THE ROLE OF QUALITY SYSTEMS AND QUALITY CULTURE IN CE LIFE-CYCLE MANAGEMENT

PATRICK SWANN
VICE PRESIDENT, QUALITY

AMGEN 40 YEARS

HIKING THIS SUMMER!

Pondering QbD for Christmas Trees?

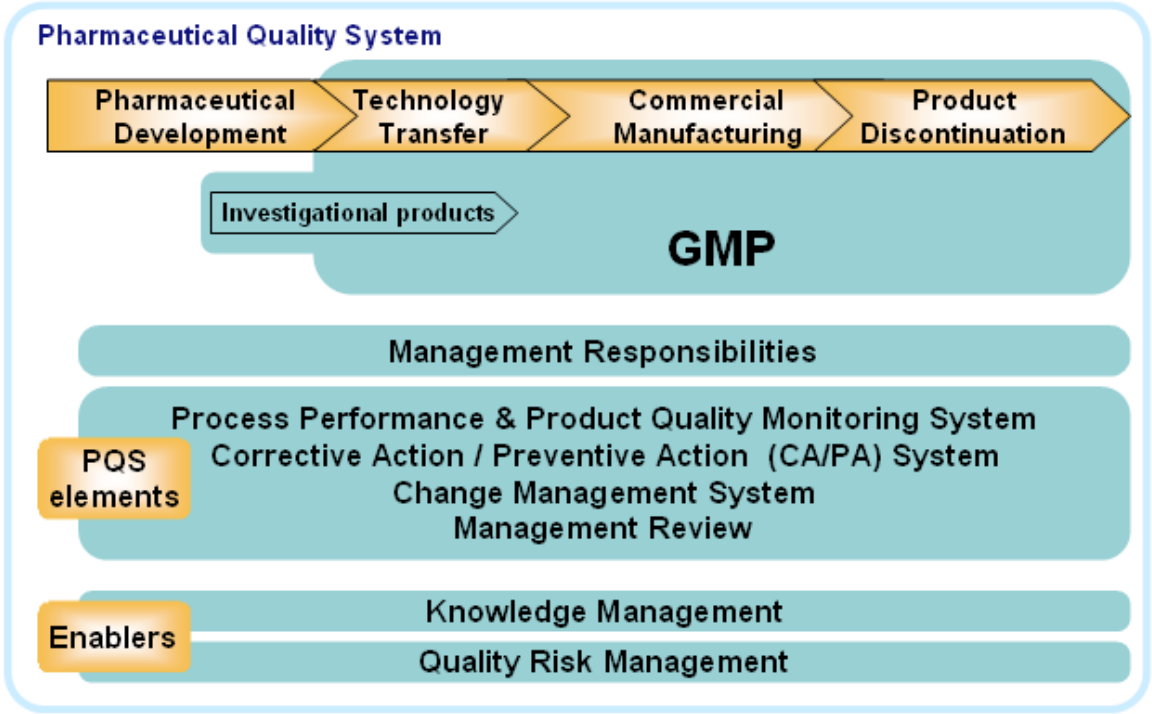
HIKING THIS SUMMER!

The trajectory at the end of a life is difficult to predict

OUTLINE

- PQS overview – Q10 Change Control
- Problem statement with respect to analytical method changes – 1VQ global perspective and a specific example
- What could CE method LCM look like? Q12 framework
- Quality Systems and Quality Culture

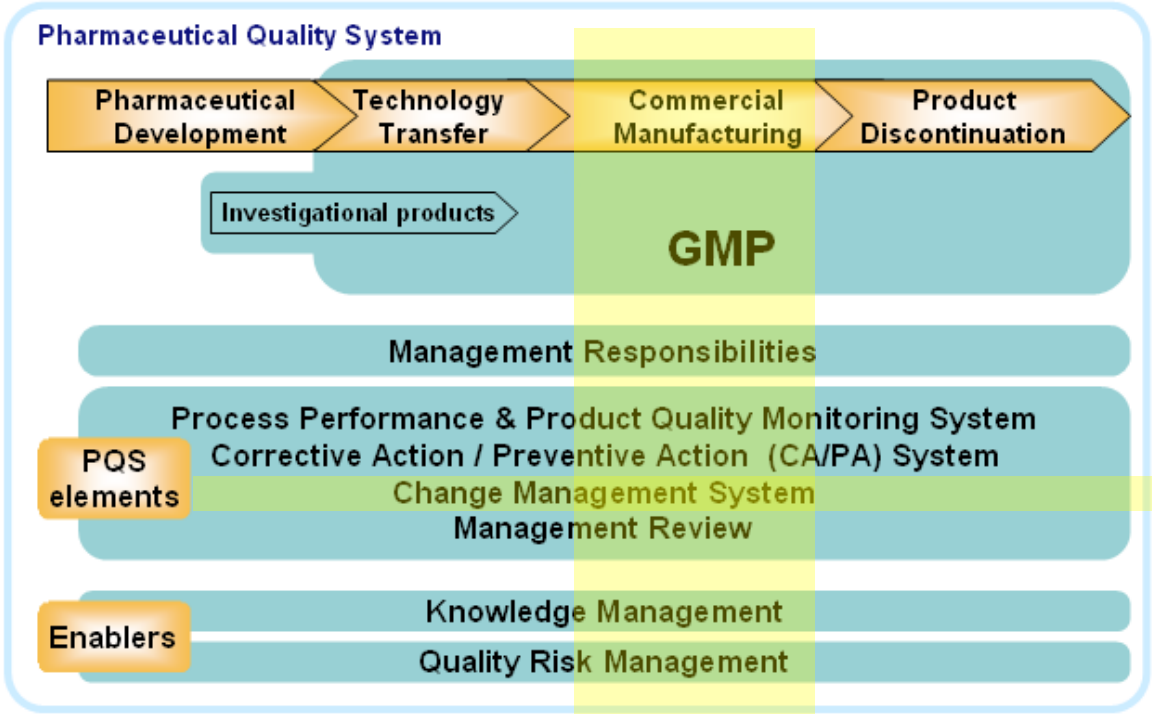
PHARMACEUTICAL QUALITY SYSTEM - Q10



Key Message: What is ICH Q10?

