cmc STRATEGY FORUM
ADVANCING BIOPHARMACEUTICAL DEVELOPMENT
LATIN AMERICA 2024

Session I
6 August

Session II
13 August

Approaches to Design an Efficient, Predictable Global PAC Management System

that Facilitates Continual Improvement and Product Availability

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1Voice of Quality

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The Vision for PACs

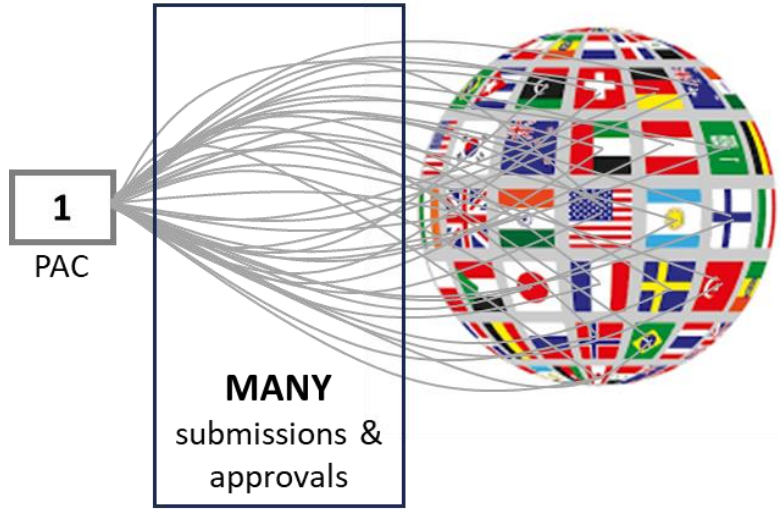
Designing and implementing an agile science and risk-based efficient, predictable global post approval change (PAC) management system that

- facilitates a state of control,
- continual improvement, and
- reduces risk of drug shortages

Global PAC Regulatory Complexity ***Explained***

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

Seen from a **company's side**



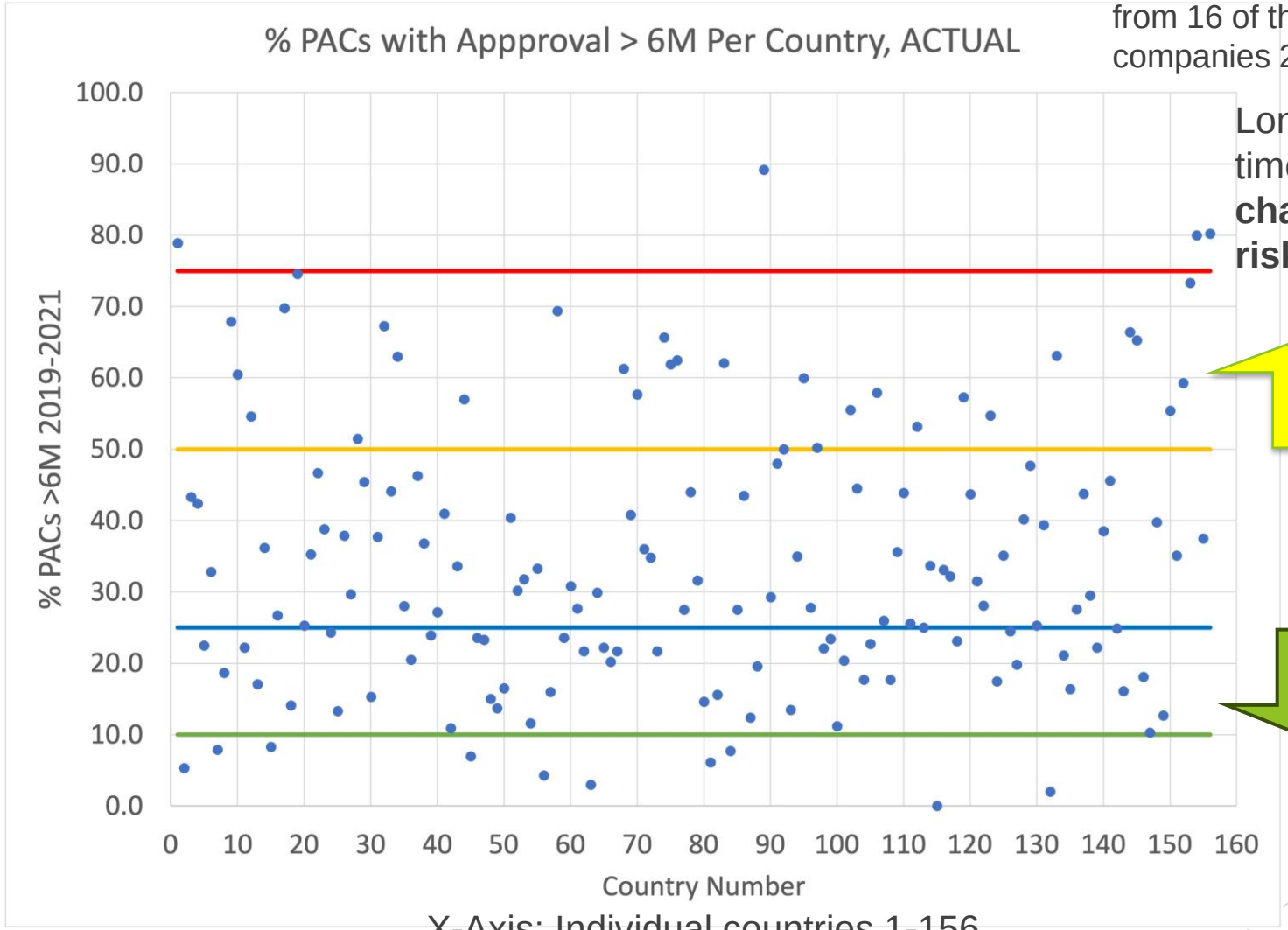
Current PAC Management is driven by
national frameworks not by science globally

