

Effective Management of Post-Approval Changes in the Pharmaceutical Quality System

Thierry Gastineau – Sanofi Pasteur, Global Head Quality Advocacy, Culture & Innovation

Marcello Colao – GSK Vaccines, Global Quality Head China



Agenda

- Importance and Complexity of Post-Approval Changes
- ICH Journey from Q8 to Q12
- Pharmaceutical Quality System and PACs Management
- Risk-based Approach to Changes – 1VoQ
- Conclusions

Importance and Complexity of Post-Approval Changes

Thierry Gastineau – Sanofi Pasteur

Post Approval Changes (PACs) are Inevitable AND Necessary

To continually improve, maintain a state of control & ensure product availability

- Facilities age
- Routine operations require updates
- Industry practices change
- Supply chain and suppliers change
- Product & process knowledge grows
- Technologies evolve
- Regulatory requirements evolve
- Acceleration of innovations, incl. new digital capabilities

PAC Classification of Common Vaccine Changes

New standard
New working seed/ cell bank
Material replacement: equipment/ raw mat
Site discontinuation
Site Name Change
Standard Shelf Life extension
Standard Material modification
Compendial alignment
Dossier Alignment

Routine
48%

Continuous Improvement
29%

Assay Modification
Assay Removal
New Assay
New Specification
Process Improvement
Specification revision

