

SUPPLY CHAIN IMPACT OF THE GLOBAL POST APPROVAL CHANGE REGULATORY COMPLEXITY

8 Approaches to Lessen the Problem

1 Voice of Quality for PAC & Sanofi Regulatory Reliance Pilot
10-OCT-2024

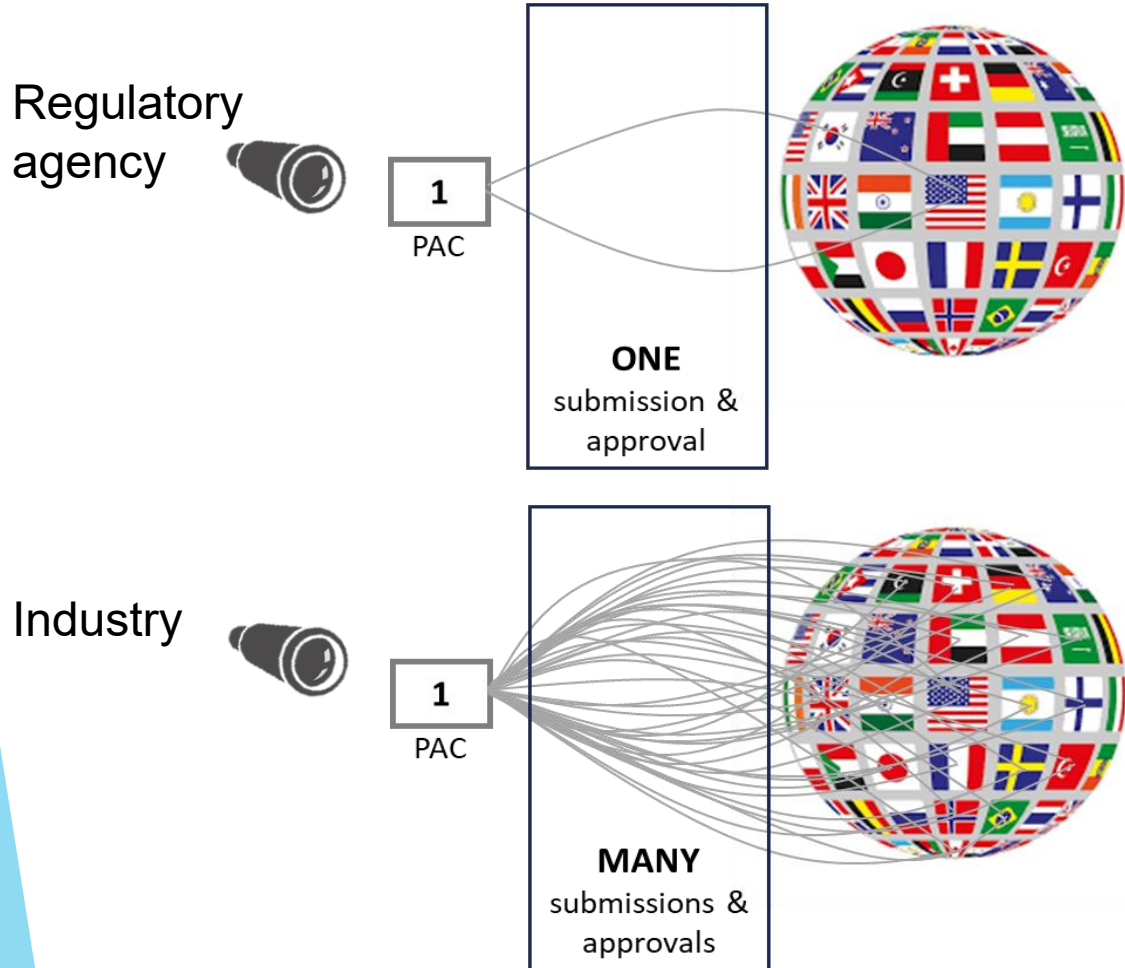
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Global PAC Regulatory Complexity (1/3)

Increases risk of drug shortage and disincentivizes continual improvement and innovation



Prior approval by multiple countries with

1. **different** reporting **thresholds**,
2. **different** requirements,
3. **different** timelines.