One PAC requires prior approval by multiple countries that have
different reporting thresholds,
different requirements, and
different timelines.

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

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***

ON TIME

EVERY TIME

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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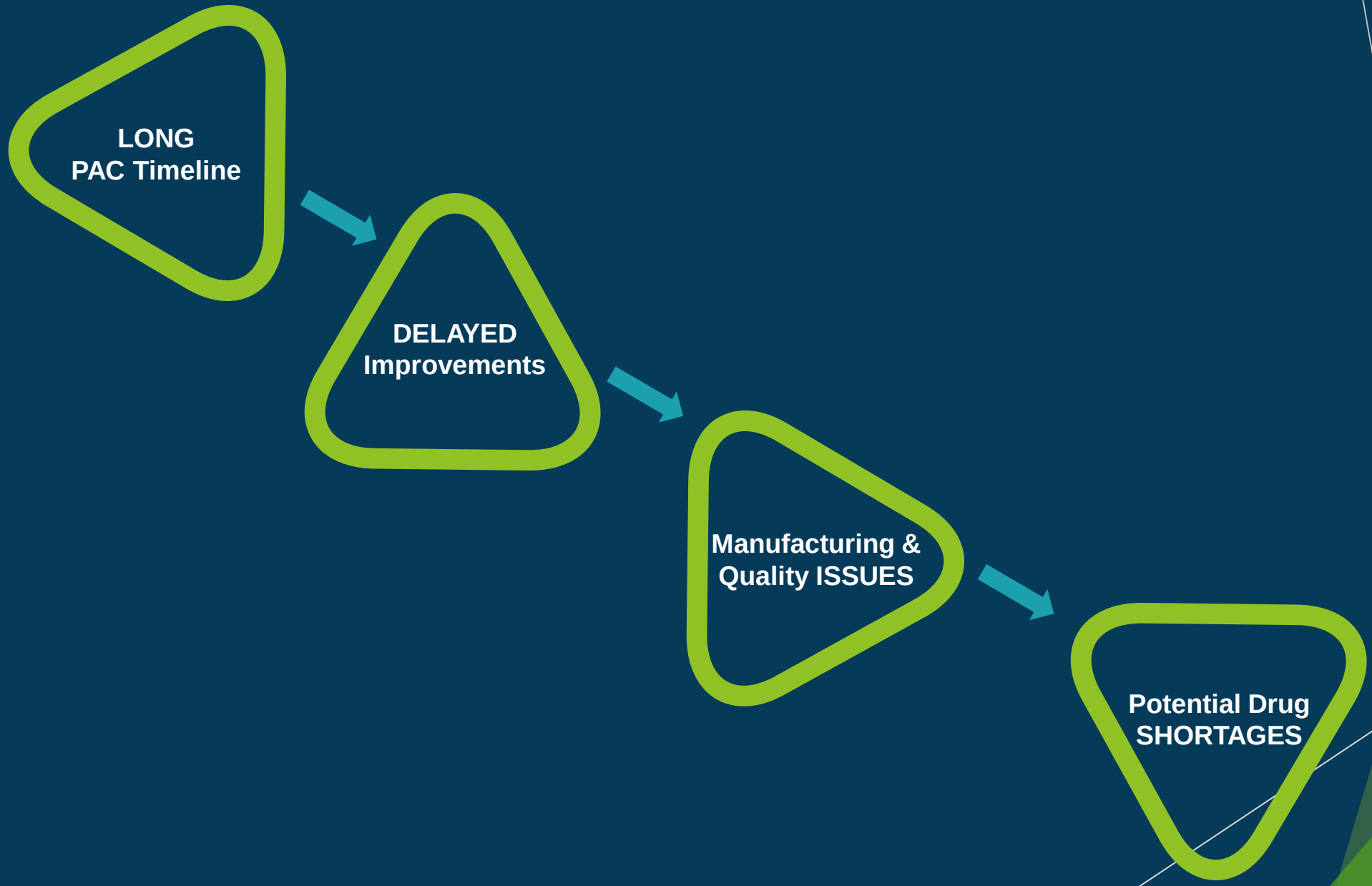
LONG
PAC Timeline
DELAYED
Improvements
Manufacturing &
Quality ISSUES
Potential Drug
SHORTAGES