Assay replacement
Process Improvement

Innovation
5%

Supply assurance
18%

New Site
Presentation discontinuation
Product discontinuation
Capacity increase

Changes
are part of
the product
life-cycle

The Challenge of PACs

Companies are globalized



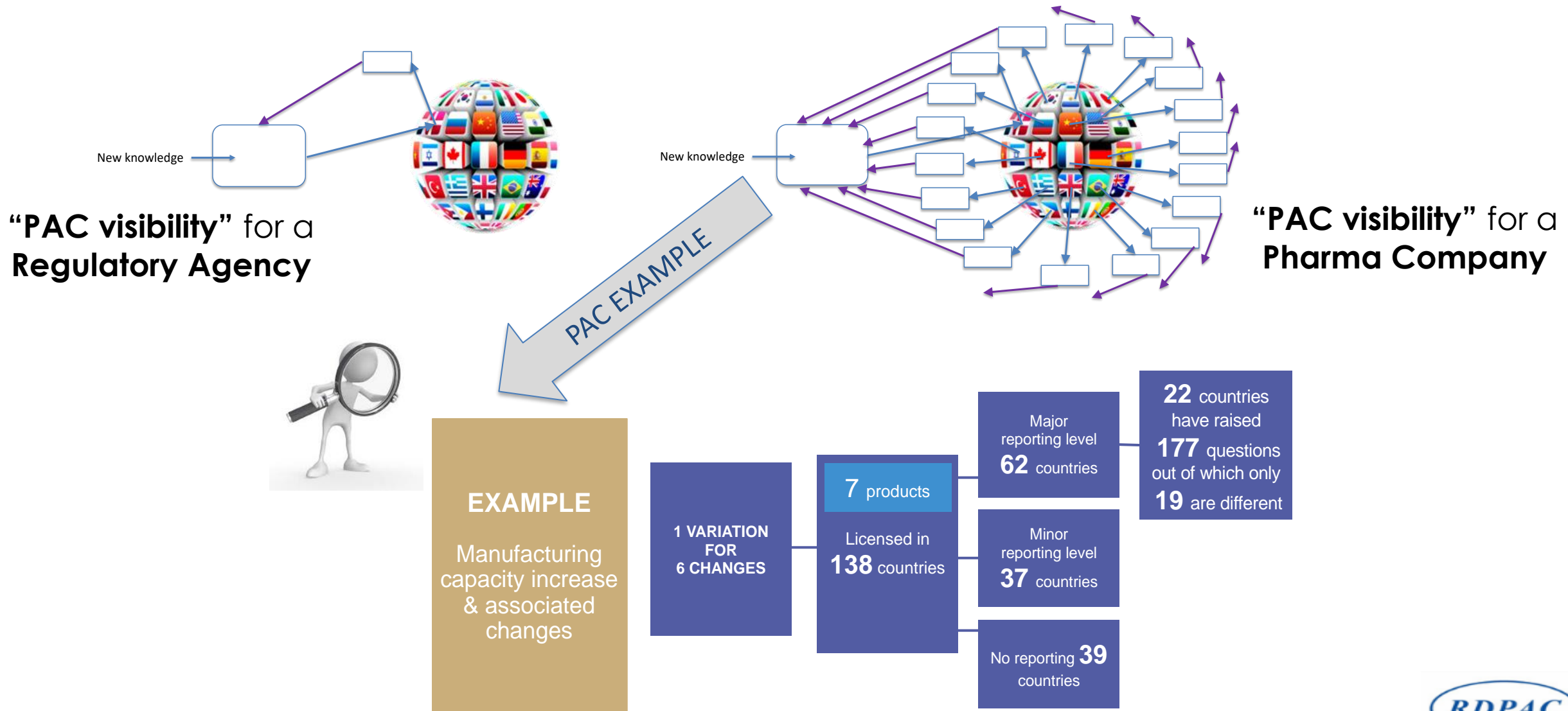
Ideally :
1 product for 1 world

Regulatory approvals are nationalized

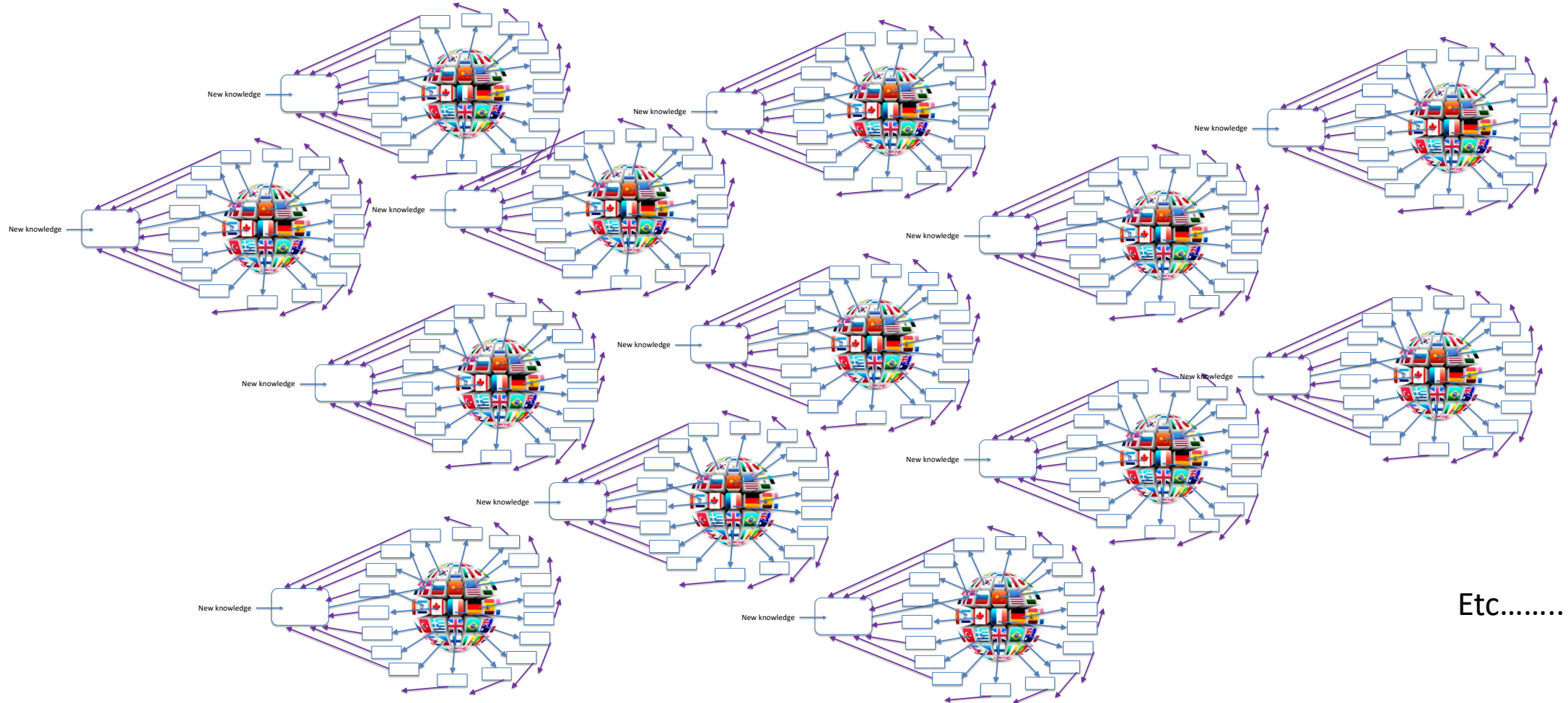


Reality :
1 product with 100+ approvals

Global PAC Regulatory Complexity



... & in Reality Many PACs at the Same Time*



*Larger companies have thousands of PACs awaiting approval at global level every year

