2024 ISPE EUROPE ANNUAL CONFERENCE

Designing an Efficient, Predictable Global Post Approval Change System

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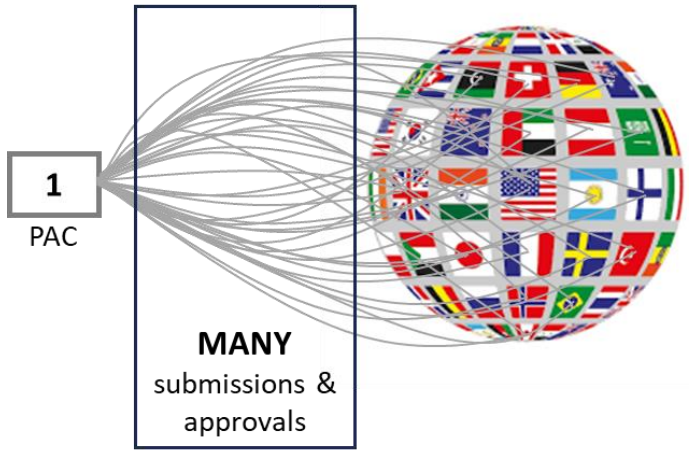
Global PAC Regulatory Complexity Disincentivizes Continual Improvement and is a Risk to Drug Supply

Seen from a regulatory agency‘s side

Seen from the company’s side

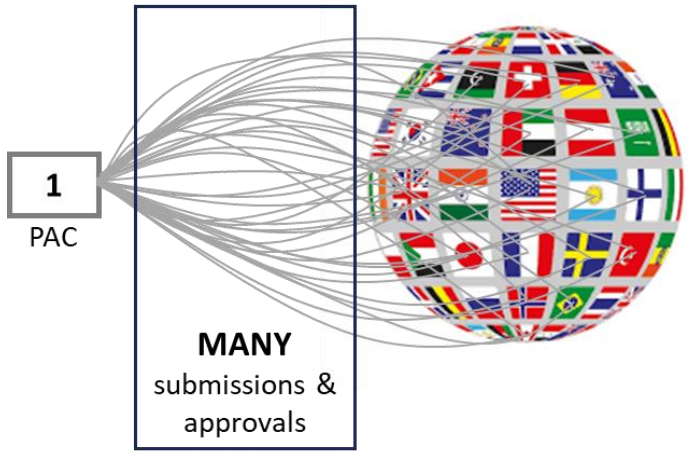


PACs are a natural and essential part of a pharmaceutical product’s commercial lifecycle

- Upgrading (aging) manufacturing and testing facilities and equipment
- Maintaining cGMP compliance and a state of control
- Implementing evolving regulatory requirements and new technologies
- Emerging new knowledge about products and processes
- Supplier changes
- Continuous improvement (which can be a legal requirement in certain countries)

One PAC requires prior approval by multiple countries that have different reporting requirements and timelines. First to last country approval often 3-5 years or more

Each Regulatory Agency PAC Assessment is Science & Data Driven, thus Likelihood of Same Conclusion High