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**

Website: https://prst.ie/1vq/

Co-leads Emma Ramnarine, PhD & Anders Vinther, PhD
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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.

Global PAC Regulatory Complexity Has Existed for Many Years

2005

ICH harmonisation for better health

*"**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

ICH harmonisation for better health

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

ICH harmonisation for better health

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

ICH Q12 Concept Paper

2022

ICMRA
International Coalition of Medicines Regulatory Authorities

"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)

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

Potential Benefits Scored by 19 CQOs (from top 25 pharma companies) in 2021

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

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

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8 Approaches to Reduce Global PAC Regulatory Complexity Suggested by 1VQ for PAC Initiative

Discussed on next slides	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

Therapeutic Innovation & Regulatory Science https://doi.org/10.1007/s43441-024-00614-9

Objective:

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

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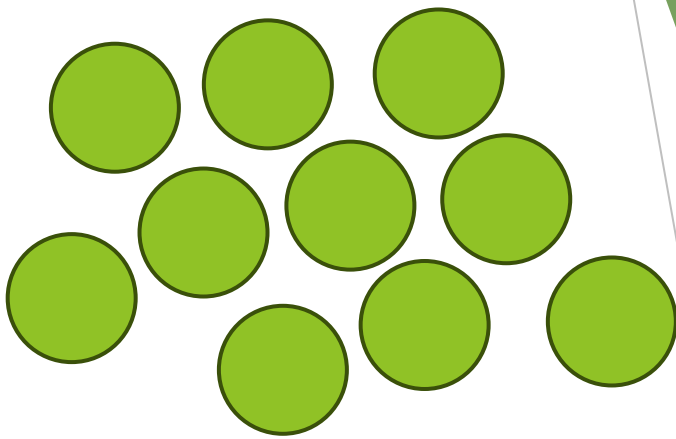
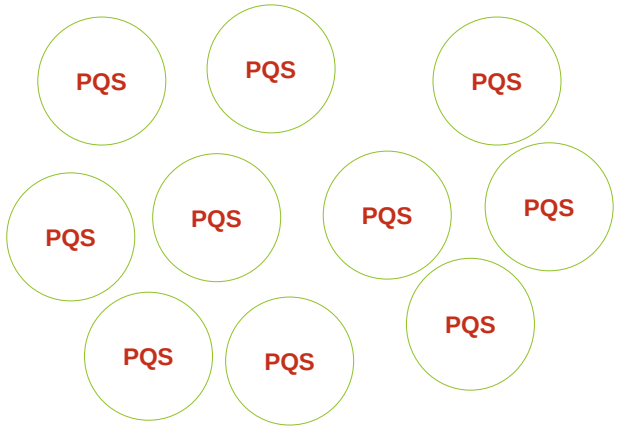
Applying ICH Q10, Annex 1, Illustrative Example