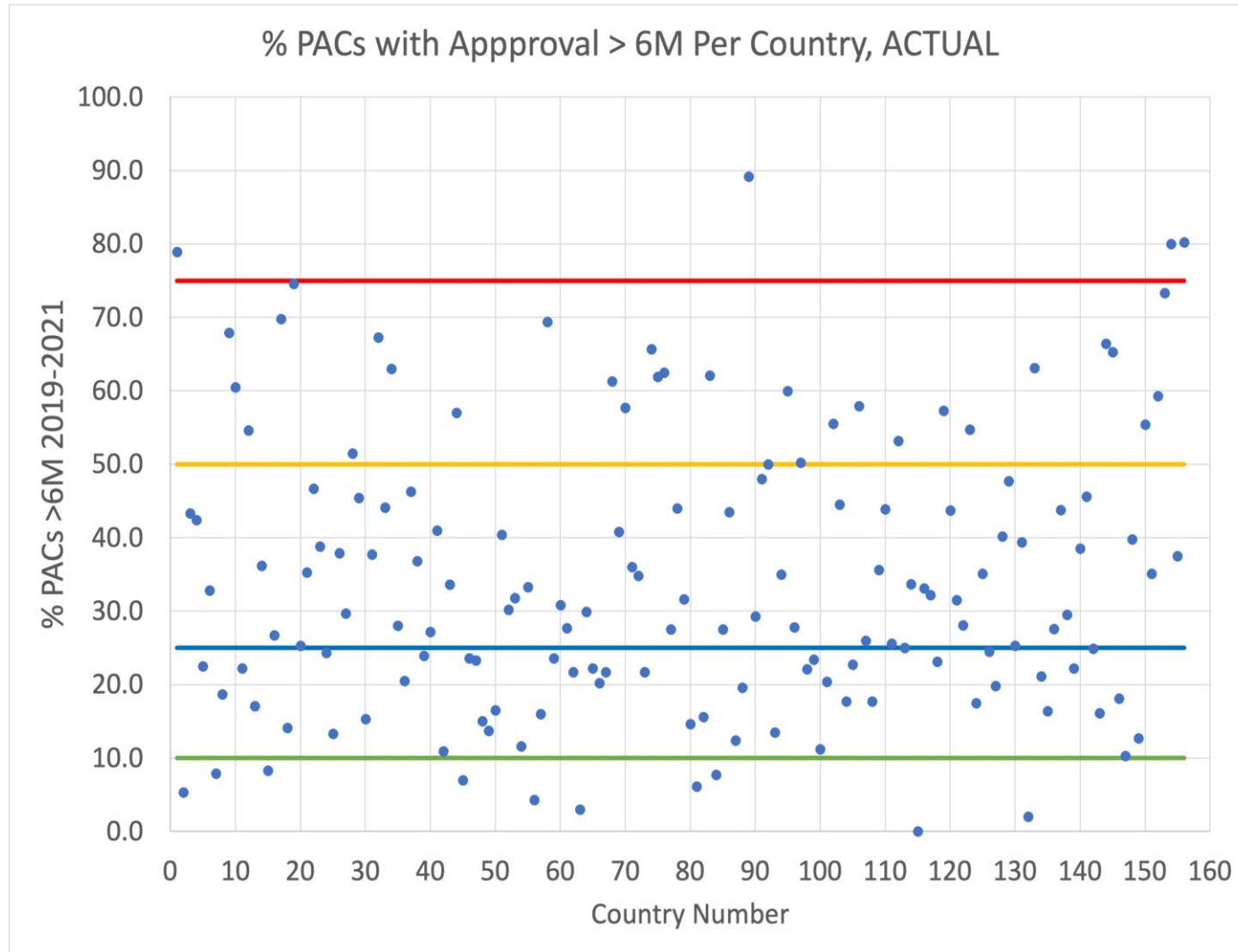


Up to 5 years

Global PAC Regulatory Complexity (2/3)

125 000+ PACs from 16 global pharma companies

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



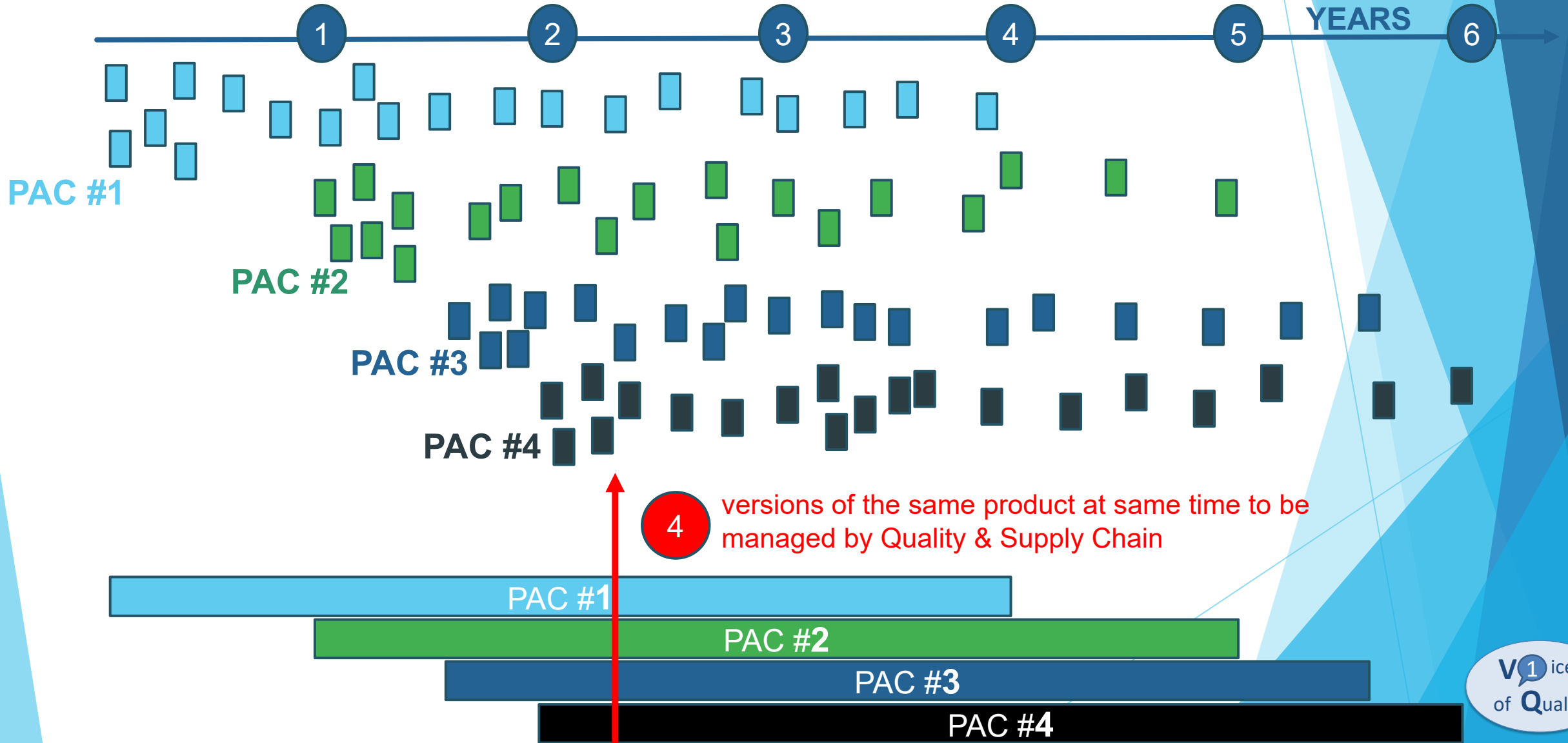
X-Axis: Individual countries 1-156

Source

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

Global PAC Regulatory Complexity (3/3)

Supply Chain Impact



One Voice of Quality for PAC (1/2)

Chief Quality Officer from **25** pharma companies, since **2018**

Recommend ways to **reduce the PAC complexity** and its impact on supply chain

abbvie

AMGEN

astellas

AstraZeneca



Biogen

Boehringer
Ingelheim

Bristol Myers Squibb

CSL Behring

Daiichi-Sankyo

GILEAD

GSK

Johnson & Johnson

Lilly

MERCK

MERCK

NOVARTIS

novo nordisk

Otsuka

Pfizer

Roche

sanofi

Takeda

teva

VIATRIS

1VQ for PAC website: <https://prst.ie/1vq/>

One Voice of Quality for PAC (2/2)

Initiative Objectives

“Determine an **aligned and standardized industry approach** to overcome barriers to proactive continual improvement and innovation and to help reduce drug shortages in the global environment.

Define and demonstrate effective management of PACs in the pharmaceutical quality system (during review and inspections) so that more **changes** can be managed in the PQS and be **reported via notification** pathways (e.g., annual report or changes-being-effected) instead of via prior approvals provided that they do not negatively impact patient risk and drug product efficacy and quality.