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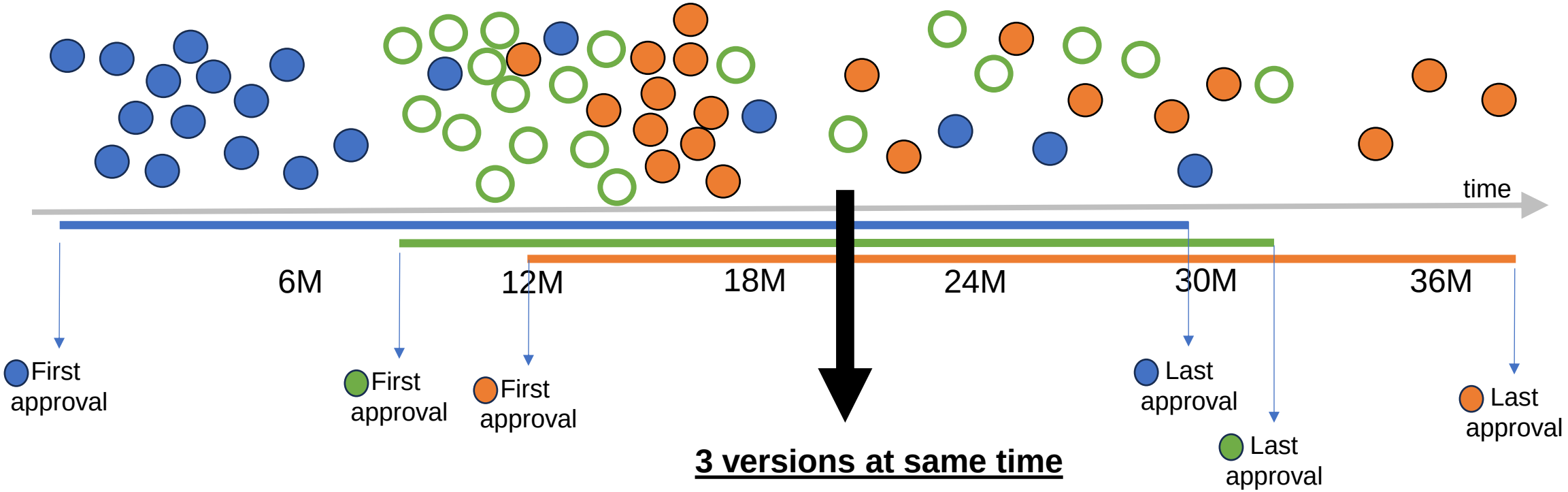
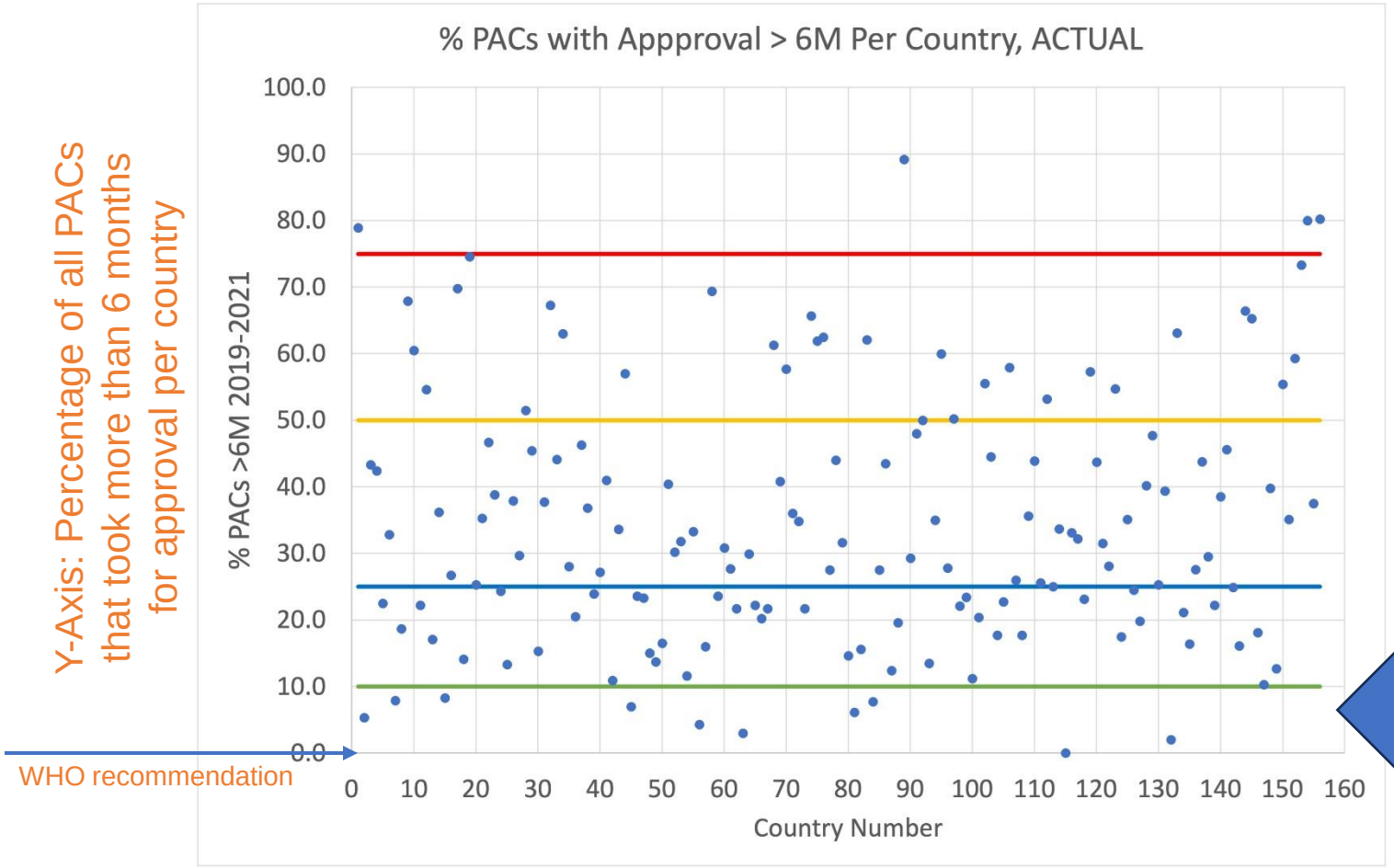
Different Approval Timelines Result in Need to Maintain Inventory of Multiple Versions of Same Product at Same Time