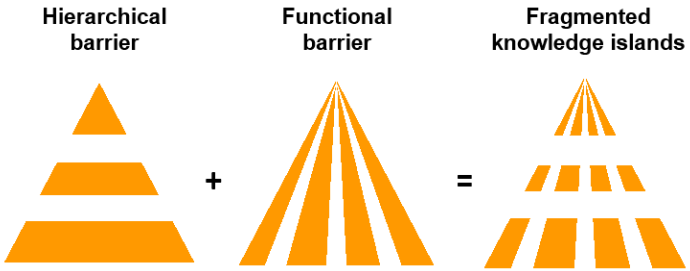
- **ICH Q10 is a guideline on the essential elements of a PQS throughout the product life cycle**
- **ICH Q10 complements Q8 and Q9**
  - ICH Q8 - strengthens the link between development and manufacturing
  - ICH Q9 - as an enabler of the PQS
- **Implementation of PQS should provide enhanced assurance of product quality**
- **GMP is applicable to the Manufacturing part of the life cycle**
  - Manufacturing of Investigational (medicinal) Product
  - Manufacturing of commercial products

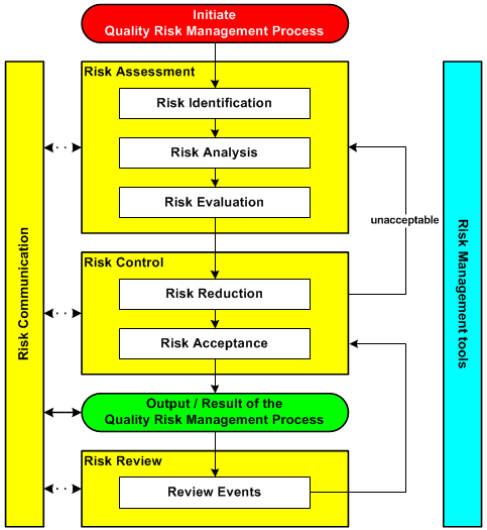
PHARMACEUTICAL QUALITY SYSTEM - Q10



ENABLERS

Knowledge Management



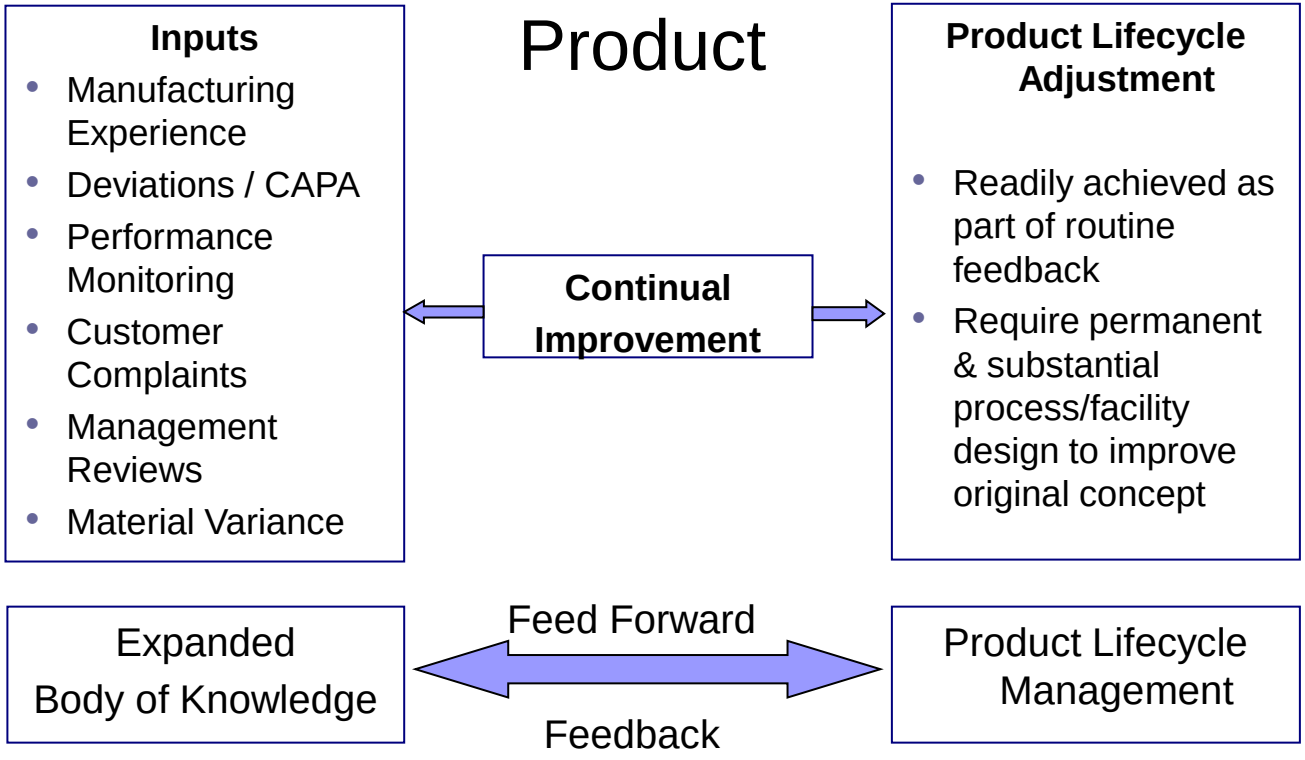


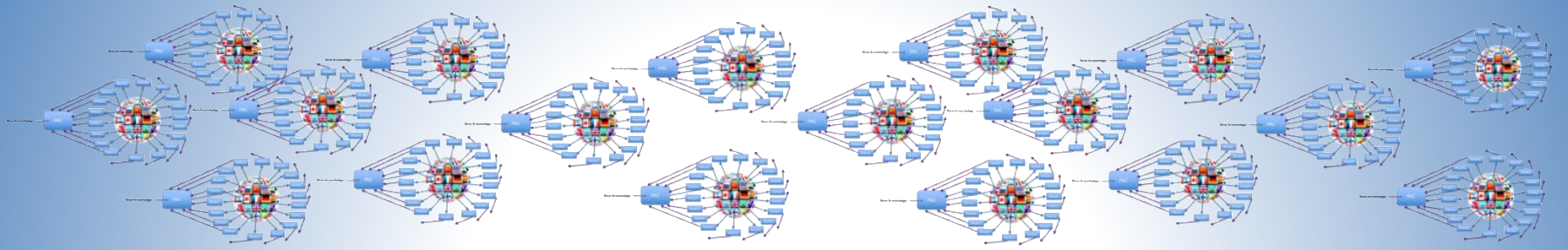
Risk Management

Facilitate Decision Making

S. Rönninger, **Knowledge Management and ICH,** *PDA J. Pharm. Sci. and Tech.*, **2015**, *69,* 326-332.

Continual Improvement of the Product





ONE-VOICE-OF-QUALITY FOR POST APPROVAL CHANGES (PACs)

