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One Voice of Quality (1VQ) for PACs & Practical experience with PACMP

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Oct 2024 –CMC Strategy Forum Europe

Life forward

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The Vision for PACs

Designing and implementing an agile science and risk-based efficient, predictable global post approval change (PAC) management system that

- facilitates a state of control
- foster continuous improvement
- reduces risk of drug shortages

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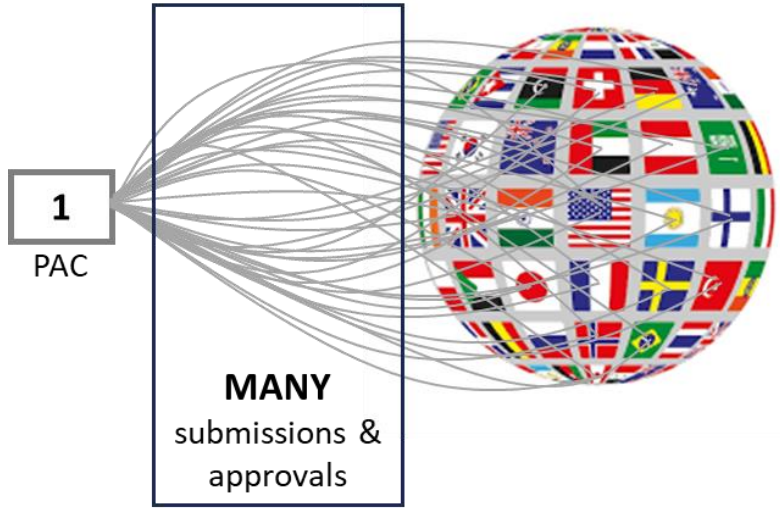
Global PAC Regulatory Complexity *in Theory*

Seen from a **regulatory agency's side**

Seen from a **company's side**



Current PAC Management is driven by
national frameworks
not by science globally

One PAC requires prior approval by multiple countries that have

- **different** reporting thresholds
- **different** requirements
- **different** timelines

First to last country approval can be often 3-5 years or more

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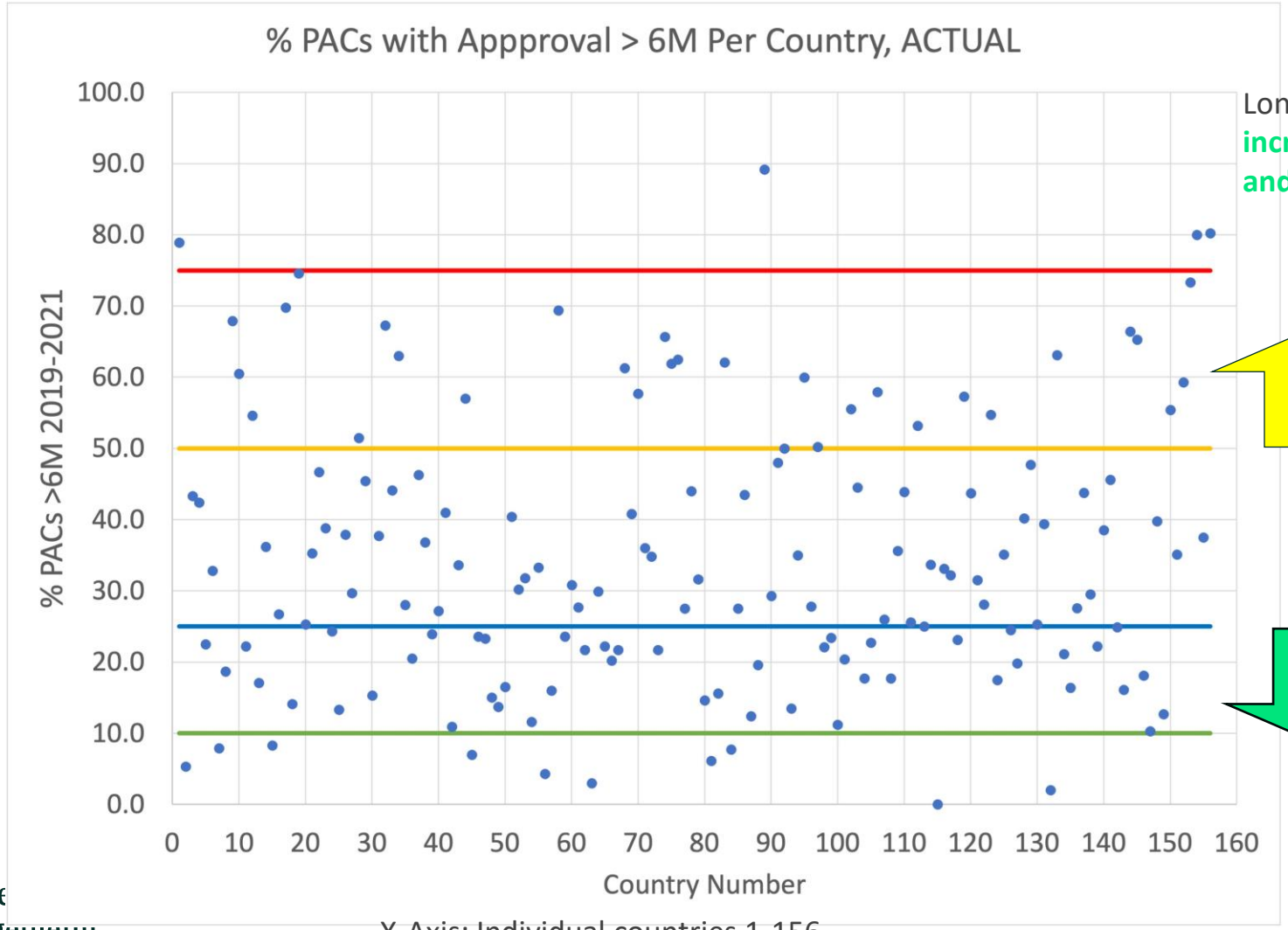
Global PAC Regulatory Complexity *in Reality*