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

Vinther & Ramnarine: Solving the Global Continual Improvement and Innovation Challenge: How an Effective Pharmaceutical Quality System Can Transform Post-Approval Change Management. *PDA J Pharm Sci and Tech* 2019, 73 517-521 (Concept Paper)

Reduce Regulatory Complexity (1/7)

ICH Q10 Annex 1

Opportunities to enhance Science and Risk Based Regulatory Approaches and Regulatory Flexibility for PACs

Scenario

Opportunities

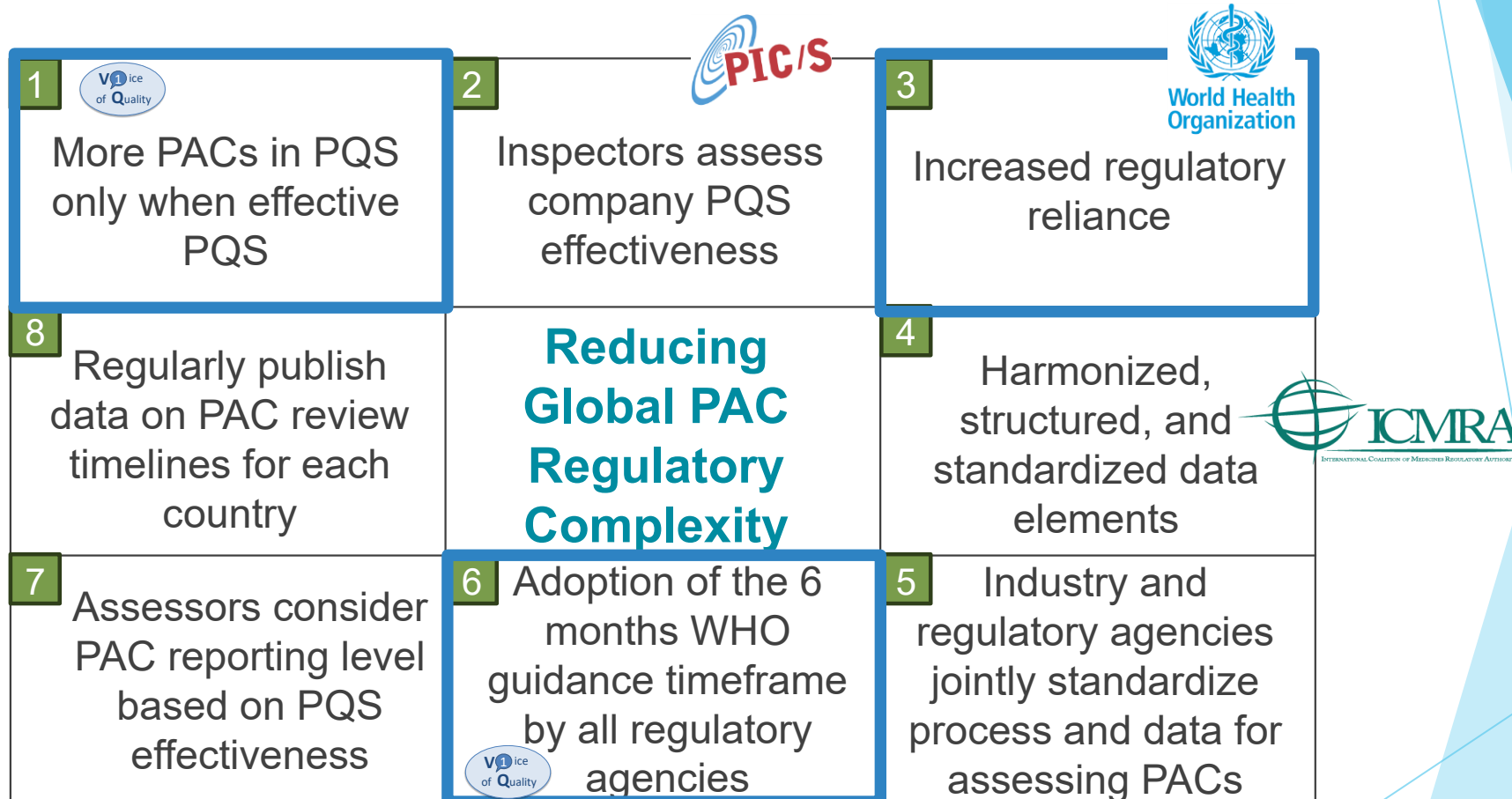
Effective PQS
+
Product/Process Understanding

Incl. use of quality risk management principles as ICH Q8, ICH Q9 and ICH Q10

- ✓ Risk based inspections
- ✓ Science based quality assessment
- ✓ **Optimise science & risk-based PAC processes**
- ✓ Innovative validation approaches
- ✓ Real-time release mechanisms

Reduce Regulatory Complexity (2/7)