Company not demonstrated effective PQS

Submit



Company demonstrated effective PQS

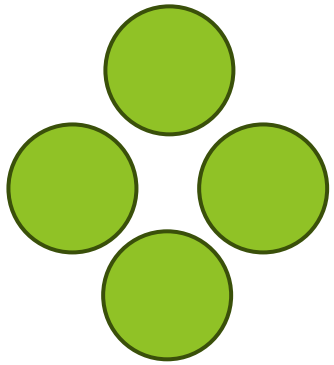


Submit to HA for prior approval?

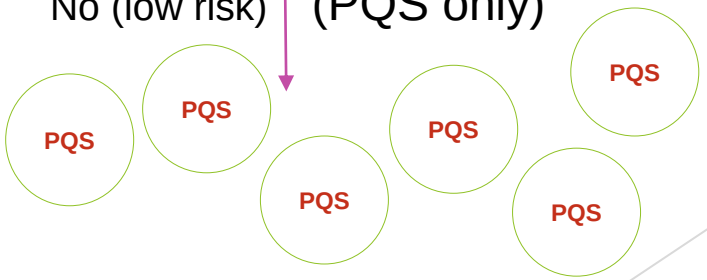
Risk-assess each individual PAC

Yes

Submit



No (low risk) (PQS only)



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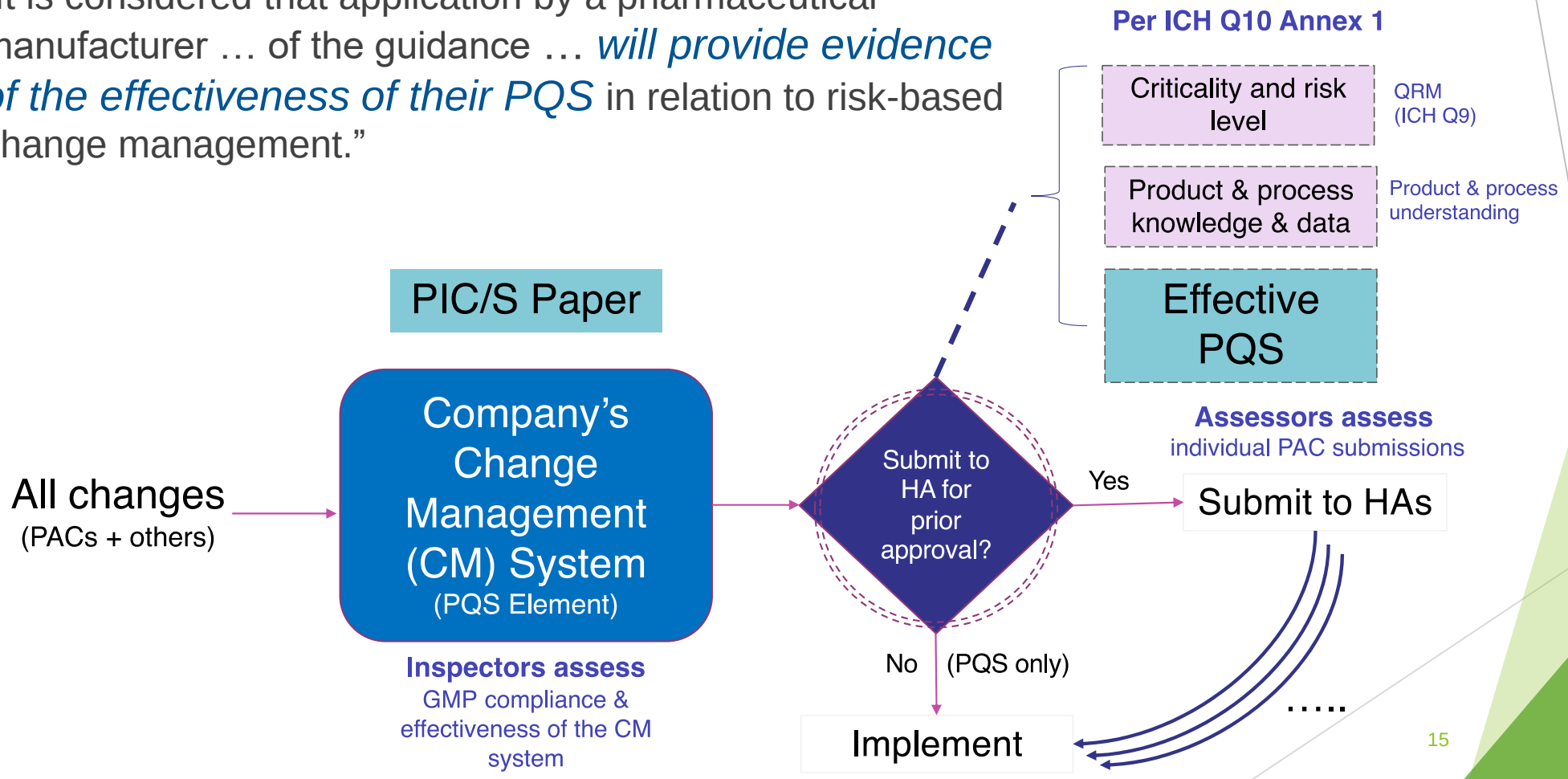
PIC/S Recommendation Paper Defines Effective PQS for Changes

