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Advantages, Opportunities & Challenges of Adopting the Post Approval Change Management Plan (PACMP)

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- **The basis for a Post Approval Change Management Plan (PACMP)**
  - Industry Perspective
  - PACMP as a Function of a Comprehensive Control Strategy
  - Regulatory Experience with Comparability Protocols
- **A Summary of PACMP Expectations & Examples**

HOW CAN PACMP BE SUCCESSFUL?

- Realize tangible benefit from investing in enhanced development
- Increase clarity of how established conditions can improve post-approval change management expectations - based on 'criticality'
- Empower/leverage the *inspectable* quality system, particularly change management, e.g., 'do & tell' & 'do & document'
- Reduce current inventory timeline for global approval of a single PAC (5-7 years)
- Increase PAC consistency & predictability for industry & regulators
- Simplify regulatory approaches to expedite continuous improvement
- Avoid 'retrospective application' such that every change needs PACMP
- Maintain appropriate balance of submission content & inspection quality assurance

ICH Q8 OPENED THE DOOR . . .

". . . the demonstration of greater understanding of pharmaceutical & manufacturing sciences can create a basis for flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided."

". . . opportunities exist to develop more flexible regulatory approaches, for example, to facilitate:

- *Risk-based regulatory decisions (reviews & inspections)*
- *Manufacturing process improvements within the approved design space described in the dossier without further regulatory review;*
- *Reduction of post approval submissions;*
- *Real-time quality control leading to a reduction of end-product release testing.*

To realize this flexibility the applicant should demonstrate an enhanced knowledge of product performance over a range of material attributes, manufacturing process options & process parameters."

ICH Q12 CREATED TO COMPLETE WHAT ICH Q8, Q9, Q10 & Q11 STARTED

ICH Q8 (R2) *Pharmaceutical Development*, 2009, p. 5 – 6.

DON'T RE-INVENT THE WHEEL

- SUPAC (US Scale-Up Post Approval Change Guidelines)
- Comparability Protocols (Draft 2003 Guideline for BTx Applications)
- EMA Commission Guideline (2010/C 17/01) & Variations Regulation (Commission Regulation EC No. 1234/2008)
- FDA PACMP Proposal 2007/2008 (Presentations by M. Nasr, C-W. Chen, J. Clark, et.al.)
- PhRMA Draft Regulatory Agreement Concept Paper (Unpublished July 2007)
- Multiple examples developed by individual companies in conjunction with QbD regulatory applications (2005 – Present)

ICH Q12 – PACMP CONCEPT

The 'post approval change management plan' (PACMP) allows for specific changes to be pre-described to regulators & agreement reached on the scientific approach & data expectations that will support the change.

- Improve clarity & predictability to plan & prosecute changes, especially complex.[1]
- Expedite approval of change application that confirm suitability of the change with pre-defined data & reduced regulatory change classification based on PACMP approval.[2]
- A PACMP can be constructed for a single change or can support multiple changes.[3]

[1] Often viewed as Major changes requiring 'prior approval' in current regulatory change systems

[2] PACMP approval prior agreement of the change management approach

[3] Annex II provides illustrative examples of different types of PACMP, an example of a PACMP for a single change (to a manufacturing site for a drug substance) & an example for the more general management of such site change.

WHAT IS A PACMP?

- *Post Approval Change Management Plan*?
- *Post Approval Change Management Protocol*?
- *CMC Post-Approval Management Plan*?
- *Comparability Protocol*?
- *Regulatory Agreement*?
- *Lifecycle Management Plan*?
- *All of the Above*?

DESCRIPTION OF A PACMP

A written, comprehensive plan,* submitted in a regulatory application, that prospectively describes post-approval changes & the assessment of the impact of those changes on product quality & includes the following elements:

- Regulatory filing category & supportive data for each type of change
- Justification for filing category for each change based on risk assessments & scientific knowledge
- Differentiation for changes to be submitted for regulatory review from those managed within a manufacturer's quality system

*A PACMP is a comprehensive plan because it can encompass many potential changes through the product lifecycle in contrast to a comparability protocol which applies to a specific change.