Communication Deck

15 Aug, 2020

V1ice of Quality

Sponsored by
Chief Quality Officers

Post-Approval Change is Inevitable

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

Managing change is a regulatory expectation, many PACs require prior approval

"Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of product and process knowledge" (EU GMPs, Part I, Chapter 1)

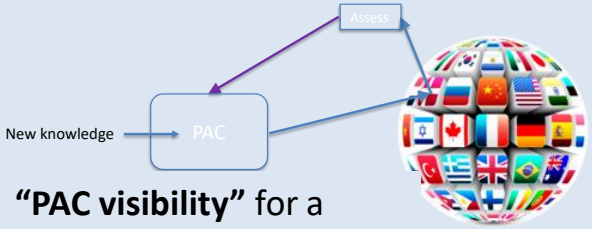
Companies are Globalized; Regulatory Approvals are Nationalized*

Ideally: one product for one world

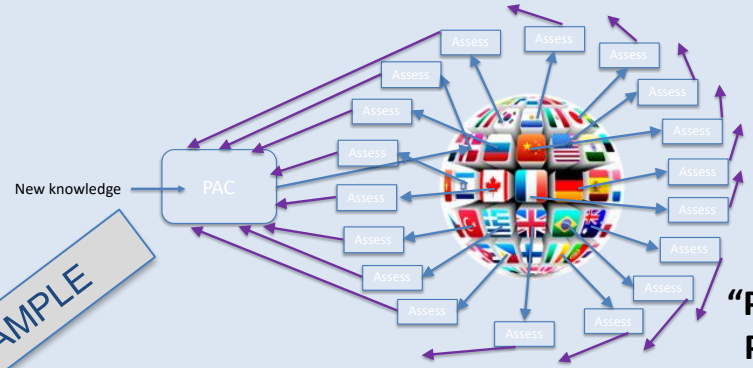
Reality: one product with 100+ approvals

*Note: or regionalized (e.g. EU)

Global PAC Regulatory Complexity – The 'One-Pager'



"PAC visibility" for a **Regulatory Agency**



"PAC visibility" for a **Pharma Company**

PAC EXAMPLE

EXAMPLE

Manufacturing capacity increase & associated changes

1 VARIATION FOR 6 CHANGES

7 products

Licensed in **138** countries

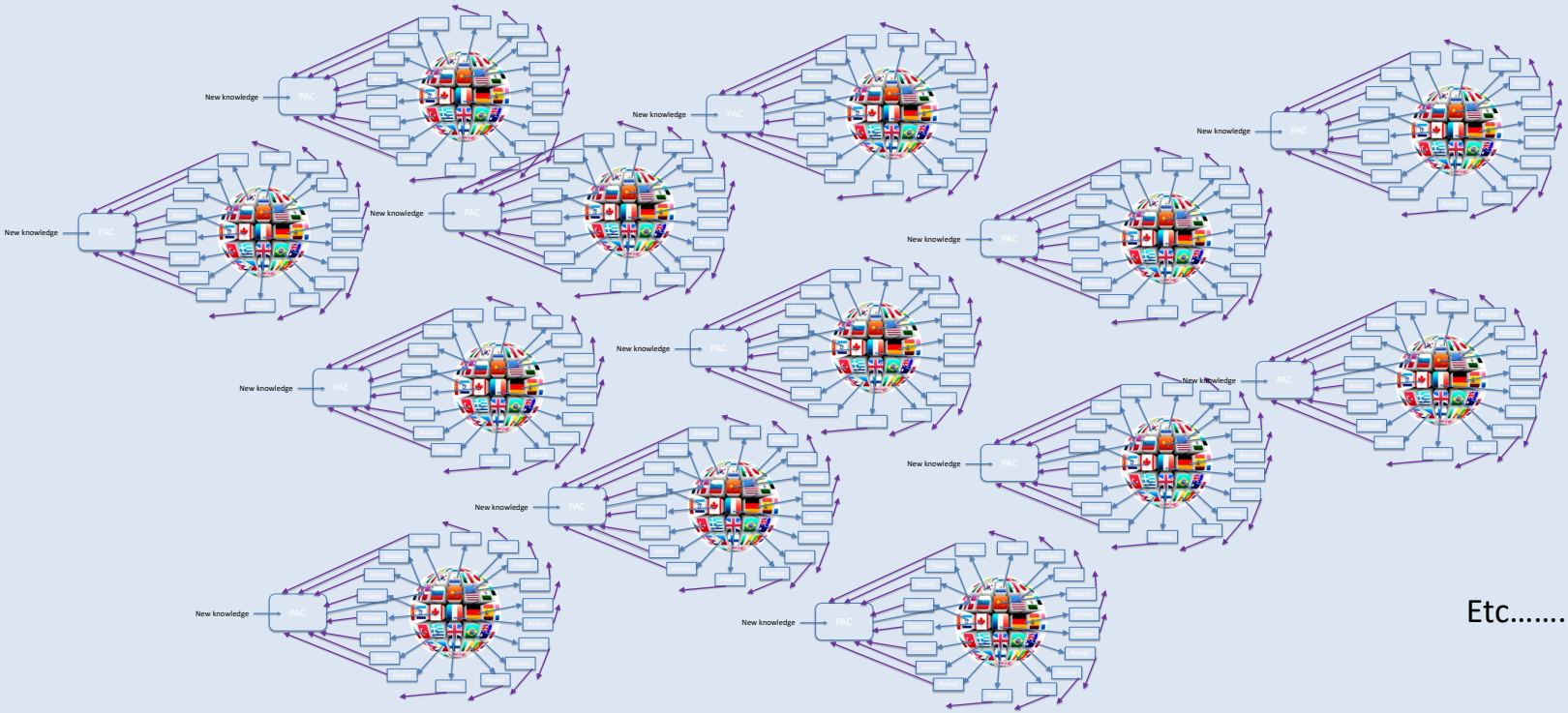
Major reporting level **62** countries

22 countries have raised **177** questions out of which only **19** are different