>125,000 PAC Data Points Demonstrate PAC Global Regulatory Complexity is a Huge Problem



>125,000 PAC data points collected from 16 of the top 25 pharma companies over a period of 3 years (2019-2021)

It usually takes 3-5 years for full global approval of each PAC

The long approval timelines increases supply chain complexity and risk of drug shortage

Less than 10 % of all (156) countries had at least 90% of all PACs taking no more than 6 months (WHO guideline) for approval

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

The Problem Has Been Known For More Than Two Decades, Reporting has Increased, While Problem Remains

2002 **VISION FOR ALL**

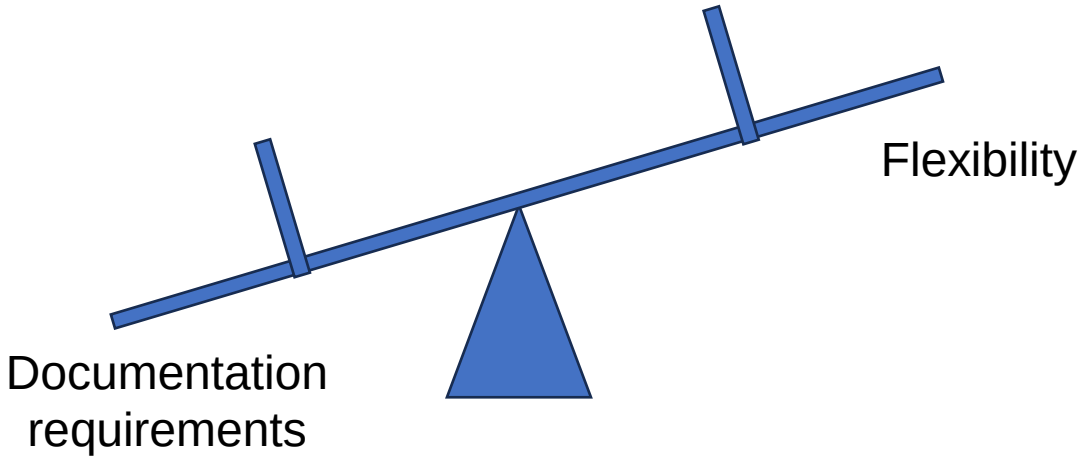
*"A maximally efficient, **agile, flexible** Pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."*

Dr. Janet Woodcock, FDA's Vision for 21st Century Manufacturing

2022 ICMRA

"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***."

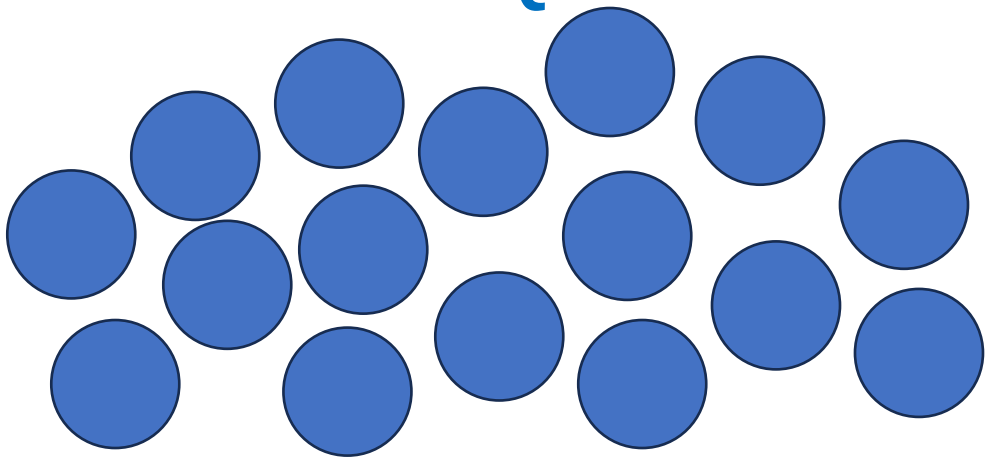
ICMRA-ICH-PIC/S-IPRP Joint PQKMS Reflection Paper