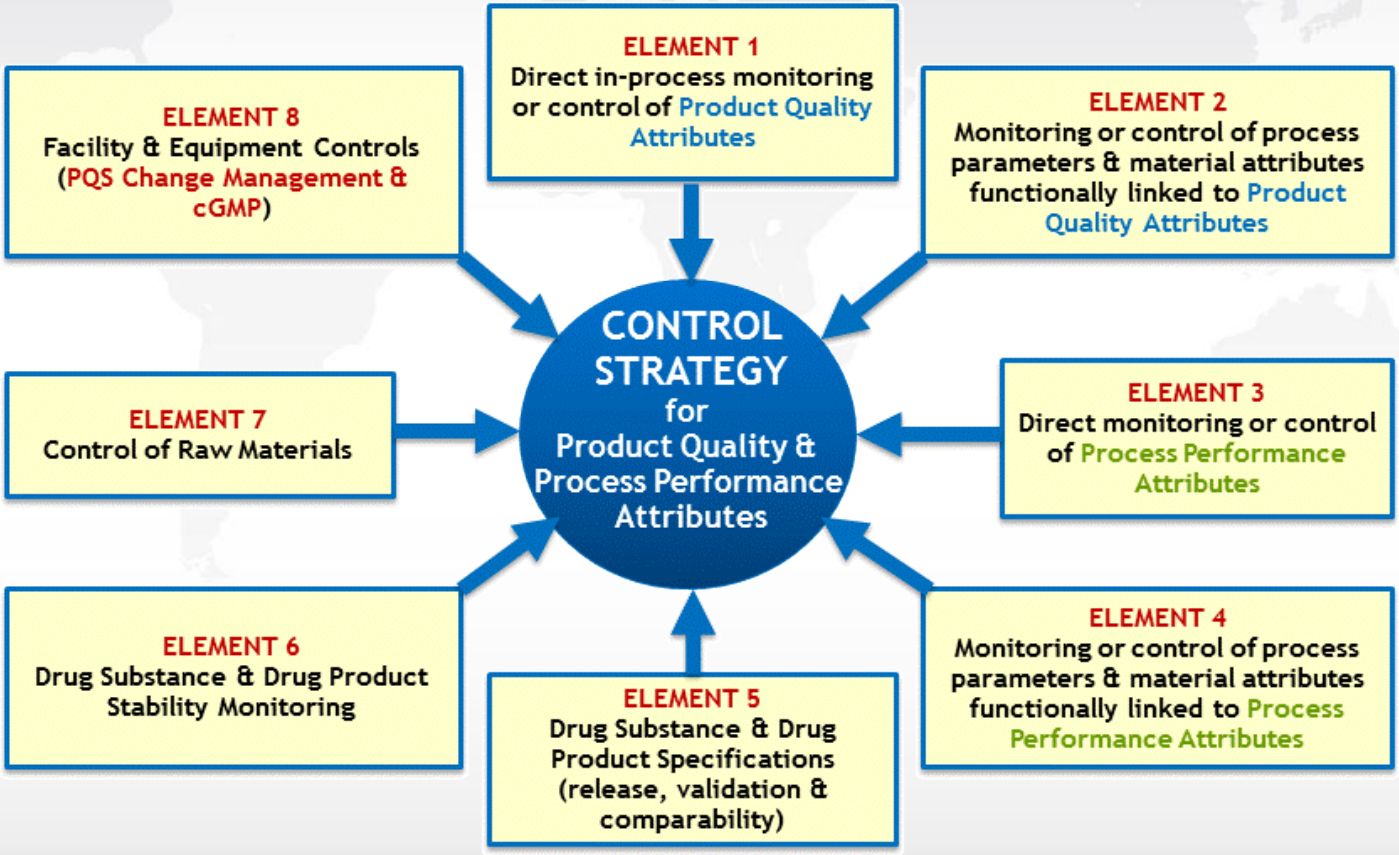
PACMP ELEMENTS EXTRAPOLATED FROM ICH Q10

*"Throughout the product lifecycle, companies are encouraged to evaluate opportunities for innovative approaches to improve product quality."**