Confidential for restricted use only

So, why improving the management of PACs ?

- The overall complexity is a **barrier to timely implementation of continuous improvements** and a **contributing factor to drug shortages**
- We need a **more agile global regulatory framework** where PACs can be implemented in days or weeks instead of months or years particularly when they **reduce patient risk, improve compliance** and/or **enhance manufacturing process or test methods**

ICH Journey from Q8 to Q12

Marcello Colao – GSK Vaccines

A Long Journey Towards 21st Century Manufacturing



ICH Quality Implementation Working Group - Integrated Implementation Training Workshop

How ICH Q8, Q9, Q10 guidelines are working together throughout the product life cycle

ICH Q8, Q9 and Q10

Nov 2005 & Nov 2008

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED THIRTPARTY GUIDELINE

PHARMACEUTICAL DEVELOPMENT
Q8(R2)

November 2005

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED THIRTPARTY GUIDELINE

QUALITY RISK MANAGEMENT
Q9

June 2008

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED THIRTPARTY GUIDELINE

PHARMACEUTICAL QUALITY SYSTEM
Q10

Current Step 4 version
Issued 6 June 2008

- High level guidances (not prescriptive)
- Science and risk-based
- Encourages systematic approaches
- Applicable over entire product lifecycle
- Intended to work together to enhance pharmaceutical product quality

ICH Q8
(2005)

ICH Q9
(2005)

ICH Q10
(2008)

ICH Q11
(2012)

ICH

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ICH Quality Implementation Working Group - Integrated Implementation Training Workshop

ICH Q-IWG Integrated Training Programme

Quality: A New Paradigm

The new paradigm emphasize:

1. Quality must be mainly built in and it will not only improve by additional testing and inspection
2. Better utilization of modern science throughout product lifecycle
3. QRM is a key enabler throughout product lifecycle
4. Robust PQS, with appropriate knowledge management, assures quality throughout product life cycle
5. An integrated approach to development, manufacturing and quality for both industry and regulators

ICH

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ICH Q10 – Pharmaceutical Quality System

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL QUALITY SYSTEM
Q10

Current Step 4 version
dated 4 June 2008

Published in **2008** to enhance the quality and availability of medicines around the world in the interest of public health

Main objectives:

- Achieve product realisation
- Establish and maintain a state of control
- Facilitate continual improvement

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Q10 – An Opportunity to Enhance Science/Risk Based Regulatory Approaches

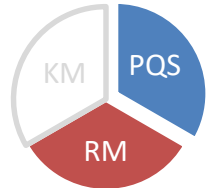
Annex 1

Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches *

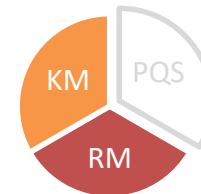
*Note: This annex reflects potential opportunities to enhance regulatory approaches.



1 - GMP compliance



2 - Risk-based inspections



3 - Science-based assessment

Companies operating under a framework comprising an effective PQS, along with sound product and process knowledge and risk management practices, should be eligible for **reduced regulatory oversight** when they demonstrate that an effective PQS is in place*

*PDA PtC paper 'PQS effectiveness for managing PAC' (2017)

Scenario	Potential Opportunity
1. Comply with GMPs	Compliance – status quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10).	Opportunity to: <ul style="list-style-type: none"> increase use of risk based approaches for regulatory inspections.
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	Opportunity to: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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.