Minor reporting level **37** countries

No reporting **39** countries

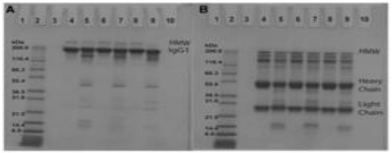
… & in Reality Many PACs at the Same Time*

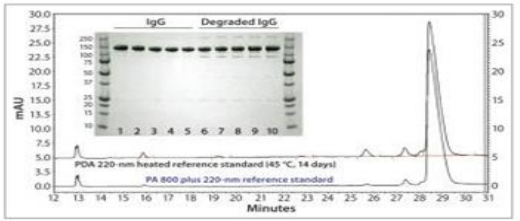


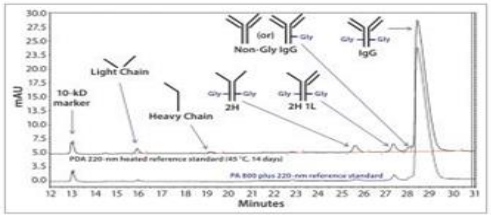
*Larger companies have ***thousands*** of PACs awaiting approval at global level every year

EVOLUTION OF ELECTROPHORESIS

- **Gel Electrophoresis**
  - Denatured state reduced or non-reduced: SDS-PAGE for size based attributes
  - Isoelectric focusing for charge based attributes
- **Capillary Electrophoresis**
  - Denatured state reduced or non-reduced: CE-SDS for size based attributes
  - cIEF for charge based attributes







PROBLEM STATEMENT AND HOW ISSUE WAS FOUND

- Stability trending data reduced SDS-PAGE for a specific drug product lot tested at Site B had the 95% confidence bound intersecting the specification prior to expiry
  - Testing that was performed at Site A did not show any apparent or perceived increased risk to drug product
  - Key background information – Regulators required specification acceptance criteria close to LOD

DIFFERENCES IN SDS-PAGE DATA BETWEEN SITES

- Drug product stability data showed 60.7% (17 of 28 data points) results at Site B are greater than or equal to LOD, while only 9.5% (4 of 42 data points) of the results generated at Site A are greater than or equal to LOD.
- In two instances, Site A and Site B tested the same sample, a ~2% main band difference was observed

Lot	Site	SDS-PAGE Result (Main Band)
Lot 1	Site B	97.4%
Lot 1	Site A	99.3%
Lot 2	Site B	98.1%
Lot 2	Site A	100.0%

LIKELY ROOT CAUSE AND IMPEDED SOLUTIONS

- Site B SDS-PAGE method appears to generate results with more sensitivity as compared to historical data (Site A)
- Enhanced sensitivity is thought to be based on the densitometer (same model used at each site)
- Should we shop on secondary markets for densitometers with equivalent sensitivity?
- Ideal solution would be to update the method (e.g. CE). However, global approval could take ~5 years (IF all jurisdictions agree)

Can we leverage principles in ICH Q10/Q12 to allow rapid implementation of low risk improvements?

Pharmaceutical Quality System and Change Management – Chapter 6

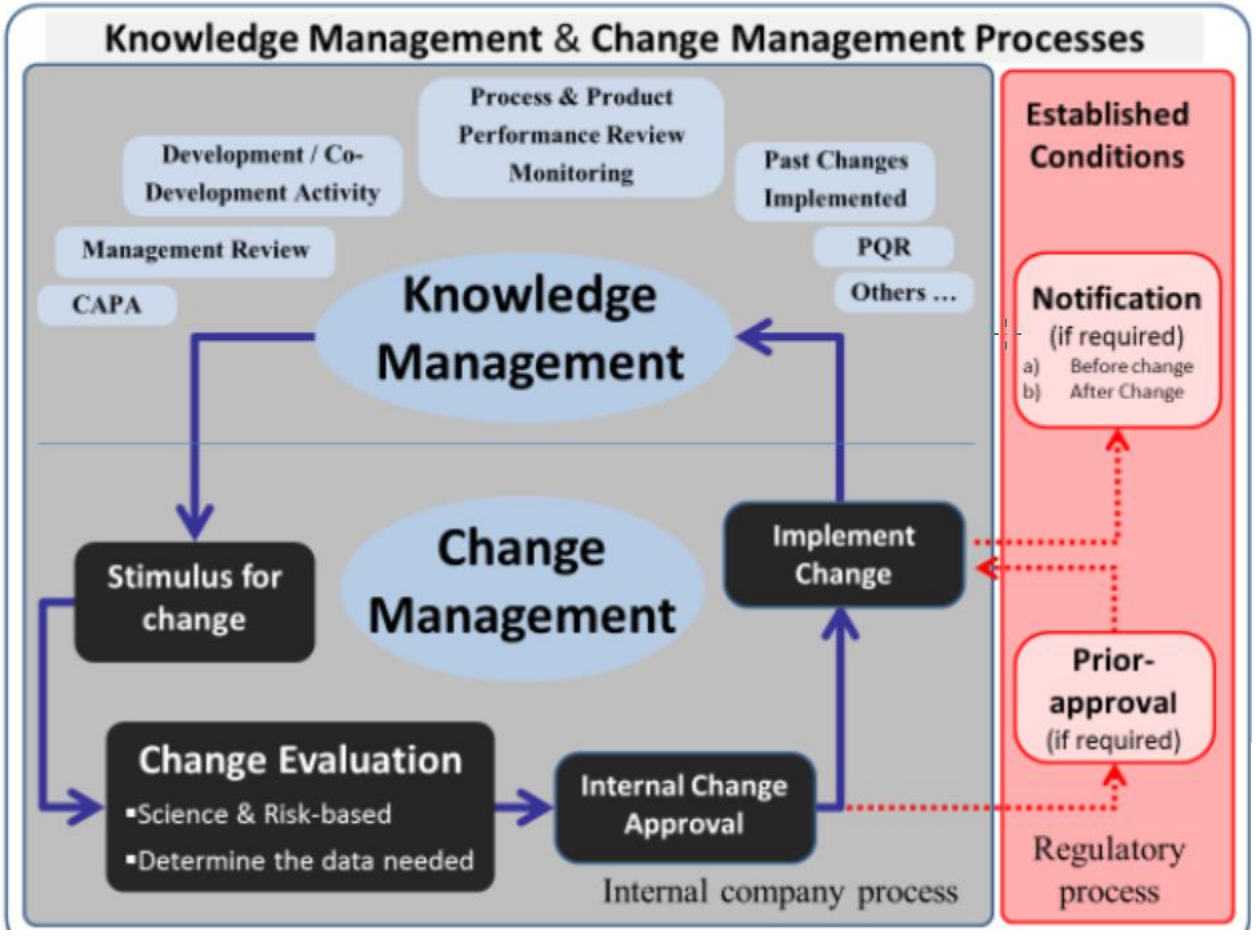
An effective PQS as described in ICH Q10 (Pharmaceutical Quality System) and compliance with regional GMP requirements are necessary to gain full benefit from this guideline