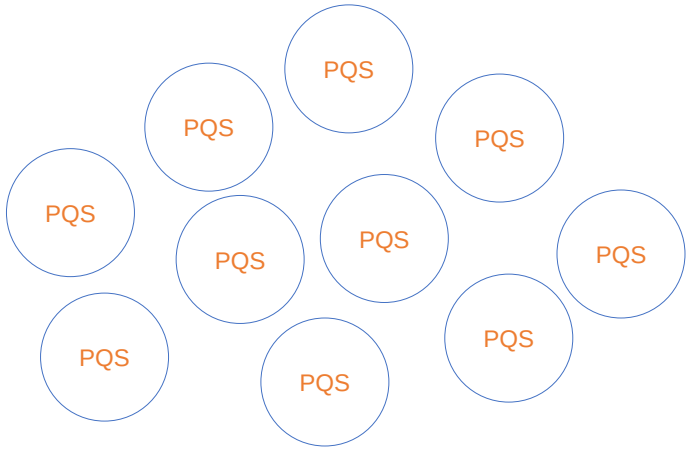


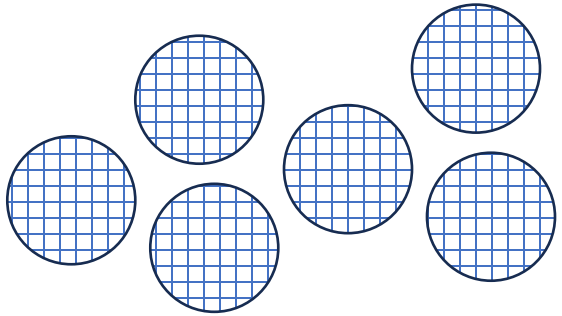
Reducing the PAC Complexity Problem Per ICH Q10 & WHO

Current situation.
16 PACs all requiring prior approval

Reducing the problem.
10 PACs managed in PQS only
6 PACs prior approval with regulatory reliance







Effective PQS

Regulatory Compliance

PQS

Lower Risk PACs Managed in the PQS Only; Effective PQS Defined by 1VQ for PAC Initiative and PIC/S