>125,000 PAC data points from 16 of the top 25 pharma companies 2019-2021



Y-Axis: Percentage of all PACs that took more than 6 months for approval per country

X-Axis: Individual countries 1-156

Long global approval timelines **increase supply chain complexity and risk of drug shortage**

~20% of all countries

<10% of all countries

Vinther, Ramnarine, Gastineau, O'Brien, Brehm, Fryrear. Therapeutic Innovation & Regulatory Science https://doi.org/10.1007/s43441-024-00614-9

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Patients Deserve to Receive Every Dose of the Medicine They Need, Every Single Day and yet *Drug Shortages are Common Across the World*

Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world. Science is the highest personification of the nation because that nation will remain the first which carries the furthest the works of thought and intelligence. Louis Pasteur

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Drug Shortage is a Complex Problem Globally with no Simple Solution. When Looking for Root Cause

We Cannot Stop at the First Why

A Common Unifying Objective

Uninterrupted supply of safe, efficacious medicines

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One Voice of Quality for Post Approval Change (1VQ for PAC) Initiative

Sponsored by the Chief Quality Officers (CQOs) from the Top 25 Pharma Companies

CQOs are responsible for the PQS & decision makers on quality matters

Since beginning of Initiative CQOs have mainly focused on **ICH Q10 Opportunity**

Vinther, Ramnarine, Gastineau, O'Brien, Brehm, Fryrear. Therapeutic Innovation & Regulatory Science https://doi.org/10.1007/s43441-024-00614-9

ICH Q10 Annex 1:
Potential opportunities to enhance science and risk based regulatory approaches and regulatory flexibility for PACs

Scenario	Potential Opportunity
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	Opportunity to: • facilitate science based pharmaceutical quality assessment • enable innovative approaches to process validation • establish real-time release mechanisms
4. Demonstrate **effective pharmaceutical quality system and product and process understanding**, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk-based approaches for regulatory inspections • facilitate science based pharmaceutical quality assessment • **optimise science and risk based post-approval change processes** to maximise benefits from innovation and continual improvement • enable innovative approaches to process validation • establish real-time release mechanisms

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Global PAC Regulatory Complexity has existed for many years

2005

*"**Delays may occur in the availability of medicines to patients** around the world".*
"Delays in the implementation of innovation and continual improvement for existing products may occur due to different expectations in the three regions"
ICH Q10 Concept Paper

2008

For companies that *"demonstrate effective PQS and product and process understanding" there is an **opportunity to "optimize science and risk-based PAC processes** to maximize benefits from innovation and continual improvement"*

ICH Q10 Guidance

2014

"The envisioned post-approval 'operational flexibility' has not been achieved"

ICH Q12 Concept Paper

2022

"The current operating environment requires prior approval by the regulatory authority of each region and country individually. For a product to be globally available to patients, this can translate to numerous and often ***duplicative regulatory review*** processes and time frames. This presents ***regulatory complexity that can significantly constrain manufacturer agility in addressing challenges such as supply chain disruptions***."