- ICH Q10 describes principles for the effective management of CMC changes under the PQS
- This guideline provides recommendations for robust change management across single or multiple entities involved in the manufacture of a pharmaceutical product
- Appendix 2 elaborates on ICH Q10 principles and describes how the PQS can be utilized effectively in the application of Q12 concepts
- If a manufacturing site has deficiencies that do not require regulatory action, but have an impact on the effectiveness of change management, it may result in restrictions on the ability to utilise flexibility in this guideline

Pharmaceutical Quality System and Change Management – Chapter 6 (2)

- Maintaining an effective PQS is the responsibility of a company (manufacturing sites and MAH where relevant)
  - Not the intent to require a specific inspection assessing the state of the PQS before the company can use the principles in ICH Q12.
- Implementation of robust change management across multiple sites (outsourced or not) is necessary
- Changes to ECs should be communicated in a timely fashion between the MAH and the regulators, and between the MAH and the manufacturing chain (and vice versa)

Figure 2: Connection Between Knowledge Management and Change Management Process



Source: ICH Q12

Established Conditions – Chapter 3 (7)

ECs for analytical procedures

- Include elements which assure performance of the procedure
- Extent of ECs and reporting categories can vary based on the degree of understanding of the relationship between method parameters and method performance, method complexity, and control strategy
- Different approaches can be used to identify ECs:
  - When more limited development studies have been conducted this may result in a narrow operating window to ensure method performance. In such cases ECs may be more extensive with fixed and/or tight conditions
  - Enhanced understanding can lead to a wider operating window that ensures method performance, where ECs can be reduced and focused on method performance (e.g., method parameters acceptable ranges rather than set points, performance criteria)

ANNEX IC: IDENTIFICATION OF ESTABLISHED CONDITIONS FOR ANALYTICAL PROCEDURES

Conditions that must be met: in order to implement the change at the corresponding reporting category

1. There is no change in the limits/acceptance criteria outside the approved limits for the approved assays used at release/ stability.
2. The method of analysis is the same and is based on the same analytical technique or principle (for example, change in column length or temperature, but not a different type of column or method) and no new impurities are detected
3. The modified analytical procedure maintains or improves performance parameters of the method
4. The change does not concern potency-testing
5. No changes made to the test method
6. The transfer is within a facility approved in the current marketing authorization for performance of other tests
7. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, change in total impurity limits)

ANNEX IC: IDENTIFICATION OF ESTABLISHED CONDITIONS FOR ANALYTICAL PROCEDURES

Supporting Data (Documentation to be submitted)

1. Updated Drug Substance Specifications
2. Copies or summaries of analytical procedures if new analytical procedures are used.
3. Validation/qualification results if new analytical procedures are used.
4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.
5. Justification for the proposed drug substance specification (for example, tests, acceptance criteria or analytical procedures).
6. Documented evidence that consistency of quality is maintained.
7. Information demonstrating technology transfer qualification for the non-pharmacopoeial assay or verification for the pharmacopoeial assay.
8. Evidence that the new company/facility is GMP-compliant.

ANNEX IC: IDENTIFICATION OF ESTABLISHED CONDITIONS FOR ANALYTICAL PROCEDURES

Capillary Electrophoresis for non-glycosylated protein (Illustropin)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Equipment – Suitable Capillary Electrophoresis System and Detector; Capillary material, diameter, length defined as EC	Conditions 1 – 4	Supporting data: 1, 4, 5	Notification Low (CBE 0, AR, Type IA, MCN, etc.)

ANNEX IC: IDENTIFICATION OF ESTABLISHED CONDITIONS FOR ANALYTICAL PROCEDURES

Capillary Electrophoresis for non-glycosylated protein (Illustropin)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Site Transfer	Conditions: None	Supporting data: 7 & 8	Notification Moderate (CBE 30, Type IB, MCN, etc.)
	Conditions: 4 - 6		Notification Low (CBE 0, AR, Type IA, MCN, etc.)

ANNEX II: STRUCTURED APPROACH TO ANALYTICAL PROCEDURE CHANGES THAT CAN BE MADE WITH IMMEDIATE OR OTHER POST-IMPLEMENTATION NOTIFICATION (LEGACY PROGRAMS WITHOUT DEFINED EC)

Not applicable to changes to:

- **Procedures with criteria that do not adequately reflect complexity (e.g. CTR)**
- **Methods based on biological etc principle or biological reagent**
- **Model-based or multivariate methods**
- **Methods described in pharmacopoeial monographs**

ANNEX II: STRUCTURED APPROACH TO ANALYTICAL PROCEDURE CHANGES THAT CAN BE MADE WITH IMMEDIATE OR OTHER POST-IMPLEMENTATION NOTIFICATION (LEGACY PROGRAMS WITHOUT DEFINED EC)

Conditions that must be met (1):

- **The physicochemical basis and description of the current and intended method should be the same**
- **The method validation acceptance criteria of the current method can be applied to the intended method**
- **Validation results demonstrate the intended method is equivalent and/or better than the current method**

ANNEX II: STRUCTURED APPROACH TO ANALYTICAL PROCEDURE CHANGES THAT CAN BE MADE WITH IMMEDIATE OR OTHER POST-IMPLEMENTATION NOTIFICATION (LEGACY PROGRAMS WITHOUT DEFINED EC)

Conditions that must be met (2):

- **Test results between the current and intended methods should be equivalent**
- **Acceptance criteria should not be changed unless tightened**
- **Toxicological or clinical data are not required as a result of the method change**

ANNEX II: STRUCTURED APPROACH TO ANALYTICAL PROCEDURE CHANGES THAT CAN BE MADE WITH IMMEDIATE OR OTHER POST-IMPLEMENTATION NOTIFICATION (LEGACY PROGRAMS WITHOUT DEFINED EC)

Ten Step Process:

1. **Evaluate the physicochemical basis and method description**
2. **A prospective analytical validation protocol, aligned with ICH Q2, should be prepared and approved internally. The validation should demonstrate that the intended method is at least equivalent to the current method**
3. **Identify appropriate system suitability criteria**

ANNEX II: STRUCTURED APPROACH TO ANALYTICAL PROCEDURE CHANGES THAT CAN BE MADE WITH IMMEDIATE OR OTHER POST-IMPLEMENTATION NOTIFICATION (LEGACY PROGRAMS WITHOUT DEFINED EC)

Ten Step Process:

4. **Execution of the validation protocol should meet all acceptance criteria**
5. **Consider new product information. The method change should have no adverse impact on safety, efficacy, purity, strength, identity, or potency of the product.**
6. **Prepare a written summary report documenting the outcome of the validation**

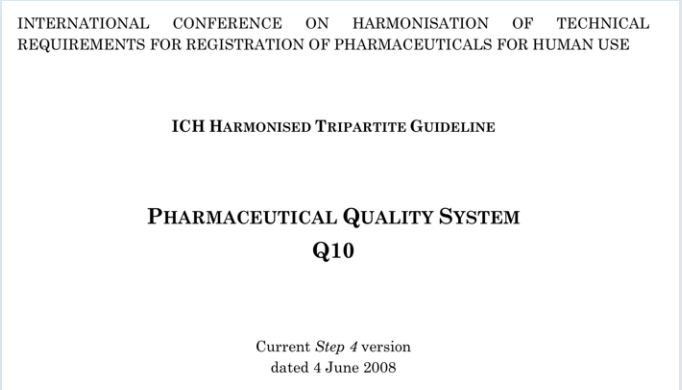
ANNEX II: STRUCTURED APPROACH TO ANALYTICAL PROCEDURE CHANGES THAT CAN BE MADE WITH IMMEDIATE OR OTHER POST-IMPLEMENTATION NOTIFICATION (LEGACY PROGRAMS WITHOUT DEFINED EC)

Ten Step Process:

7. **Follow internal change process as defined in the PQS**
8. **Provide a post-implementation notification of the method change to the regulatory authority after the change is implemented as per regional reporting requirements**
9. **Complete post-change monitoring via PQS change control system**
10. **All information related to this change should be available for regulatory inspection**

The objectives of industry Quality leaders are the same as the ICH Q10 objectives

- Achieve Product Realization
- Establish and Maintain a State of Control
- Facilitate Continual Improvement



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

ICH HARMONISED TRIPARTITE GUIDELINE

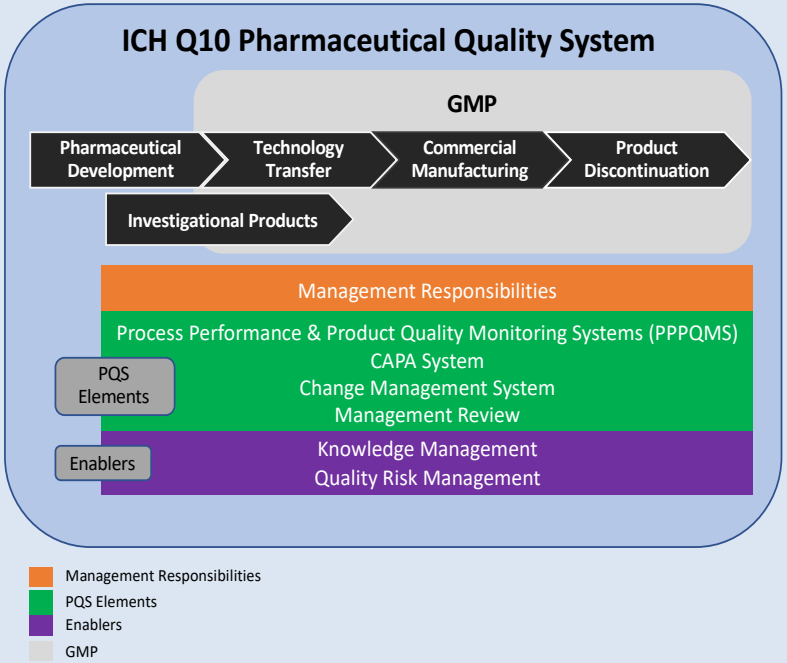
PHARMACEUTICAL QUALITY SYSTEM

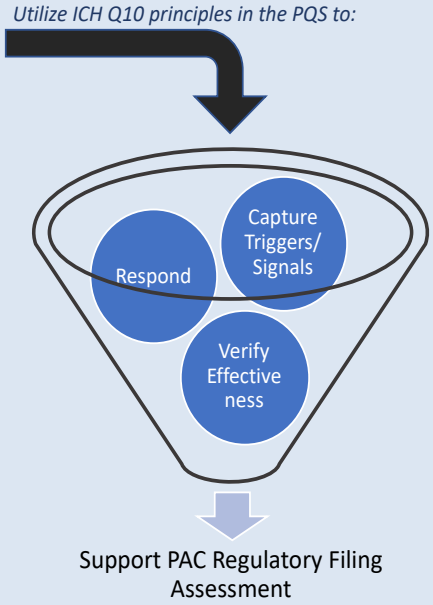
Q10

Current *Step 4* version
dated 4 June 2008

Note: The objective is not a reduction of regulatory complexity in itself. Reduction of regulatory complexity is a necessary means to achieve product realization, maintain a state of control and to continually improve

Solution - Demonstrating Effective PQS & Product and Process Understanding






PDA Journal of Pharmaceutical Science and Technology

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

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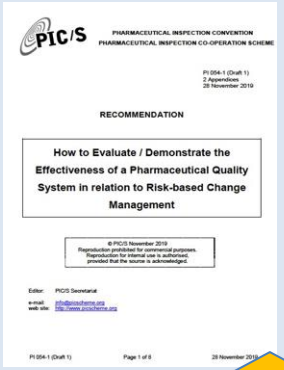
PIC/S
PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME
PI 054-1 (Draft 1)
2 Appendices
28 November 2019
RECOMMENDATION
How to Evaluate / Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management
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PI 054-1 (Draft 1) Page 1 of 8 28 November 2019

PIC/S Recommendation Paper

– How to Evaluate/Demonstrate the Effectiveness of a PQS in Relation to Risk-Based Change Management (November 2019)

Voice of Quality

A change should not increase product quality and/or patient safety risks

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 ≠ 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