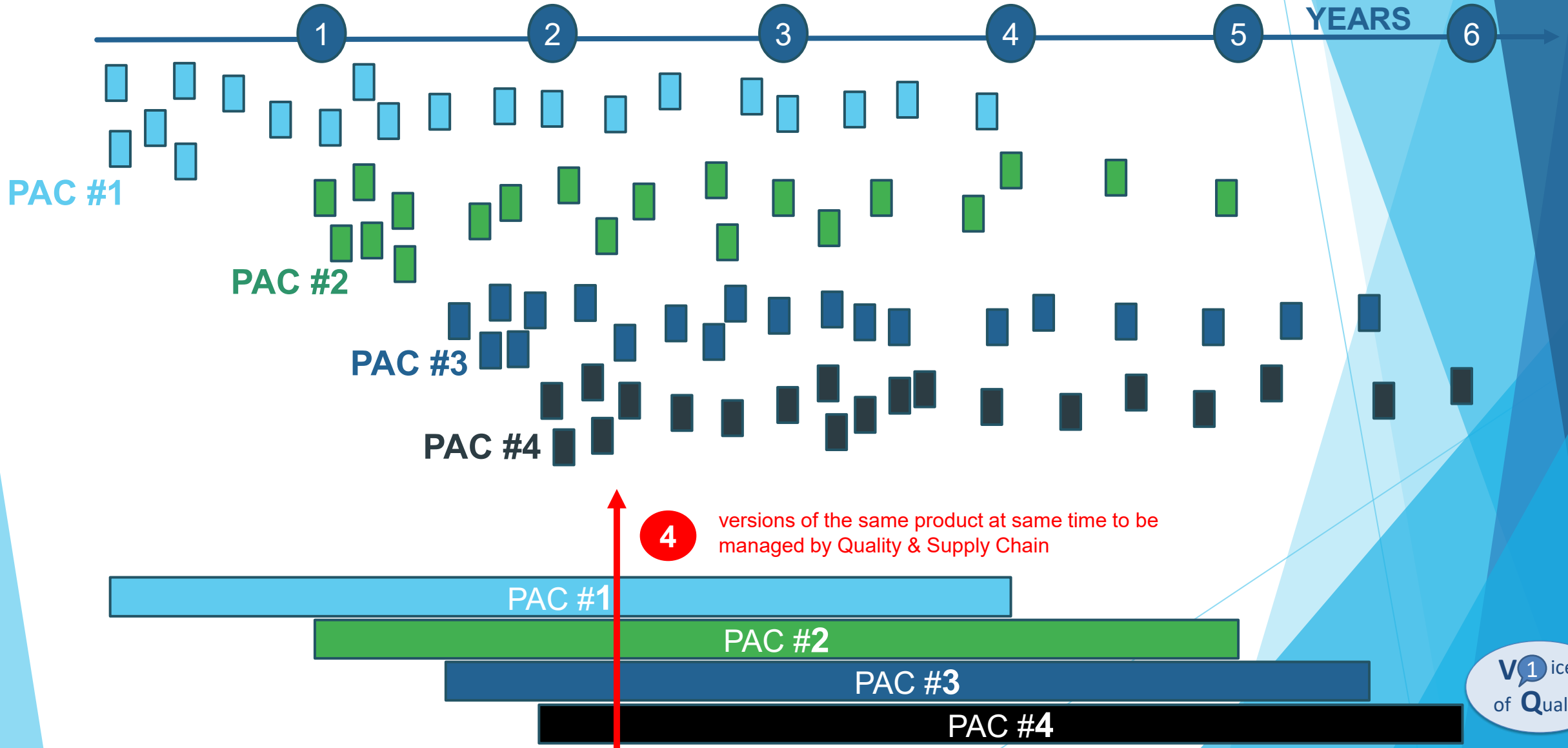
8 approaches of 1VQ



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

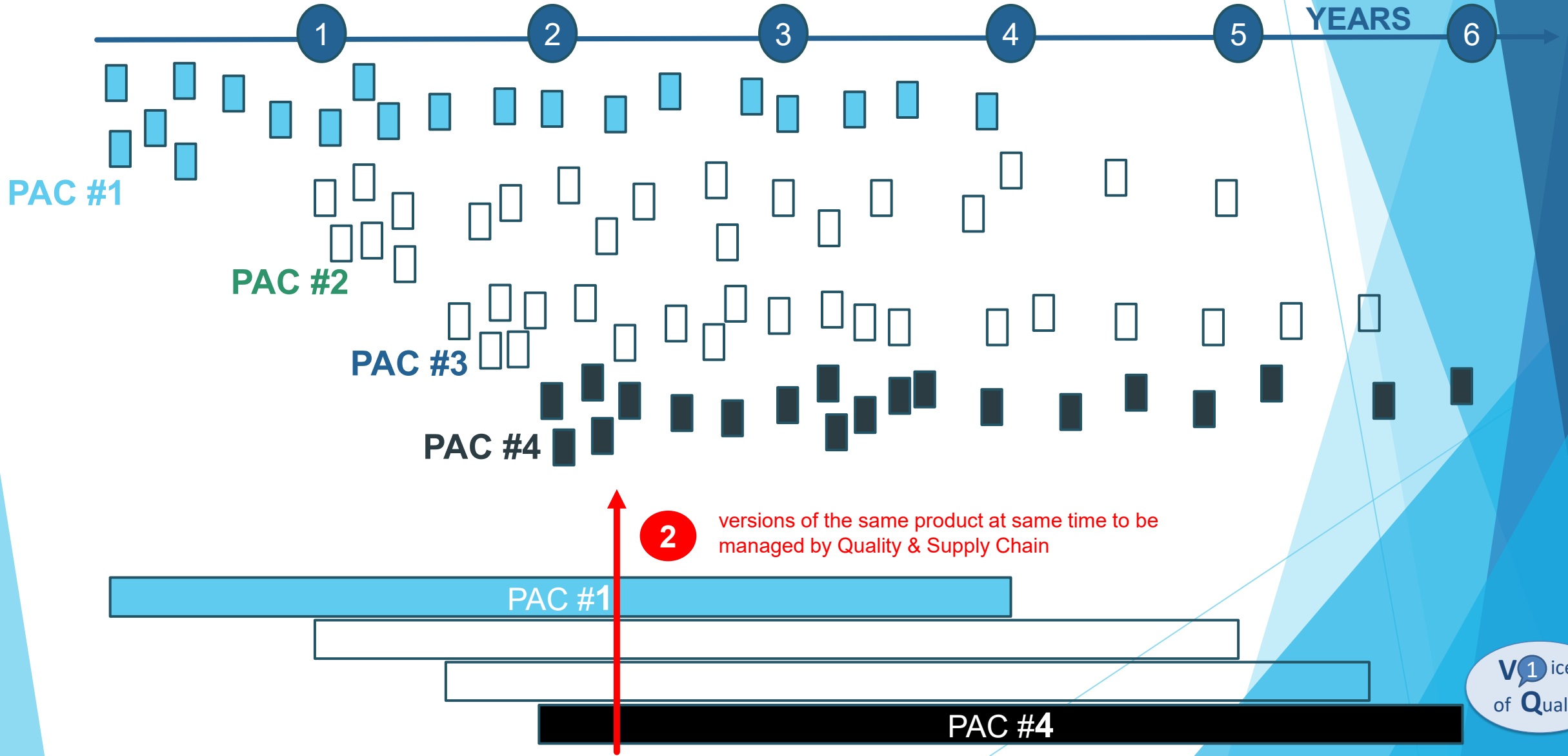
Reduce Regulatory Complexity (3/7)