ICMRA-ICH-PIC/S-IPRP Joint PQKMS Reflection Paper

Global PAC Regulatory Complexity has not improved

(as anticipated by the ICH Q10 business plan)

Average score*	ICH Q10 2005 Business Plan Stated Potential Benefits
3.6	Improved process performance
3.2	A reduction in the costs of internal failures (rejects, reworks, reprocessing and investigations) as the quality system guideline drives improvement
2.6	A reduction in the costs of holding duplicate stock and operating multiple processes as improvements and changes are made more effectively across all regions
2.5	A reduction in the costs of preparing / reviewing certain regulatory submissions
2.9	Enhanced assurance of consistent availability to the patient

* Potential benefits scored by 19 CQOs (from top 25 pharma companies)

Things have…

1. gotten significantly worse/complex
2. gotten slightly worse/complex
3. no change
4. improved slightly (less complex)
5. improved significantly (less complex)

Since ICH Q10 was published in 2008

→ ICH Q10 has not delivered yet on the potential benefits expected when completed in 2008

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Eight Approaches to Reduce Global PAC Regulatory Complexity (suggested by 1VQ for PAC Initiative)

1 More PACs in PQS only when effective PQS	2 Inspectors assess company PQS effectiveness	3 Increased regulatory reliance
8 Regularly publish data on PAC review timelines for each country	**Reducing Global PAC Regulatory Complexity**	4 Harmonized, structured and standardized data elements
7 Assessors consider PAC reporting level based on PQS effectiveness	6 Adoption of the 6 months WHO guidance timeframe by all regulatory agencies	5 Industry and regulatory agencies jointly standardize process and data for assessing PACs

PQS: Pharmaceutical Quality System

Objective:

A science and risk-based global regulatory framework that facilitates timely implementation of PACs