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

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



Effective PQS for Changes, Continued

"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***."

Note: 1VQ for PAC Initiative also defined effective PAC for managing PACs (in line with PIC/S). Paper also outlines risk-based approach to assess individual PACs

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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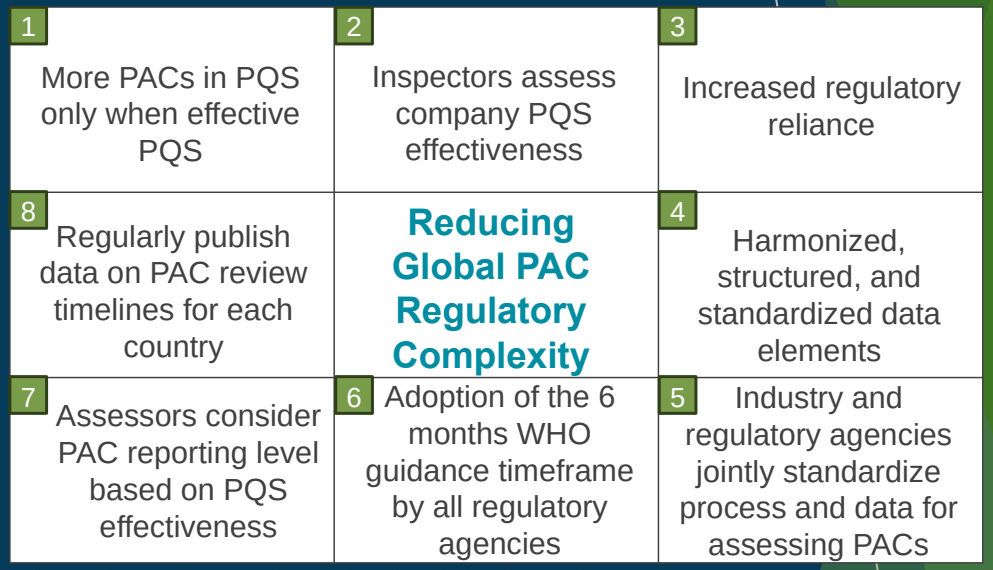

Therapeutic Innovation & Regulatory Science https://doi.org/10.1007/s43441-024-00614-9

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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Food for Thought

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

Thank you

Website:
https://prst.ie/1vq/

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