Let's look at different scenarios



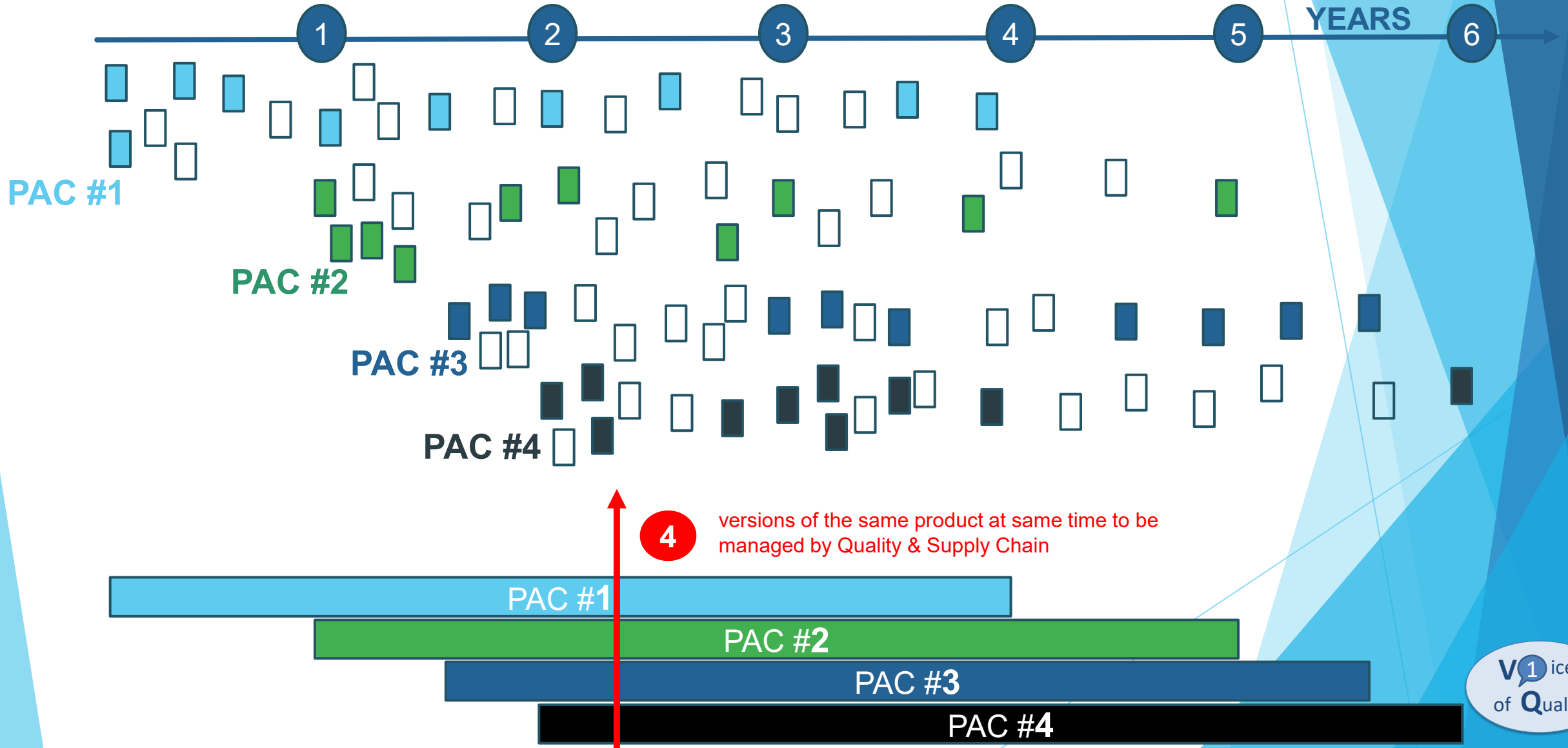
Reduce Regulatory Complexity (4/7)

More PACs in PQS



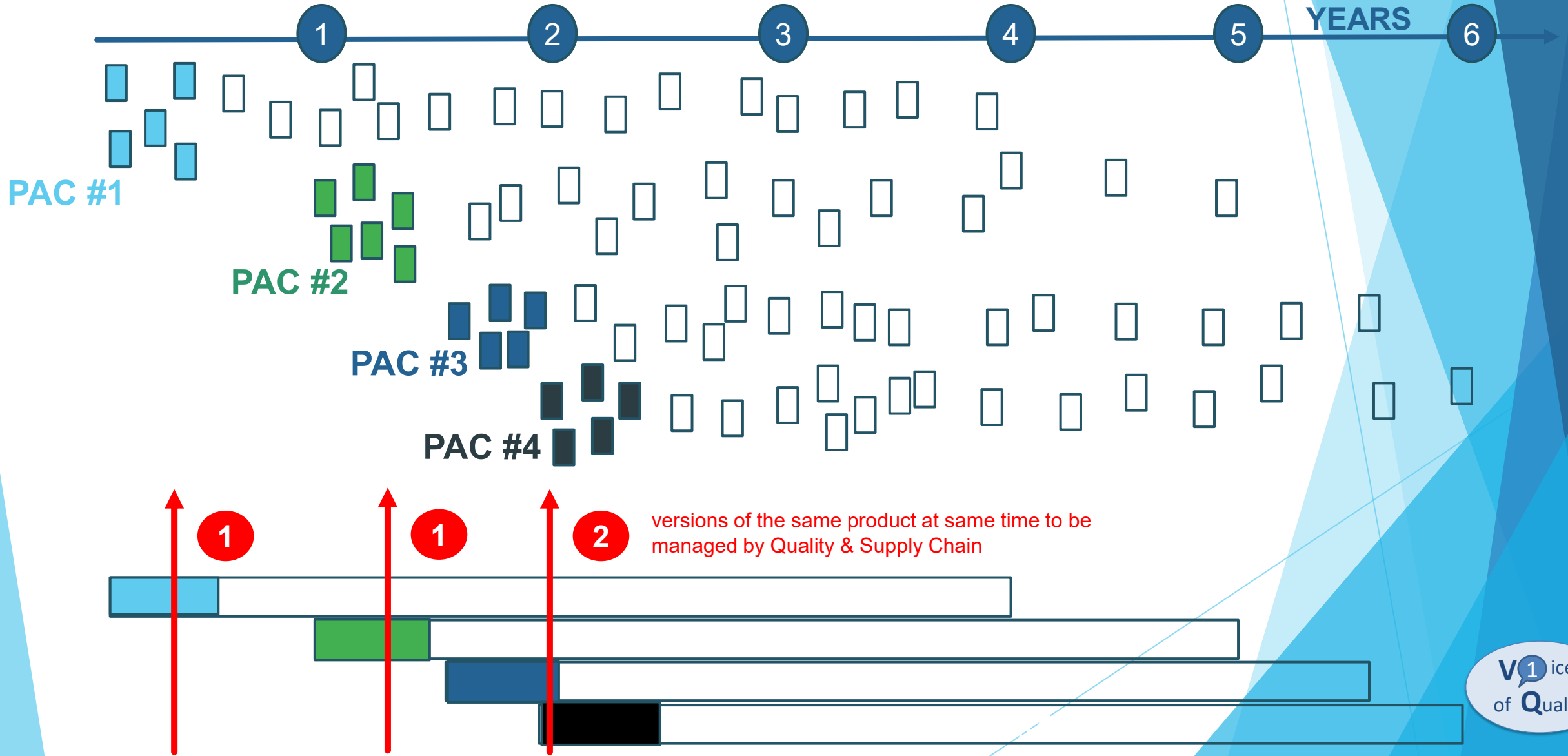
Reduce Regulatory Complexity (5/7)