4 - PAC regulatory flexibility

Q12 as Continuation of Q10

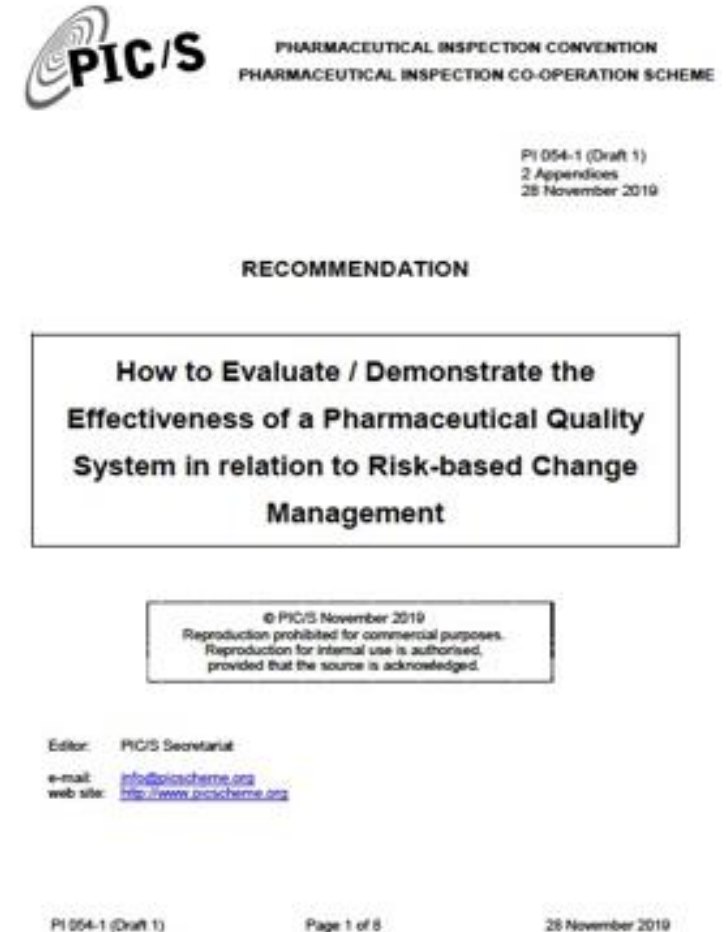
- ‘This guideline... **complements and adds to the flexible regulatory approaches** to post-approval CMC changes described in ICH Q8(R2) and Q10 Annex 1’
 - **Established Conditions** → critical / legally binding information, necessary to assure process performance & desired quality
 - **Risk-based categorization of changes**
 - ❑ Sufficient risk (to product quality) → **Prior-approval**
 - ❑ Moderate to low risk → **Notification**
 - ❑ Lowest risk → **Internally managed** and documented within the company PQS
- ‘An **effective PQS** as described in ICH Q10 and compliance with regional GMPs are **necessary to gain full benefit from this guideline**’
- ‘... **effective communication between assessors and inspectors** can facilitate regulatory oversight of product lifecycle management.’

Pharmaceutical Quality System and PACs Management

Thierry Gastineau – Sanofi Pasteur

What is an Effective PQS for PACs Management?

- Q10 – Main elements of PQS & key enablers
- Q12 – Change management, enabled by knowledge management, and management review
- PIC/S draft recommendation published in November 2019
 - Guidance on evaluating and demonstrating the effectiveness of a PQS in relation to risk-based change management
 - Inspectors perspective



What is PIC/S?



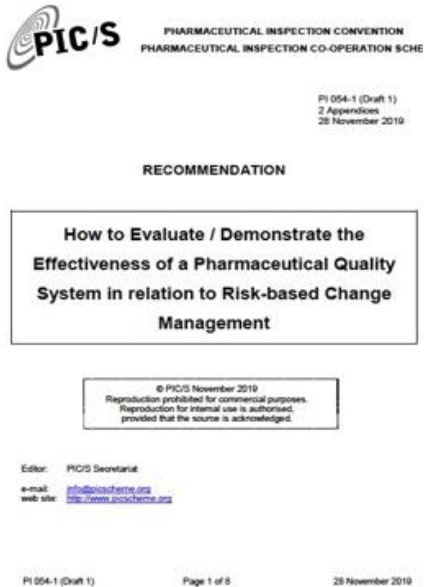
- Established in 1995
- 53 participating authorities across the world (USA, EU, Canada, Australia, Japan, Indonesia, Korea, Malaysia, Mexico, Singapore, South Africa, Thailand, Argentina, ...)
- Mission : ***to lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products.***