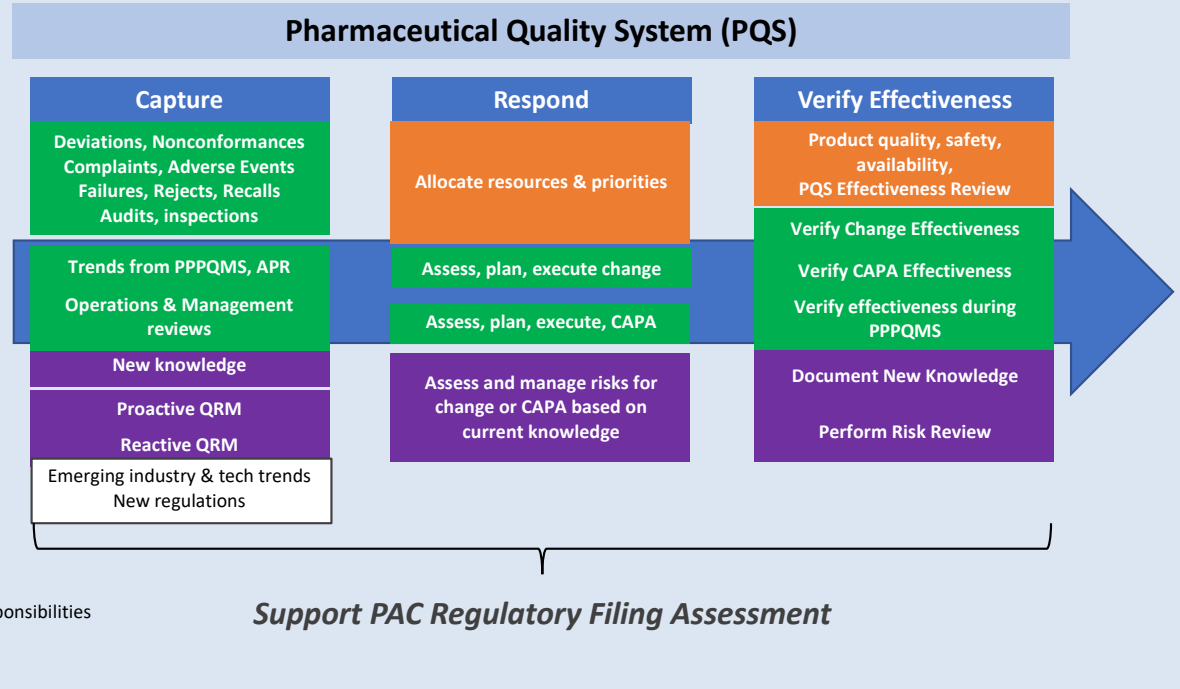
- ☐ Risks drive change planning, timelines and priority
- ☐ Change acceptance & effectiveness criteria are pre-defined
- ☐ Risks with current state until change is implemented
- ☐ Interim controls to monitor or mitigate current situation until change has been implemented
- ☐ Implement risk controls identified
- ☐ 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)

https://www.picscheme.org/en/publications?tri=date

Solution - Maintaining State of Control, Facilitating Continual Improvement and Effective Management of PACs through the PQS



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What do we mean by an enhanced science and risk-based approach?

Voice of Quality

ONE SIZE DOES NOT FIT ALL

More knowledge & better risk controls should enable more flexibility and faster implementation.

Should enable alignment 1) between company & regulator and 2) among regulators. Science knows no borders

Company performs risk assessment using latest product & process knowledge
Proposes change category based on PAC risk level, risk controls, & effectiveness of PQS

Level 1 Calibration & Alignment between company and assessor on PAC risk level, category & implementation timelines

Level 2 Calibration & Alignment between different country assessors on PAC risk level, category & implementation timelines

PACs assessed per ICH Q10 Annex 1 at individual level

Practical PAC Examples

1. Administrative changes to excipient suppliers (e.g. name change, address change) -published
2. DP batch/scale change with no change to equipment MOC or technology
3. Automated colony counter for water, EM testing, product testing
4. Reference standard changes
5. DS/ DP shelf life extension
6. Compendial excipient change
7. Analytical instrument upgrade
8. PACs that tighten controls compared to registered conditions
    i. Tightening of acceptance criteria on tests performed on the product or raw materials or excipients
    ii. Addition of a test performed on the product or raw materials or excipients
    iii. Addition or tightening of a validity criterion for an analytical method
    iv. Addition of a Critical Process Parameter in the batch record of the product
9. Manufacturing equipment/line change
10. Replacement of API suppliers
11. Replace ID testing of starting material/ DS with ID visual verification
12. Change in thermal shipping solution used for transport of product
13. Addition of a lab for adventitious agent testing

Each example following the published 4-step risk-based assessment; applying ICH Q9 & ICH Q10, Annex 1


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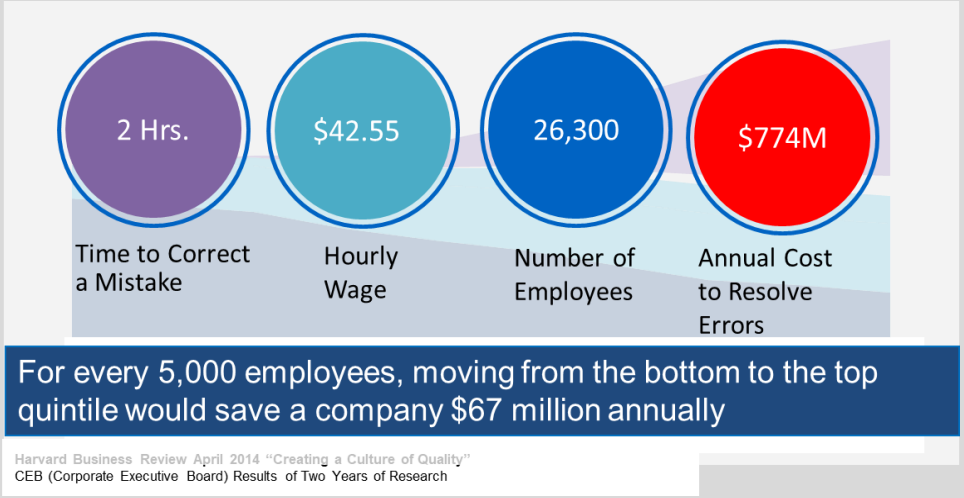
Intended to
a) stimulate dialog with regulatory agencies to consider downgrading PAC reporting category for specified changes;
b) encourage application of ICH Q9 by regulatory agencies