Reliance



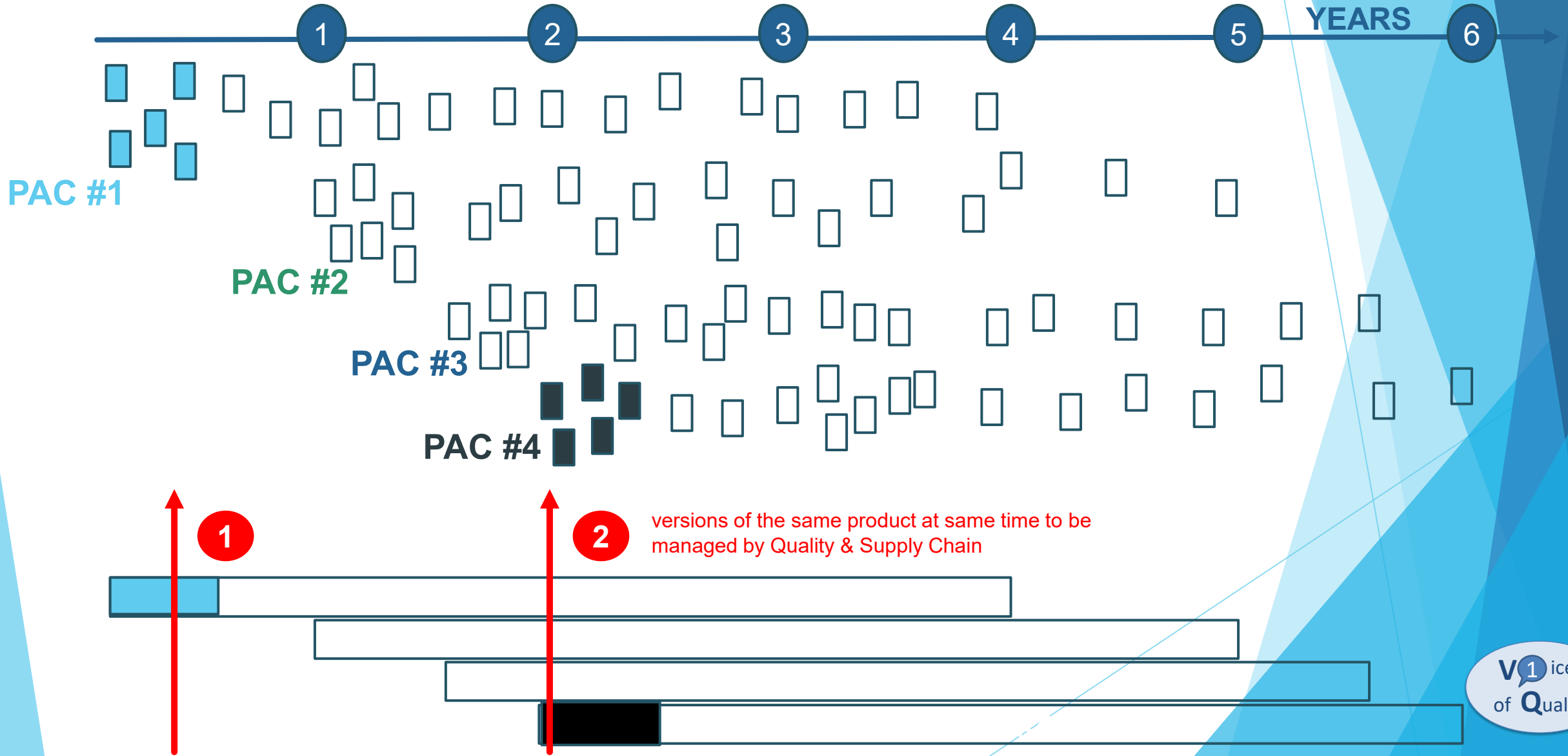
Reduce Regulatory Complexity (6/7)

Agile Reliance



Reduce Regulatory Complexity (7/7)