PIC/S Checklist - Objective



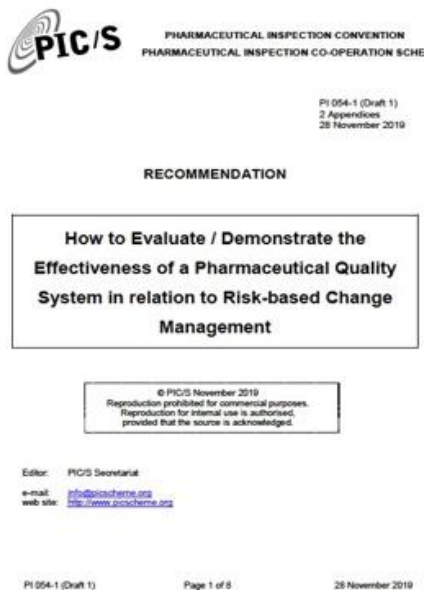
- Practical guidance for GMP inspectors when seeking to evaluate the effectiveness of a company's pharmaceutical quality system (PQS) in relation to risk-based change management. It covers all relevant steps in the change management process – change **proposal**, change **assessment**, change **planning and implementation**, change **review and effectiveness checks**. It indicates within each step the aspects that render the PQS to be effective in that area.
- They do not introduce any new GMP requirement.

Change Proposal



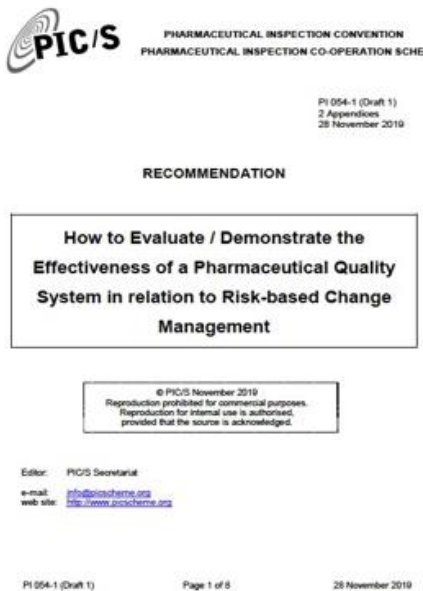
- Trigger for change
- Objectives, scope, expected outcomes and benefits of the change
- Impact to other products, processes, systems or sites
- Relevant experts involved
- Risk of not doing the change (e.g. loss of improvement opportunity)
- Impact on filings or regulatory commitments
- Timely evaluation and decision to accept/reject
- Management of risk if proposed change is not implemented

Change Risk Assessment



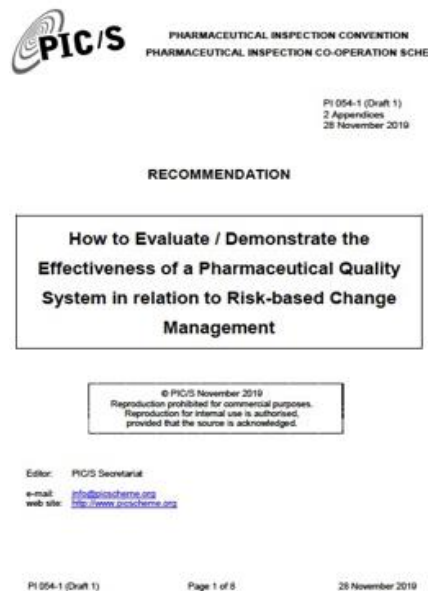
- Change impact assessment \neq change risk assessment
- Level of rigor and effort commensurate with risk. Appropriate QRM tool
- Assess potential risks of the change (to product quality, safety, efficacy) and benefits
- Risks to other products, processes, systems
- Risk controls (current and needed)
- Risks assessed using current product/process knowledge & appropriate data
- Change categorization based on risks

Change Planning & Implementation



- Risks drive change planning, timelines and priority
- Change acceptance & effectiveness criteria are pre-defined
- Risks with current state until change is implemented
- Interim controls to monitor or mitigate current situation until change has been implemented
- Implement risk controls identified
- Update risk assessments (as needed) during and after implementation
- Update regulatory filings as appropriate

