
192–1000	High: Risk control action(s) required. Risks with RPN values ≥360 (indicated in ***boldface italic*** type) require immediate notification of appropriate management and decision makers.
72–160	ALARP: Reduce risk to As Low As Reasonably Practicable
8–64	AC: Acceptable

Note: The RPN is the product of the PRN and the score for probability of detection. Due to the standardized scoring criteria, 30 different RPNs are mathematically possible.

Inspection Management (overlap with Inspection/ PQS session)

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**

Site inspection assessment - risk ranking tool
(overlap with Inspection/ PQS session)

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

Comparability Approach

Transfer to a new site with facility fit changes with no expected change to product characteristics

Out of scope of protocol concept

Category	Components
A	The basic package: • QC lot release data, including potency • extended physico-chemical characterization methods • accelerated degradation, with real-time stability and commitments • process-related impurity levels (host cell proteins, DNA, Protein A)
A+B	Biological characterization: • Fcγ receptor assays, FcRn, ADCC • Biacore or other binding assays
A+B+C	Animal PK or PK/PD studies: • rodent PK may suffice • may need primates for PD
A+B+C+D	Clinical PK (comparability bridging study): • direct comparison to licensed process material in human subjects
A+B+C+E	Clinical experience or efficacy • may need to confirm efficacy, lack of AEs, lack of immunogenicity • might be a “clinical experience” study, or head-to-head vs. licensed process

Overall Comparability Plan for Site Transfer

- Drug Substance must meet all release and in-process specifications, as well as comparability acceptance criteria (e.g., tolerance intervals [TI, 95/99]) derived from entire manufacturing history
  - Specifications provide assurances of product quality
  - Comparability acceptance criteria provide assurances of consistency with previous processes
- Analytical profiles from selected characterization tests are consistent with pre-change material in side-by-side comparisons
- Process performance attributes
  - Cell culture performance
  - Purification process yields
  - Impurities levels
- Drug Substance degradation studies consistent with pre-change material

Submissions without Real Time Stability Data
(link to lifecycle strategy)

Qualification Lot Stability Plan

Material	Lot Description	Test Conditions	Data at Time of Filing
Drug Substance	Three qualification lots and three control lots	40°C/75% RH	14 days (completed) data provided in CBE-30
	Three qualification lots	5°C	Data provided in AR
	Three qualification lots	–20°C	Data provided in AR
Drug Product	One qualification lot	5°C	Data provided in AR

AR = Annual Report; RH = relative humidity.

- Traditionally rate-limiting to site transfer timelines, this approach speeds time to regulatory submission and introduction to the market

Process validation

- Provides an overview of validation project plan and validation master plan for the site transfer in accordance to the current PQS system

- Summary of validation studies performed to support the site transfers, e.g. studies adopted from donor site and new studies at the recipient site will be part of the step-2 implementation submissions (CBE-30 or type Ib)

Summary

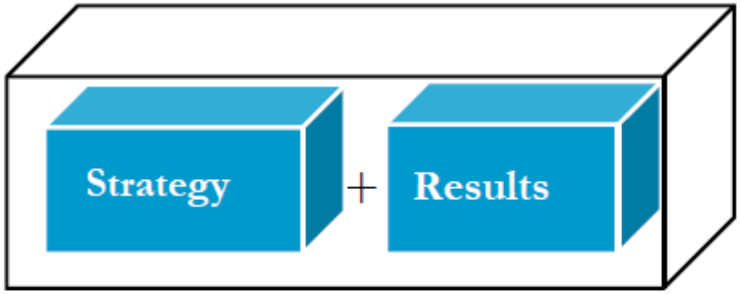
eCP Strategic Component	ePACMP step 1 contents (registration of protocol)	ePACMP step 2 contents (change implementation)
Overall Strategy (Scope and Limitations)	Defined scope and limitations	Demonstrate requirements of scope met, including process changes associated with transfer
QRM	Description of QRM program and approach to site transfer risk assessment	Documented risk control strategy and executed risk management report **summary**
Comparability & Stability	Comparability plan, real-time stability commitments and acceptance criteria (**product Specific**)	Data demonstrating that acceptance criteria are met
Process Validation	Overview of validation program	Summary of facility/equipment differences and applicable validation; **Validation summary** data support the process, facility/equipment, and method transfer
Inspection	Description of Site inspection assessment - risk ranking tool	Outcome of inspection risk ranking tool defines actual change submission requirements

Example 2: J&J/ Janssen

- Risk-based (step-2) Variation classification in case of changes for biological products in accordance with an approved Post Approval Change Management Protocol (*presenter: Ronald Imhoff*)

Current PACMP procedure for chemical and biological products

Figure 1: Post Approval Change Management Protocols



Currently
Evaluation of a proposed variation as a 'whole' (Strategy + Results)

Early Step 1:

Submission of a Change Management Protocol

Type II Variation

Fast Step 2:

Reporting of implementation of a change in accordance with an approved protocol

Type IA_{IN} or IB

Why is step 2 for biologal products per definition IB ?