Agile Reliance + More PACs in PQS



Accelerate CMC post approval changes

The story of a regulatory reliance pilot

sanofi



Lyne Le Palaire
Quality Advocacy Leader



Post Approval Change Vaccine Reliance Pilot

Transfer of a legacy WHO prequalified vaccine Filling & Packaging activities



37 COUNTRIES IMPACTED

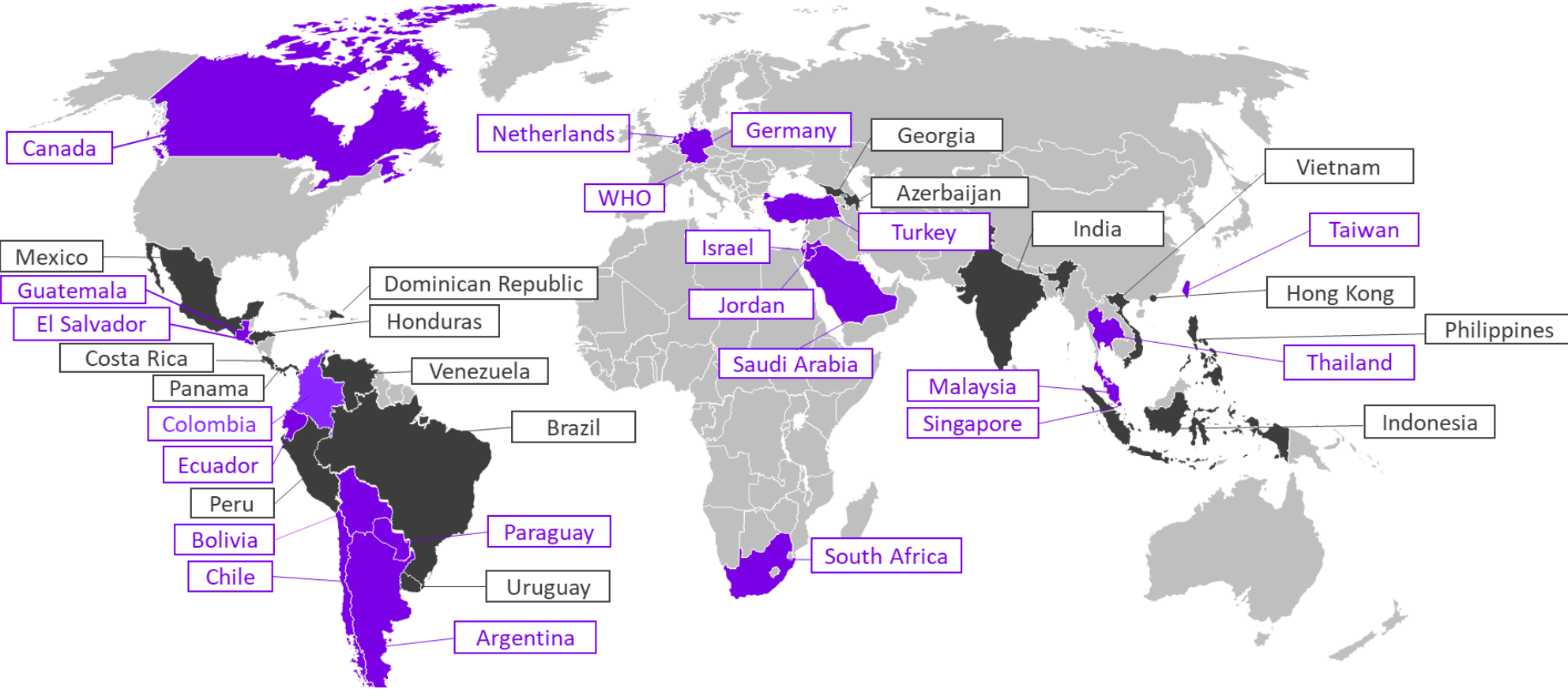


FROM 4 YEARS to 6 MONTHS
Regulatory approvals x 8 time faster



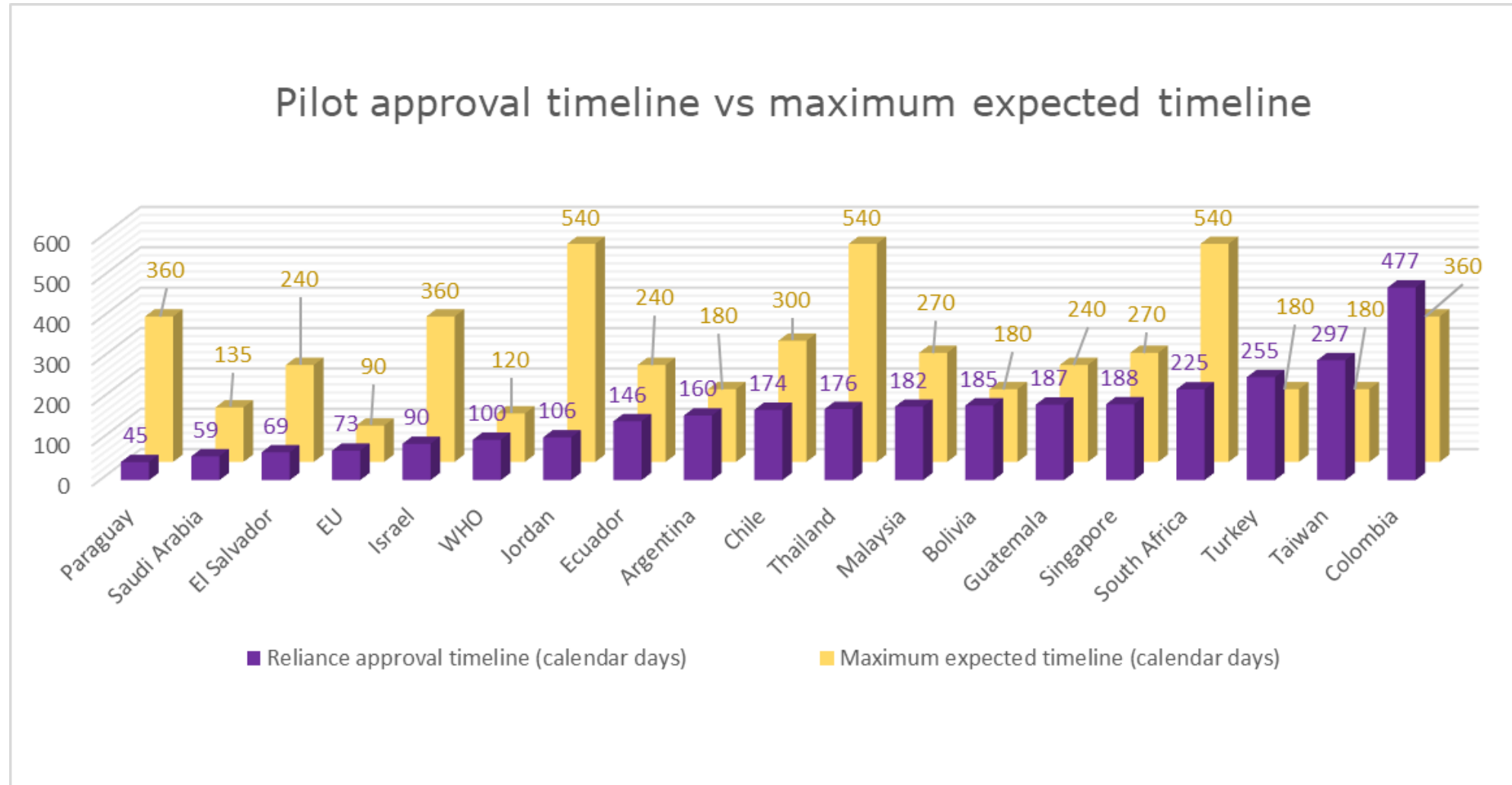
21 countries participated in the Pilot

57 % of participation



Participated in the pilot & approved the variation | Did not participate in the pilot

Approval Timelines



Pilot success ingredients



A COLLABORATION with



1 STANDARD DOSSIER

✓ Submitted in all countries

- based on EU CTD dossier content and Health Canada / WHO requirements
- local requirements NOT met based on scientific rationale
- 100% of NRAs responding to our survey found the content adequate

✓ Including Health Canada **unredacted assesement report** & answers to questions

✓ In **English** for all NRAs except administrative local documents

Pilot success ingredients



1 TIMELINE

- **6 months** , after approval granted by Health Canada as the Responsible NRA
- **90% of NRAs responding consider the timeline was appropriate to review the dossier**

1 Q&A TOOL & DOCUMENT

- **Transparency of questions** asked by other NRA, including Health Canada, & Sanofi **answers** during the review
- **75% of NRAs responding could find Q&A they would have asked in the tool**

ADDITIONAL RELIANCE

- ✓ **GMP Inspection** : Reliance on the GMP certificate of the French site issued routinely by ANSM
- ✓ **NO testing** as considered as not necessary by Health Canada for this type of change

Reliance challenges observed

DUPLICATION OF DATA

Legalized CPP requested in addition to unredacted assessment report

LACK OF HARMONIZATION ON :

- Data requirements
- Reporting levels : from PAC with limited reporting to new registration
- Ability to have alternate sites/batch release
- Timing for introduction of changes
- Ability to work outside the process
- Parallel variations : site registration + site transfer

Outcome of Sanofi Pilot

- **57% participation rate** encouraged by WHO & PAHO in some countries
- **60% of NRAs approved** within the **6 months** timeframe / **95%** within **10 months**
- Majority of **approvals** received **earlier than** or within **historical timelines**
- Active use of the **Q&A tool** by the NRAs
- Presented at **19 Conferences** (NRAs & Industry)
- **Publication in PDA**

Change is Possible ...