Change Review & Effectiveness



- Change met its intended objectives and effectiveness
- Identified risk controls implemented
- Residual risks assessed
- Any unintended consequences or risks addressed
- Indicators of effectiveness post-implementation are met
- Any post-implementation actions needed are completed
- Update risks (as needed) post effectiveness assessment. Capture new knowledge and lessons learned
- Ongoing monitoring (e.g. as part of PPPQM, management review)

Based on ICH Q12 and Q10, there will be a Paradigm Change in the Way to Manage PACs

Reporting PACs based on **worldwide heterogeneous regulatory guidelines** which apply to all companies, **regardless their level of PQS maturity** and product knowledge



Reporting PACs based on companies **risk assessment**, providing appropriate **PQS maturity** and **product knowledge**, by applying ICH Q9, Q10 and Q12

Risk-based Approach to Changes

Marcello Colao – GSK Vaccines

Industry Solutions – One Voice of Quality

Senior Q Leaders
from 20+ companies
got together to answer
the question...

Voice
of Quality

PDA Journal
of Pharmaceutical Science and Technology



Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) - Through Enhanced Science and Risk-Based Approaches Industry One-Voice-of-Quality (1VQ) Solutions

Emma Ramnarine, Anders Vinther, Kimberly Bruhin, et al.

PDA Journal of Pharmaceutical Science and Technology 2020,
Access the most recent version at doi:[10.5731/pdajpst.2020.011734](https://doi.org/10.5731/pdajpst.2020.011734)

‘How can we (Industry Quality)
build trust with regulatory agencies so that more PACs can
be managed in the PQS only ?’

...or in other words, how can
a company be trusted to
make the PAC decision that
today resides with the
regulatory agency?

2

Create a standard risk-based assessment of PACs that incorporates latest product and process knowledge

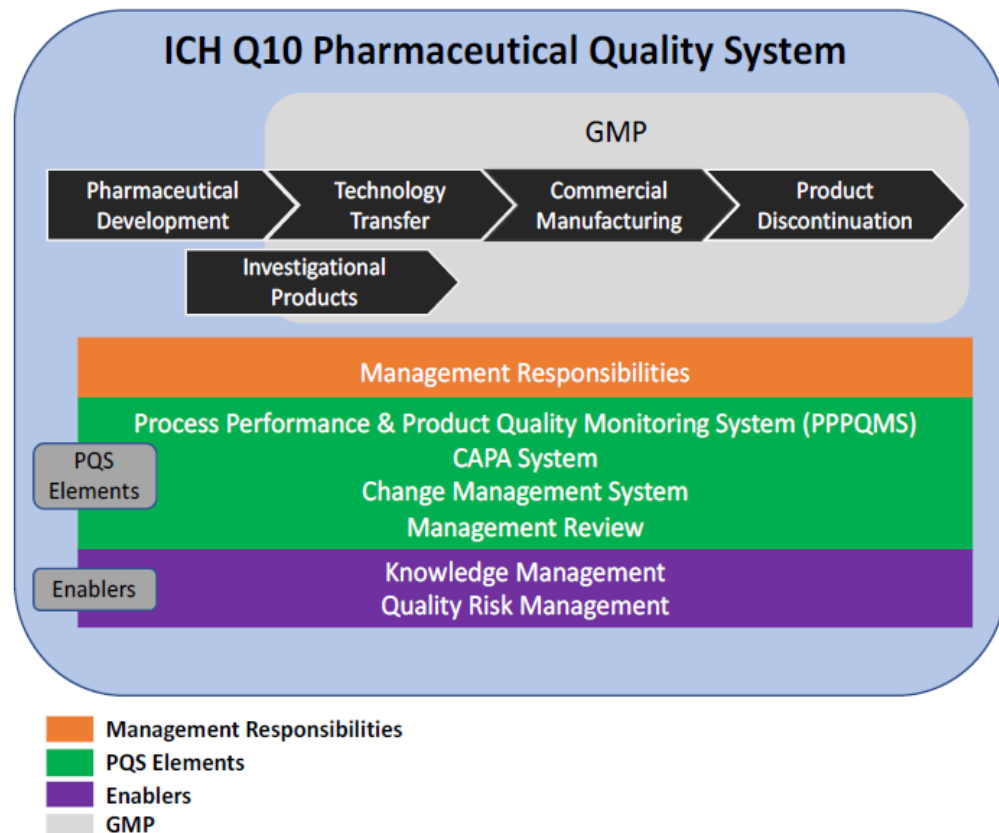
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Demonstrate how PACs can be effectively managed in the PQS so that more changes can be managed in the PQS or via notification pathways instead of prior approvals