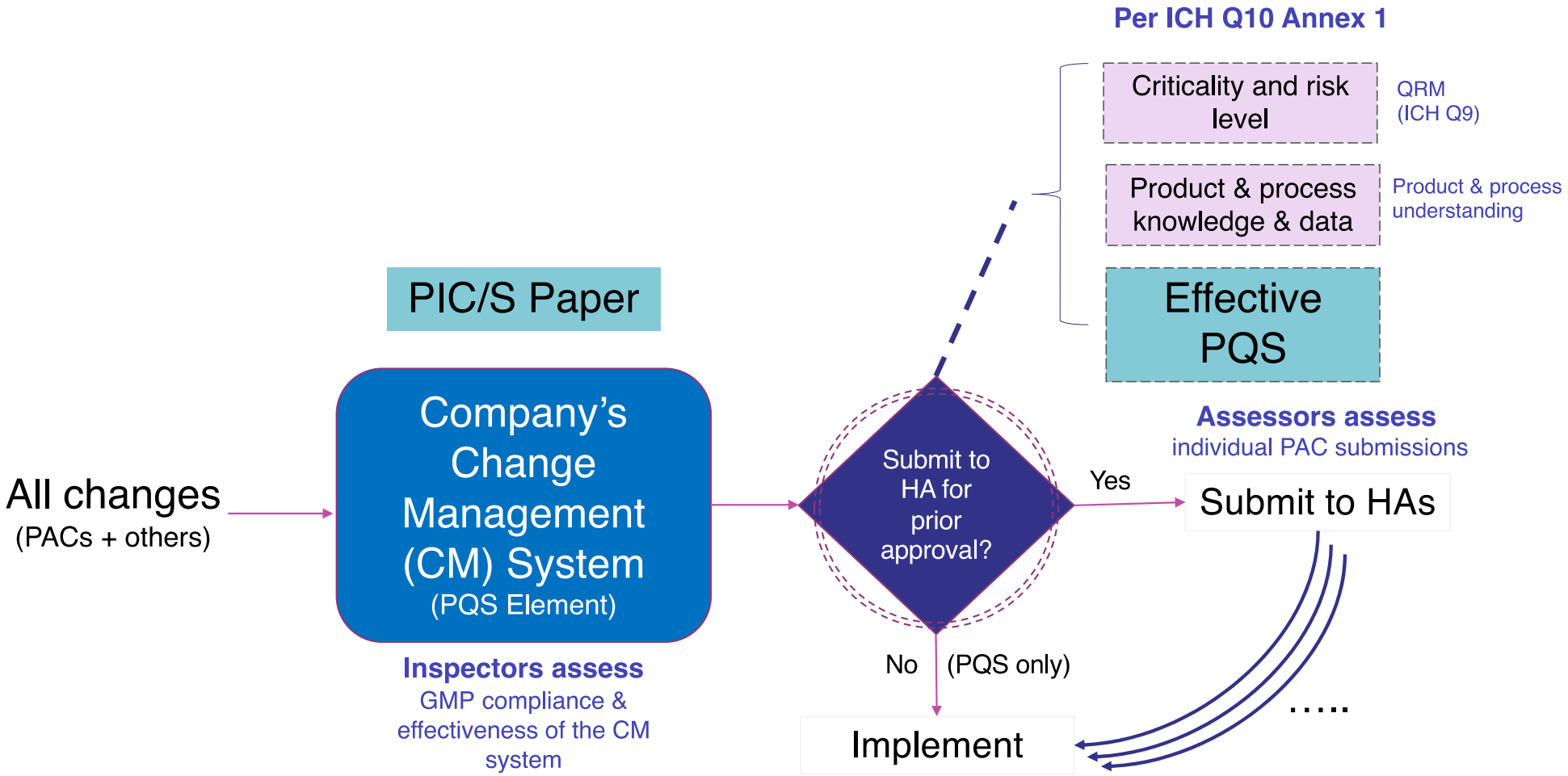
PIC/S Recommendation Paper

3.5 It is considered that application by a pharmaceutical manufacturer … ***will provide evidence of the effectiveness of their PQS*** in relation to risk-based change management.

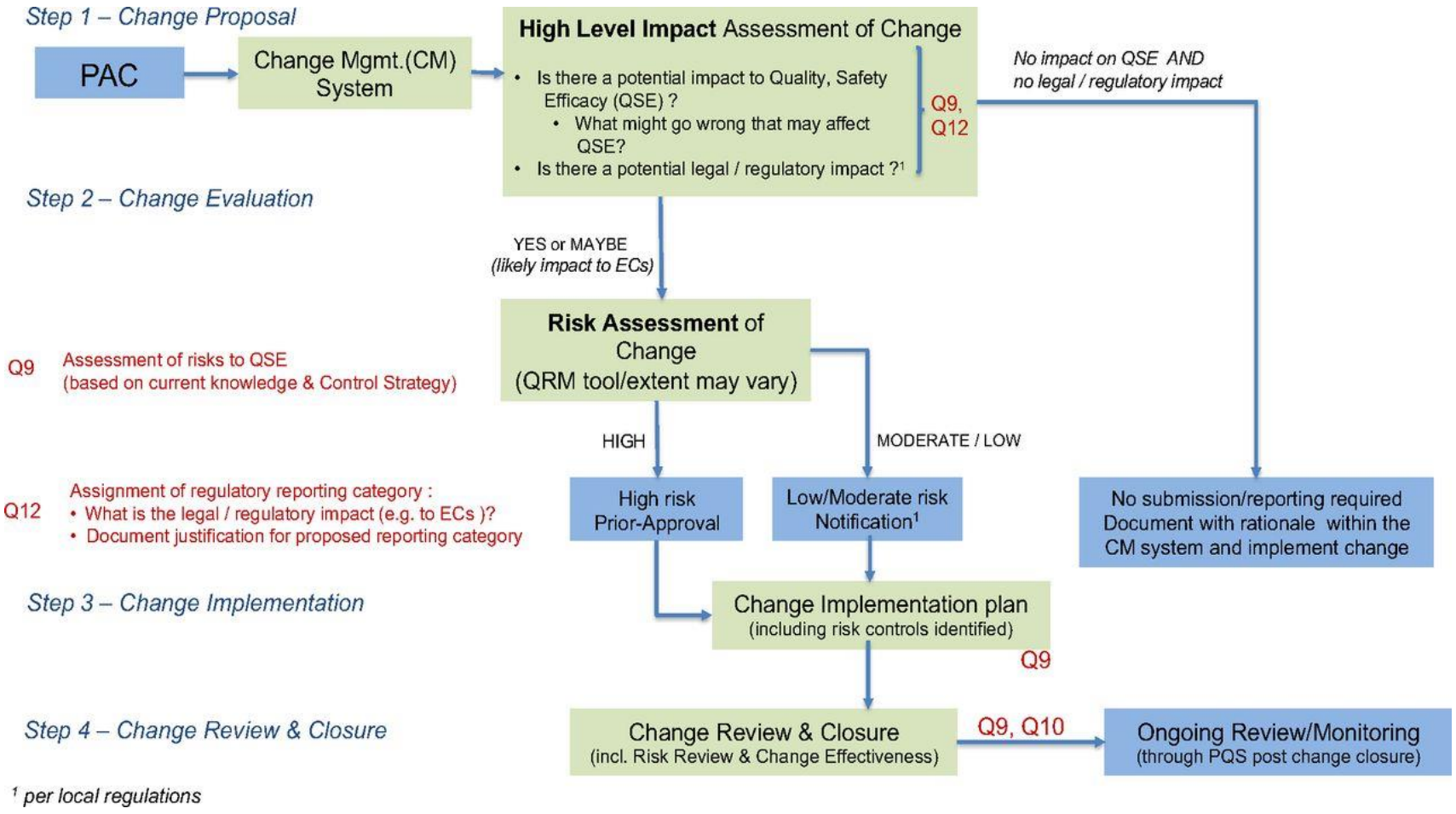
3.6 Effective change management is important not only in the context of the aforementioned PIC/S GMP requirements, but also in the context of ICH Q10, which sets out the ***potential for risk-based regulatory oversight for companies that demonstrate an effective PQS*** is in place (see Appendix 1). This guidance may also be useful in supporting implementation of the principles and concepts in the ICH Q12 guideline where ***mature risk-based change management within an effective PQS is considered foundational to enable greater regulatory flexibility in reporting of post-approval changes***."