QUALITY CULTURE IS RECOGNIZED BY ACADEMIA, INDUSTRY AND REGULATORS AS KEY FOR MANUFACTURING QUALITY



- Culture is a foundation that must be tied to company's core values. It is a journey that takes time and effort to build and maintain.
- Employees in the top-quintile culture of quality saw 75% fewer significant mistakes than those in the bottom quintile
- Building a strong quality culture results in significant savings

Strong quality culture ensures reliable patient supply

QUALITY CULTURE ATTRIBUTES

Leadership Commitment

Commitment to Quality

- Accountability and Quality Planning

Enabling Capable Resources

- Safety
- Rewards and Recognition
- Feedback & Staff Development

Communication & Collaboration

Quality Communications

- Quality Communications

Management Review and Metrics

- Management Review Metrics

Internal Stakeholder Feedback

- Internal Stakeholder Feedback
- Quality Culture Survey

Collaboration with Assessors (*optional*)

- Operations Readiness & Knowledge

Technical Excellence

Utilization of New Technologies

- Manufacturing Technologies

Maturity of Systems

- Training
- Business Conduct
- Quality Risk Management

Continuous Improvement

CAPA Robustness

- Root Cause
- Human Error

Clear Quality Objectives and Targets

- Continuous Improvement

Employee Ownership & Engagement

Understanding Quality Goals

- Impact on Product Quality
- Patient Impact

Staff Empowerment and Engagement

- Process Ownership & Engagement
- QMS Processes

These are the soft factors in a QMS

Parenteral Drug Association (PDA): Cylia Chen & Steve Mendivil: Overview of the on-site assessment tool

STRONG CORRELATION BETWEEN QUALITY BEHAVIORS AND MATURITY QUALITY PROGRAM

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Quality Culture Survey Report

Pritesh Patel, Denyse Baker, Rick Burdick, Cylia Chen, Jonathon Hill, Morgan Holland and Anil Sawant

PDA Journal of Pharmaceutical Science and Technology September 2015, 69 (5) 631-642; DOI: https://doi.org/10.5731/pdajpst.2015.01078

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Abstract

The Parenteral Drug Association conducted an anonymous global survey of *quality culture* in the pharmaceutical industry to determine whether there is a relationship between certain quality behaviors and certain quality attributes, and whether these quality attributes could be used as surrogates (or proxy variables) to assess quality culture. Other studies have shown that an unhealthy quality culture is a root cause of many quality or compliance issues seen by sites and organizations. Statistical analysis of survey data suggests that certain attributes are driving good behaviors, and the demographic data suggests that this relationship holds irrespective of the geographic location of the site. Executive survey respondents had a more optimistic view of the current state of quality culture than survey respondents at large, with cross-functional vision showing the biggest gap (*P*-value = 0.07, *F*-Test). The top five quality attributes that can serve as surrogates for quality culture were (**1**) Management communication that quality is everyone's responsibility, (**2**) Site has formal quality improvement objectives and targets, (**3**) Clear performance criteria for feedback and coaching, (**4**) Quality topics included in at least half of all-hands meetings, and (**5**) Collecting error prevention metrics. These identified mature quality attributes are related to management responsibility, and continual improvement of the pharmaceutical quality system sections of ICH Q10, and therefore may be amenable to be incorporated in audit programs or in regulatory inspections. Additional research and discussion is required to build a coherent approach.

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RESEARCH

The Impact of Quality Culture on Operational Performance—An Empirical Study from the Pharmaceutical Industry

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ABSTRACT: Quality culture as an enabler of high-quality performance and subsequently as a source of compe advantage is increasingly discussed among operational excellence (OPEX) and quality executives. Research st indicate an impact of quality culture on performance, especially on the success of quality improvement progr such as Total Quality Management initiatives. A continual challenge in quality culture research, however, remair lack of practical and accepted metrics to assess culture. In 2014, the Parental Drug Association (PDA) conduc quality culture survey within the pharmaceutical industry. The results indicate a positive and significant correl between quality (culture) behavior of a production site's employees and quality (system) maturity, which repre the maturity of the quality system in place. As the maturity of the quality system is more comfortable to asse objective criteria, the positive correlation between quality (culture) behavior and quality (system) maturity ma exploited by using the latter as an indicator for quality culture. This paper confirms this positive relationshi

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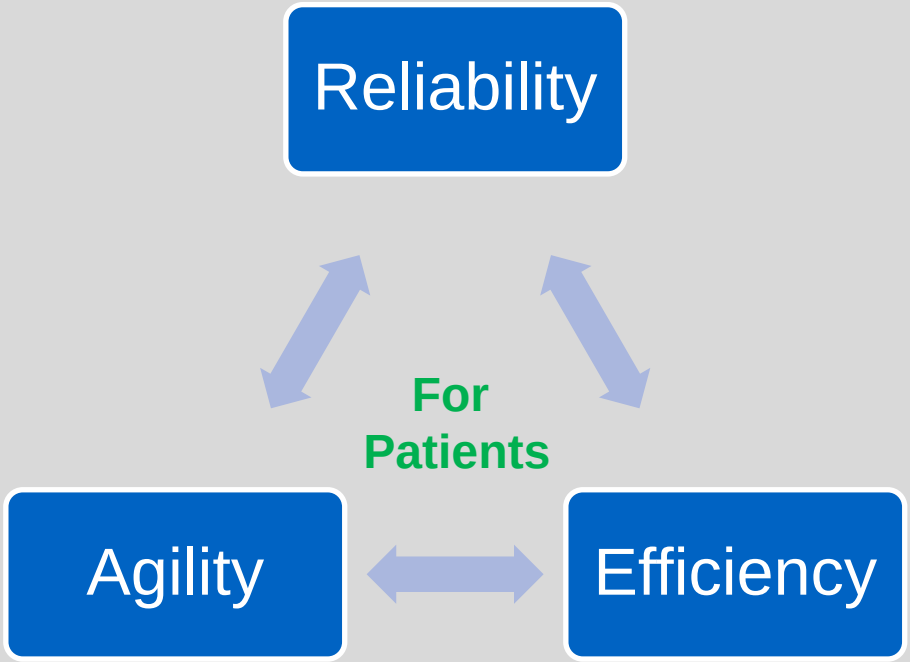

Driving towards more PQS-only managed method changes increases agility and efficiency without compromising reliability

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