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

2021

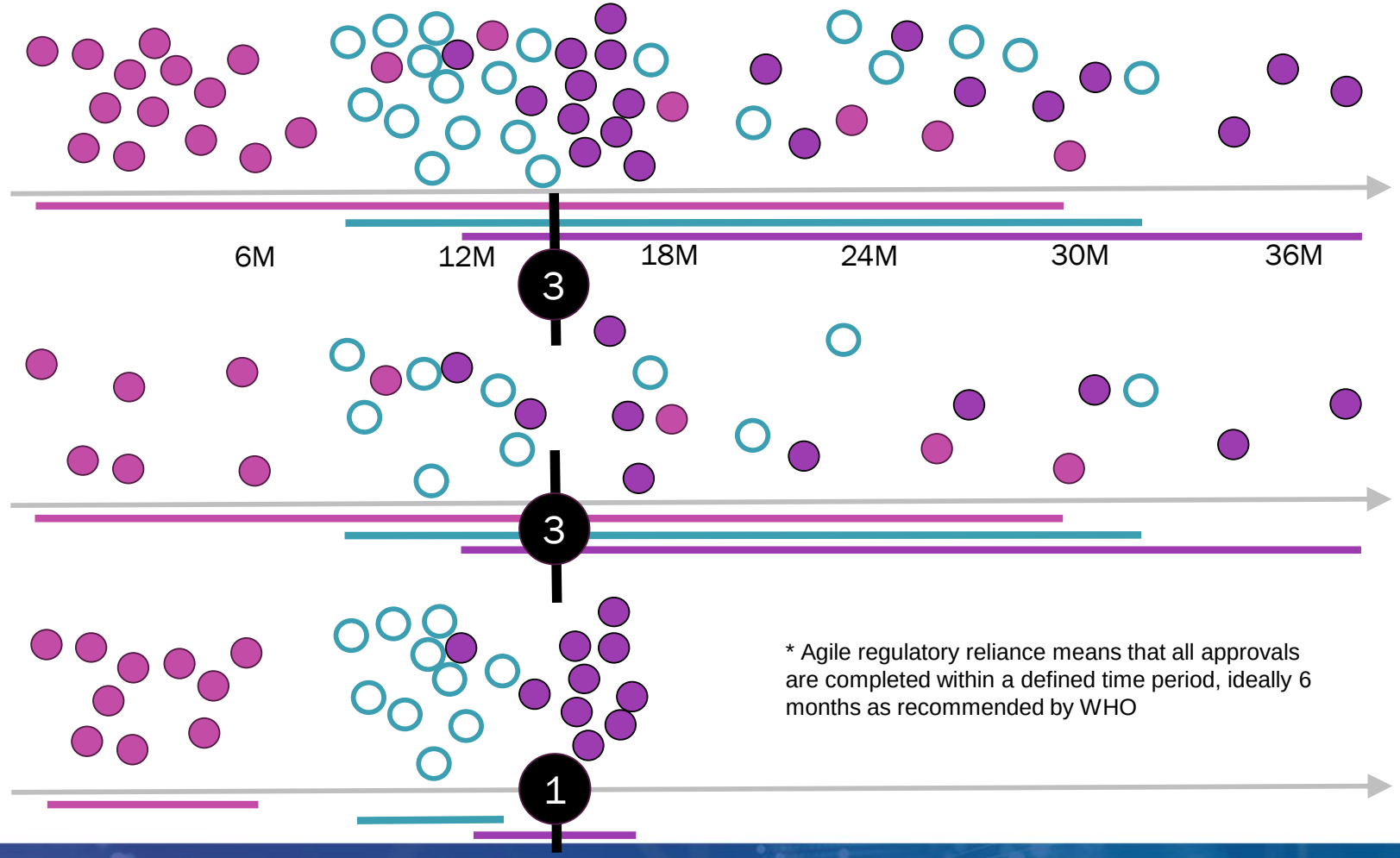
PIC/S

"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.

Ramnarine E., Vinther A., Bruhin K. et al. (2020) 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

Regulatory Reliance Only Helps Reduce Inventory Complexity When it is *Agile*



In this example regulatory reliance resulted in 50% reduction of prior approval PACs but no change in # product versions in inventory

In this example agile regulatory reliance resulted in 50% reduction of prior approval PACs AND simplification of product inventory

* Agile regulatory reliance means that all approvals are completed within a defined time period, ideally 6 months as recommended by WHO

8 Approaches to Reduce Global PAC Regulatory Complexity

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

Complex vs Complicated Problems

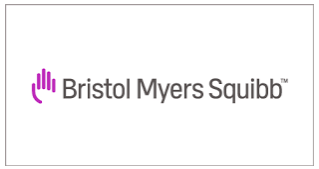
Complicated problems *originate from causes that can be individually distinguished; they can be addressed piece by piece; for each input to the system there is a proportionate output; the relevant systems can be controlled and the problems they present admit permanent solutions.*

Complex problems *and systems result from networks of multiple interacting causes that cannot be individually distinguished; must be addressed as entire systems, that is they cannot be addressed in a piecemeal way; they are such that small inputs may result in disproportionate effects.*

When a complex problem is misdiagnosed as a complicated problem, individual attempts by a stakeholder, while reasonable and well-intended, can often make the problem worse

Ways That We (Industry) Can Help Alleviate the Problem of Global PAC Regulatory Complexity

- The problem with global PAC regulatory complexity has existed for more than 20 years. Reporting has increased for companies. Attempts so far have treated the problem as complicated, and thus the problem still exists
- Industry can
  - Continue to **bring awareness** to the problem and consequences of the lack of continual improvement including risk of drug shortages
  - **Implement** within their company's PQS the **PIC/S Change Management Recommendation Paper** and the **1VQ for PAC Initiative recommendations** on how to demonstrate an effective PQS for PACs
  - For companies demonstrating an effective PQS, **request** the ICH Q10 & Q12 envisioned **flexibility** to manage more low-risk PACs managed in the PQS only (a 'one-size-fits-all' approach has become an impediment to timely continual improvement)
  - Work together to improve the system through **global standardization** managing it as a complex (not a complicated) problem
  - **Seek collaboration** opportunities with regulatory authorities to jointly pilot (and improve) proposed solutions for specific PAC examples



Sponsored by the CQOs from the Top 25 Pharma Companies

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

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