- **Process Performance & Product Quality Monitoring**
  - Assure performance w/in a state of control
  - Identify opportunities for continuous improvement
- **Change Management**
  - Assurance of appropriate science & risk-based assessments
- **Control Strategy**
  - Established by QRM
  - Mfg. process parameters, controls & operating conditions
  - API, component & product specifications & material attributes

*ICH Q10

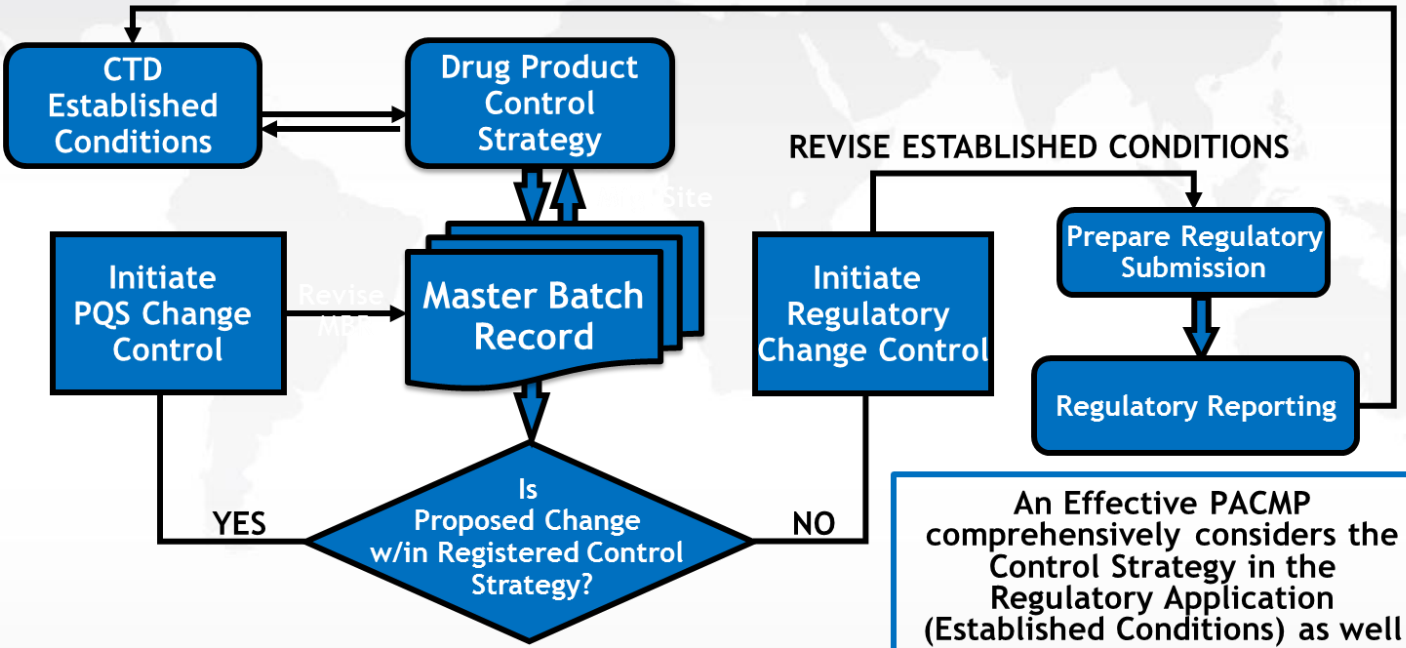
PACMP = COMPREHENSIVE CONTROL STRATEGY



PACMP REGULATORY EXPECTATIONS

- Detailed description of the proposed changes & their justification
- Risk assessment of the impact of each change on product quality
- Robust justification of the approved control strategy to detect & manage risks associated with proposed changes
- Description of studies, methods & criteria used to evaluate changes
- For biologics, the approach to demonstrate comparability
- Report-ability for each change with appropriate justification
- For multiple changes, description of how changes are related & justification for integrating studies to demonstrate quality assurance

CHANGE MANAGEMENT



An Effective PACMP comprehensively considers the Control Strategy in the Regulatory Application (Established Conditions) as well as the robustness of Change Management in the PQS