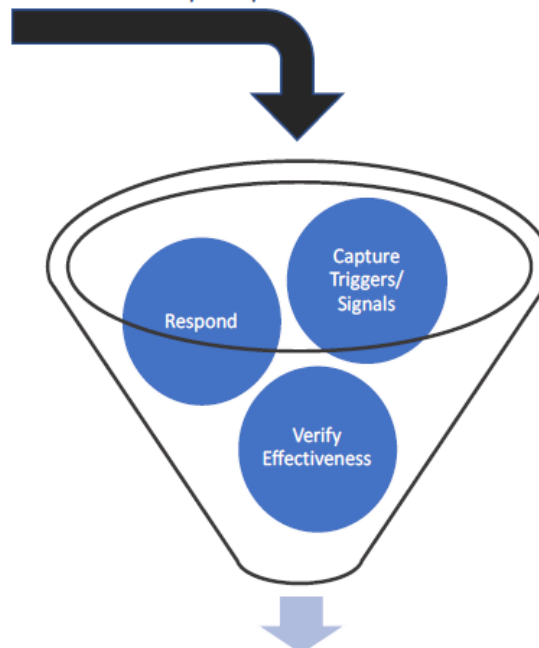
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Develop industry examples of PACs that can be managed in the PQS only

Risk-based Assessment of PACs



Utilize ICH Q10 principles in the PQS to:



Support PAC Regulatory Filing Assessment

PDA Journal
of Pharmaceutical Science and Technology



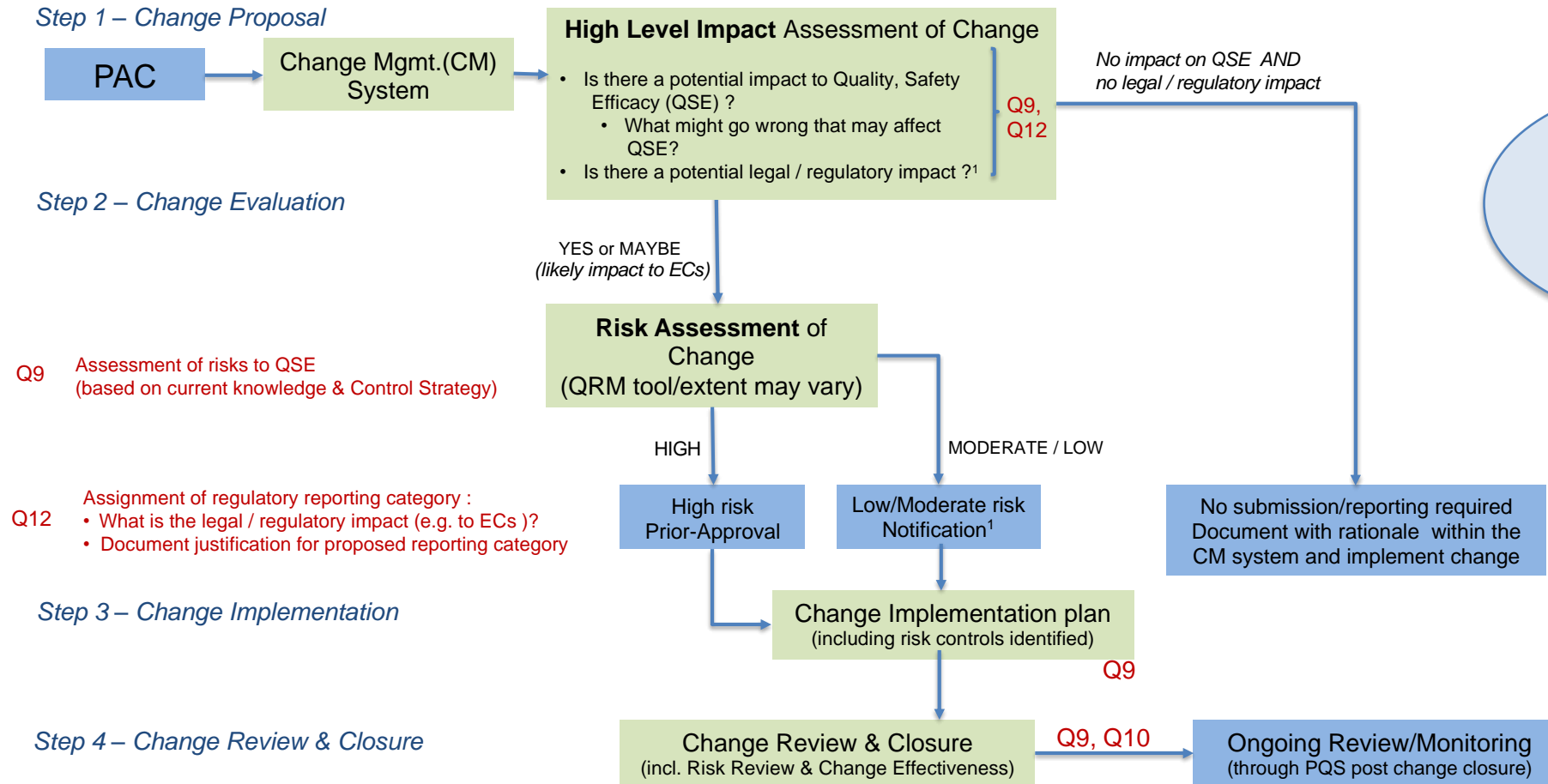
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<https://journal.pda.org/content/early/2020/05/28/pdajpst.2020.011734>