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520 cases (e.g., non-critical changes, repetitive changes), an approval of the second step
521 may not be required, as it will be managed within the applicant's pharmaceutical quality
522 system.

2

- The use of a PACMP is enabled through an effective quality risk management system (ICH Q9) and change management system as part of a sound pharmaceutical quality system (ICH Q10).

- Components of a PACMP include the following elements:
  - A detailed description, including a rationale, of the proposed change(s). The differences before and after the proposed change should be clearly highlighted.
  - Specific tests and studies to be performed, such as: characterization, release, stability as appropriate, in-process controls. The PACMP should include a description of the analytical procedures and proposed acceptance criteria for each test or study.
  - A quality risk management plan to assess the impact on product quality following implementation of the change(s), and if multiple changes are to be implemented, addressing the potential risk from the cumulative effect of multiple changes and/or how they are linked.
  - Supportive data from previous experience with the same or similar products related to: development, manufacturing, characterization, release, and stability to allow for risk mitigation
  - Discussion on the appropriateness of the approved control strategy to oversee the planned changes
  - Proposed reporting category for the implementation of step 2 of the PACMP

Examples of PACMP

Type of change	Risk level
Reprocessing: re-filtration (0.45 and 0.2 µm in series) of Protein A clarified harvest in the event of a filter integrity failure	Very Low
Reprocessing: Repeating the viral removal filtration in the event of a filter integrity failure	Low
Reprocessing: Re-concentration in the event of over-dilution in the Concentration / Diafiltration manufacturing step	Low
Scale up: Change in size (width) of chromatography column. No impact on Critical Process Parameters (established condition)	Very Low
Addition of drug substance manufacturing site (within company). No change in manufacturing process. New site already inspected by an European Inspectorate	Medium

Reprocessing: Re-filtration of Protein A clarified harvest in the event of a filter integrity failure

PACMP (step 1) contains:

- Description of the change
- Data from reduced scale studies; 2 successful independent filtrations
- Commitment to perform one commercial scale study
- Proposed tests with acceptance criteria
- Risk assesment
- Commitment that reprocessing is within established hold time

- Does this require review of the results by the Agency (step 2) before the change can be implemented?

Proposed reporting category (step 2) based on risk assessment taking into account amongst others

- complexity of the change
- available (reduced scale) data to support the proposed change
- impact on product quality (CQA/CPP/CMA)
- product and process understanding
- status of PQS

Risk level	Variation classification for step 2
Very low	**Do and Record** (PQS & Product Quality Review)
Low	**Do and Tell**: Type IA
Medium	**Do and Tell**: Type IA_{IN}
High	**Tell and Do**: Type IB

Proposed variation classification for step 2 of the PACMP

Type of change	Risk level	Risk-based Variation classification . How to file the data?
Reprocessing: re-filtration (0.45 and 0.2 µm in series) of Protein A clarified harvest in the event of a filter integrity failure	Very Low	**Do and Record** (PQS & Product Quality Review)
Reprocessing: Repeating the viral removal filtration in the event of a filter integrity failure	Low	**Do and Tell**: Type IA
Reprocessing: Re-concentration in the event of over-dilution in the Concentration / Diafiltration manufacturing step	Low	**Do and Tell**: Type IA
Addition of drug substance manufacturing site (within company). No change in manufacturing process. New site already inspected by an European Inspectorate	Medium	**Do and Tell**: Type IA_{IN}

Proposed variation classification for step 2 of the PACMP

Type of change	Risk level	Risk-based Variation classification . How to file the data?
Scale up: Change in size (width) of chromatography column. No impact on Critical Process Parameters (established condition)	Very low	**Do and Record** (PQS & APR)
Change in anion exchange resin (chromatography column). Has impact on Critical Process Parameters (established condition)	Low	**Do and Tell**: Type IA
Major change in fermentation process (continuous perfusion to fed batch) Has impact on Critical Process Parameters (established condition)	High	**Tell and Do**: Type IB

Summary

- The current PACMP procedure where step 2 for biological products is per definition a type IB variation is too restrictive.

- The variation classification for step 2 proposed in step 1 (type II variation) should be risk-based. Options are **do and record** (PQS), **do and tell** (type IA or IA_{IN}) and **tell and do** (IB)

- This principle could also be applicable for chemical substances.

Questions

- The proposed reporting category for step 2 should be risk based. What would be an appropriate tool for this risk evaluation and how is the reporting category then defined?
- Linked to bullet 1.
  How should the Commission's Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2010/C 17/01) that supports the Variations Regulation (Commission Regulation (EC) No 1234/2008) be adapted?
- What are the challenges of implementing this in all ICH regions?
- Is there a need to differentiate between chemical and biological products?

Questions, continued

- Question from previous presentation (expanded protocols): **what needs to be in ICH Q12 to enable such expanded approaches in all regions?**