REPORTING CATEGORY EXAMPLE FOR APPLICATIONS WITH QBD

TYPE OF CHANGE	IMPACT	NOTIFICATION		
		FDA	EMA	PMDA
CPP that Requires Concomitant Change to Control Strategy	Changes to process steps or process parameter ranges that impact CQAs of DS &/or DP & require a concomitant change to the control strategy.	PAS	TYPE 2	PCA
	Changes to process steps or process parameter ranges that require a change to the intermediate control strategy (such as a change in the point of control of an intermediate CQA) that has no impact on DS or DP CQAs.	CBE	TYPE 1B	PCA
CPP w/o Concomitant Change to Control Strategy	Revision of CPP Design Space boundaries without impact to CQAs of DS or DP.	AR	TYPE 1A	MCN
CPP w/in Design Space	None	PQS	PQS	PQS
NCPP				

PAS = Prior Approval Supplement CBE = Changes Being Effected AR = Annual Report PQS = Pharmaceutical Quality System
NCPP = Non-Critical Process Parameter PCA = Partial Change Notification MCN = Minimal Change Notification

FREQUENT POST APPROVAL CHANGES

Manufacturing Site & Scale

- Where development & commercial experience demonstrate site & scale independence:
  - Change in Site – Annual Report
  - Change in Scale – Pharmaceutical Quality System

Stability to support post approval changes

- Where DS/DP has been shown to be equivalent & DS/DP is stable
  - No additional stability studies required

Change to analytical methods

- Where new method is validated & demonstrates equivalent or better confirmation of a CPP or CQA
  - Annual Report or internal change management

Packaging

- For packaging materials in direct contact with drug substance
  - Annual Report where six months of accelerated stability results demonstrate all acceptance criteria are met

EXAMPLE OF PACMP FOR DRUG SUBSTANCE

POST APPROVAL CHANGE	EVALUATION	ACCEPTANCE CRITERIA	POST APPROVAL COMMITMENT	US REGULATORY NOTIFICATION
Change in Mfg. Process Reagents, Solvents, etc.	• Risk Assessments • Revised MBR • Batch Verification	Conformance to CQA/Specifications	Full Stability Commitment for One Batch	AR - Intermediates CBE-30 - DS
New or Alternate Rework Procedure				
Mfg. Site Change w/Approved Mfg. Process		Conformance to CQA/Specifications + cGMP Inspection		AR
Change in w/in Design Space		Conformance to CQA/Specifications		CBE-30
Change to IPC	• Trend Analysis • Risk Assessments	Conformance to CQA/Specifications	None	AR
Extension of Retest Period	Results from Extension of Stability Protocol	Meet Approved Protocol Criteria	None	AR
Change in Packaging Material	• Risk Assessments • Equivalent or Improved MVTR	Conformance to CQA/Specifications Results from 6 mos. Acc Stability for 3 Batches or Lean Stability	Full Stability Commitment for One Batch	AR
Mfg. Scale Change	• Risk Assessments • Revised MBR • Batch Verification	Conformance to CQA/Specifications	None	AR or PQS

Adapted from several industry examples of Post Approval Protocols & Plans

EXAMPLE ELEMENTS OF A PACMP FOR A LARGE MOLECULE

PACMP ELEMENT	DESCRIPTION
Proposed Change	Transfer from facility 1 (2K disposable) to facility 2 (12K fixed stainless) including associated facility fit elements (NEXT SLIDE)
Rationale	Meet anticipated commercial demands
Risk management	QRM tools used in development will be updated reflecting changes
Proposed studies	Additional development required to support changes (NEXT SLIDE). Analytical comparability (including accelerated stability). Validation & ICH stability from full scale GMP batches. Development data supports expiry
Acceptance Criteria & Conditions	No change in release or stability specifications or acceptance criteria in line with this change. Pre-defined comparability criteria will be established to support change
Reporting Category	Downgrade to moderate to enable implementation
Supportive information	Updated CTD sections with information/data where that is available at time of PACMP submission. Protocols filed for sections where data is not available (NEXT SLIDES)