PIC/S How to Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management. 2021

PIC/S Defines Effective PQS for PAC



1VQ for PAC: Effective Management of PAC in PQS Science and Risk-based Approach



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Ramnarine E. Industry One-Voice-of-Quality (1VQ) Solutions: Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS)-through Enhanced Science and Risk-Based Approaches, PDA Journal of Pharmaceutical Science and Technology, 74(4), pp. 456–467, Vinther A., Bruhin K. et al. (2020)

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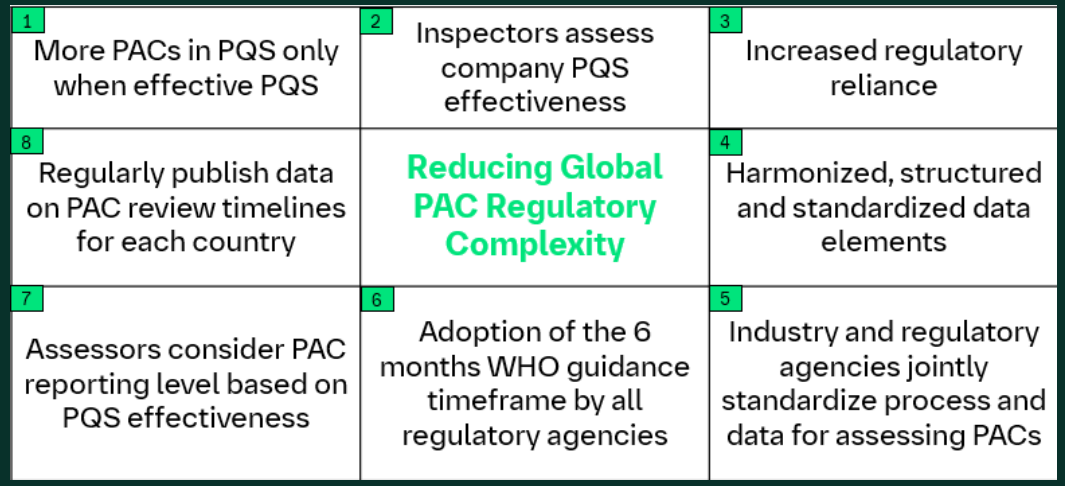

To make this happen we need to work together and address current challenges with a systems thinking approach, not by individual stakeholder actions in isolation

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Take Home Message

- The problem of global regulatory complexity PACs has been acknowledged as a problem for more than two decades. The problem has not become smaller.
- Numerous approaches have been attempted to solve the problem, usually by one stakeholder at a time (e.g. one national regulatory agency), or as an intention with no commitment for implementation (e.g., ICH Q series, WHO guidance).
- Increased reporting burden for companies will not solve the problem. History has proven this to be true.
- Not until we treat this problem as – COMPLEX – will we be able to lessen it.
  Complex problems require systems thinking and collaboration by all stakeholders.
- That we haven't tried….. yet