Risk-based Assessment of PACs & Regulatory Reporting Category

¹ per local regulations

<https://journal.pda.org/content/early/2020/05/28/pdajpst.2020.011734>

Example of PAC managed within PQS (lowest risk)

Automatic Colony Counter

- Change: switch from 'Visual colony counting & manual result reporting' to 'Automated colony counter & result reporting integrated with LIMS'
- Rationale for managing within the PQS (without reporting to Authorities)
 - Employs the same analytical technique of membrane filtration & medias described in compendia
 - Does not require a specification change
 - Enhances product quality as contamination can be detected and resolved earlier
 - Provides better precision, accuracy and data integrity
 - Is overseen by the PQS:
 - ❑ Change Control, instrument qualification & method validation, annual product reviews, method reviews, internal audits & agency inspections



Example of PAC categorized as 'Notification' (low risk)

Extension of aseptic filling session

- Change: Extension of aseptic filling session (in isolator)
- Rationale for 'Notification' categorization:
 - Change validated with media fill simulations (3 consecutive runs) to demonstrate no impact on sterility of filling line → low risk confirmed
 - No change of manufacturing process
 - ❑ No modification of critical process parameters
 - ❑ No modification of batch size
 - ❑ No modification of process controls
 - ❑ No impact on final lyophilization step
 - No increase in risk associated with the previous process
 - ❑ No introduction of new types of aseptic manipulations
 - No impact on registered information

Example of PAC categorized as 'Prior-approval' (significant risk)

Additional manufacturing site / building

- Change: Addition of a manufacturing site / building
- Rationale for Prior-approval categorization:
 - Not exactly same equipment
 - May be not same batch size
 - Impact on registered information
- Providing
 - Appropriate scientific comparability between facilities
 - Clear batch genealogy, based on effective PQS
 - Possibility to use alternative manufacturing facilities in order to get supply flexibility and prevent shortages due to forced shut-downs

Conclusions

- The current **regulatory complexity** associated with PACs management represents a **burden** to supply continuity as well as to continuous improvement and innovation
- Q12 may be transformational to shift **focus on what really matters** (ECs) and towards changes that represent a higher risk to product quality, safety and efficacy
- Implementation of an **effective PQS** is essential for a company to achieve product realization, maintain a state of control, and facilitate continual improvement
- Level of regulatory oversight of PACs should be proportional to the effectiveness of the PQS
- Companies with higher level of PQS effectiveness should be **recognized** and **credited**
- **Global harmonization** is key to achieve a **paradigm shift** in PACs management

→ **Benefit for Regulators, Industry and ultimately Patients**

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Thank you for your attention



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R&D based Pharmaceutical Association Committee, Rm 506, Office Building 1, Landmark Tower,
No.9 North Dongsanhuan Road, Chaoyang District, Beijing 100004, China. +8610-6590 7696