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Update on 2K/12K strategy

Analysis by market on acceptability of registering "alternative" DS processes

- Same process Scaled up or Alternative Process

8-9 main facility/scale dependent differences identified

	Process Area	Facility/Scale Difference	Mitigation/ Justification
1	Upstream, scale-up	Longer Inoculum Expansion	➢ Process development studies ➢ UVCA
2	Bioreactor equipment	2K: plastic/disposable; 12K: stainless steel	➢ MSAT/PharmSci pilot plant ➢ Process development studies
3	Bioreactor, base titrant	2K: sodium hydroxide; 12K: sodium carbonate	
4	Bioreactor	Control & range of process parameters (pH and temp)	➢ Process development studies
5	Harvest process	2K: depth + 0.2 µm; 12K: centrifuge, depth + 0.2 µm	➢ MSAT/PharmSci pilot plant
6	Viral clearance	Viral inactivtion: Triton Conc (1.0% to 0.25%), Incubation Time; Virus Retaining Filtration: Loading; AEX/CEX: Resin Lifetimes	➢ VC studies in support
7	DS, container	2K: PETG Bottles; 12K: Celsius Bags	➢ Development stability; ongoing
	DS, storage temp	2K: -70 °C; 12K: -40 °C	
8	Stainless exposure	2K: bags; 12K: In-process hold vessels SS	➢ MSAT Hold studies in SS ➢ Reduced hold times at 12K. ➢ Sig. SS exposure at 2K (e.g. UFDF, Chrom skids)
9	In-process holds Under Evaluation	Downstream in-process holds times and temperatures (refrigerated versus ambient)	➢ In-process holds studies

Bio Therapeutics Pharmaceutical Sciences

PACMP CONTENT: ILLUSTRATIVE EXAMPLE (DRUG SUBSTANCE)

CTD	PACMP CONTENT	POST APPROVAL CHANGE SUBMISSION CONTENT
PACMP	Change Protocol	Confirmation supplement aligned to protocol
3.2.S.2.2	12K Process Description	Replace 2K w/12K process description
3.2.S.2.5	Process Validation Protocol(s)	12K process validation data
3.2.S.2.6	2K Development & Analytical Comparability Results	Development & analytical comparability data
3.2.S.7.1	12K Stability Protocols to 2K Content	Replace w/section containing 12K S.7.1 (studies & updated conclusions)
3.2.S.7.3	Additional 12K Supportive Data & ICH Stability Data (where available)	Update stability inclusive of all available data

WHAT IS THE VALUE OF A PACMP?

- Establishes a paradigm for Product Lifecycle Management
  - Serves as a source of mutual understanding of post approval commitments between applicant, reviewer & inspector
  - Highlights the importance of a Comprehensive Control Strategy
    - ✓Focuses on relevant regulatory assessment criteria
    - ✓Regulatory Commitments including design space
    - ✓Change Management
  - Provides an incentive for continuous improvement
  - Extends risk-based/scientific approach beyond product development & initial commercialization
  - Improves product Lifecycle Management planning
- Reduces the volume of prior approval supplements & variations
- Expedites approval of changes

VOLUME OF PACM-PROTOCOLS

PACM PROTOCOLS 2010-2014 APPROVED BY EMA

SCOPE	TYPE II	MAA
New site for manufacture and/or QC testing of the drug substance	11	1*
New site for manufacture and/or QC testing of the drug product	14	2
Change to the manufacturing process of the drug substance	7	1
Scale-up of the drug substance manufacturing process	1	
Change to the preparation of a cell bank	1	1
Change to the manufacturing process of the drug product	3*	1*
Change to the container closure system of the drug substance or drug product	2*	
Other	1	
TOTAL	46 PACMPs: - 42 for biologics - 4 for chemicals	

* Includes one PACMP for a small molecule

Pascal Venneugues, EMA, EU DIA 2014.

QUESTIONS FOR DISCUSSION

- What content should be included in the PACMPlan?
- Should the PACMPlan be a product Lifecycle Management Plan as opposed to a protocol with limited scope?
- Should the PACMPlan make accommodations for a variety of options, i.e., PACM & Comparability Protocols, etc.?
- Should the PACMPlan be a Regulatory Commitment?
- How often should the PACMPlan be updated?
- How much quality is enough quality?

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