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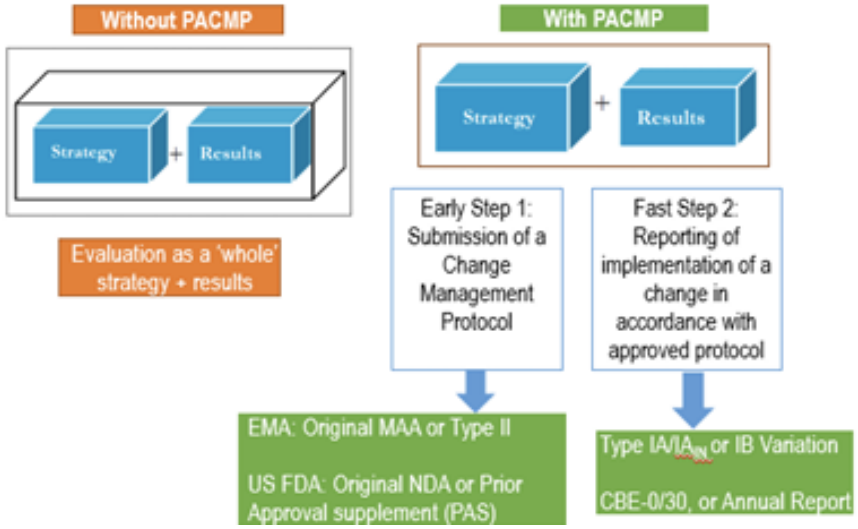
PACMP - Examples

PACMP (Post Approval Change Management Protocol)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 March 2012
EMA/CHMP/CVMP/QWP/586330/2010
Committee for Medicinal Products for Human Use (CHMP)

Questions and answers on post approval change management protocols

efpia
European Federation of Pharmaceutical Industries and Associations

Final, 7th July 2020

Reference Document on Post-Approval Change Management Protocols (PACMPs)

- Cave: US in case PAI is needed no „downgrading“

Example 1 (EMA)

- 2012 – one of the first PACMP with EMA
- Additional drug substance manufacturing site for biological product

- No scientific advice meeting to discuss comparability approach

- Protocol submitted with outline of comparability approach e.g. release, stability and additional characterization testing
- No further supportive data included

  ➔approved without questions

- Data submitted as Type IB

  ➔approved without questions

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Example 2 (EMA)

- Additional drug product filling line for biological product
- Protocol submitted with outline of comparability approach
- No further supportive data included

  ➔approved without questions

- Data submitted as Type IB
- Deficiency letter

  ➔ approval delayed

  ➔ no real benefit regarding faster approval

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Example 3 (EMA)

- Drug substance process change and additional drug substance manufacturing site for biological product submitted as part of ICMRA pilot program
  (Lead: EMA; Reviewer: FDA, PMDA, Health Canada; Observer: Switzerland, Brazil)
- With new process deletion of process parameters have been proposed
- PPQ was manufactured according to new process
- Protocol submitted in parallel to all authorities involved

- Data package not submitted in parallel
- Deficiency letter received from individual authorities
- Approval ongoing

ICMRA: International Coalition of Medicines Regulatory Authorities

Example 3 (EMA)

- One authority had concern with deletion of testing parameters

  -> results of deleted parameters were requested

  -> reintroduction of testing has been necessary

  ➔ Learning: Clear description of change in protocol including details to allow authority to react

Example 4 (MRP)

- Additional drug substance manufacturing site for biological product
- Supply critical situation -> additional site urgently needed

- Several meetings with authority (RMS) to discuss
  - Timelines
  - Changes to be introduced with additional manufacturing site
  - Data to be submitted
  - Strategy to achieve faster approval e.g. use of PRIME Toolbox
  - Keep authority informed on progress of change
  - Keep authority informed on status of inspection (new facility)

Example 4 (MRP)

- Protocol submitted
- Changes could be introduced even after protocol has been approved
- Agreement to submit less stability data (3 months) and only 1 PPQ batch
- Commitment to only supply market once process validation was successful (3 PPQ batches)

  ➔ This would have resulted in a 3 months earlier submission of the data and therefore an earlier approval

However - change of assessor during procedure:

- Data from all 3 PPQ batches have to be shown
- Agreement to receive deficiency letter and provide data with response document

Example 4 (MRP)

Positive

- Authority was very cooperative
- Additional changes could be introduced later in the process
- Mistakes in dossier could be clarified during review
- Almost no question in the context of the deficiency letter

Challenge

- Change of assessor led to additional request
- Meeting frequency resulted in additional workload (preparation of meeting request / briefing book)

Thank you