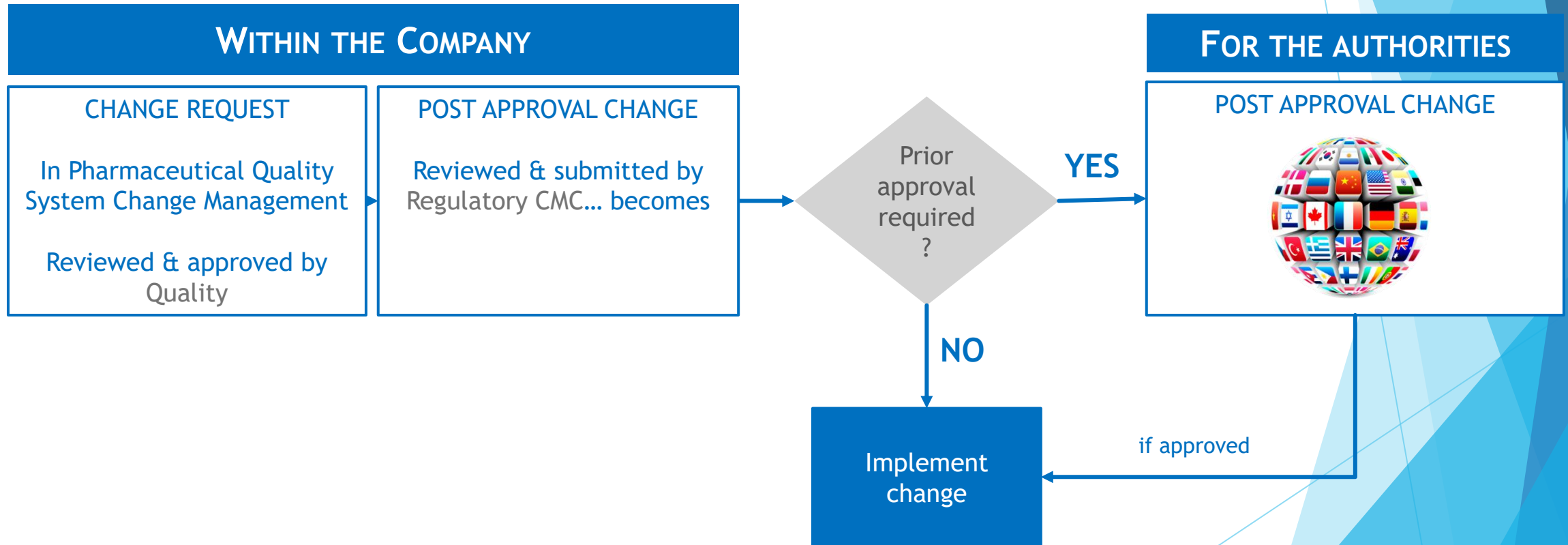
...When Senior Leaders Speak with One Voice

1VQ for PAC has

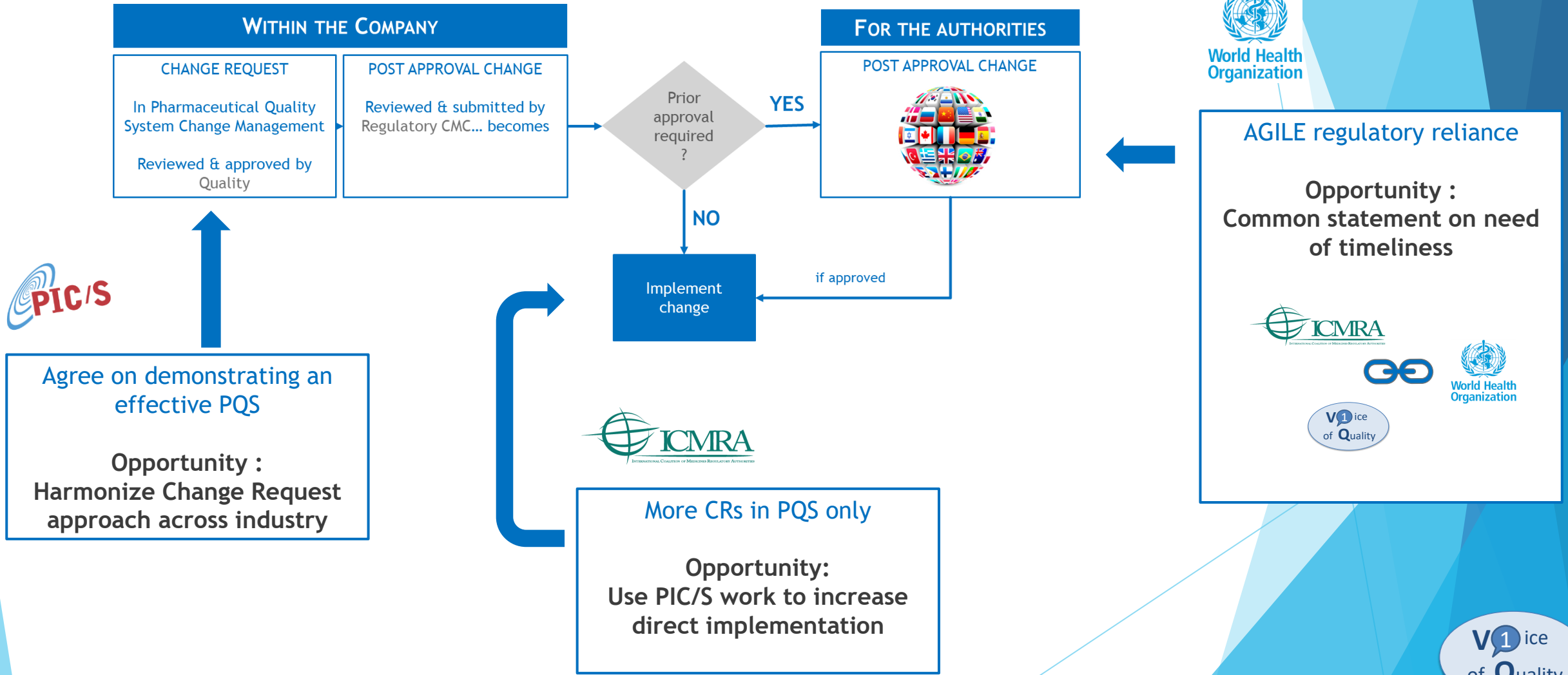
- ✓ **Brought awareness of the complex PAC problem** to ICMRA, EMA, FDA, WHO, PIC/S, industry
- ✓ **Influenced ICMRA to initiate PQKMS**
- ✓ **Influenced PIC/S to write Change Management Recommendation Paper**
- ✓ **Defined and published solutions for effective PQS** for PAC management & risk-based approach for PACs
- ✓ **Published MR metrics for PAC management**
- ✓ **Advocated 8 approaches to lessen the problem**

Flow of change...

... Quality & Regulatory perspectives



Change Management Opportunities



1 VQ for PAC Vision

Working with PIC/S

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/s12241-024-00614-9>

Working with WHO & ICMRA

Designing & implementing an agile science and risk-based efficient, predictable global PAC system that facilitates state of control, continual improvement and reduces risk of drug shortages

From Vision to Reality

When senior leaders come together to speak with one voice even difficult change can happen. 1VQ for PAC Initiative has

- Created awareness of the complex PAC problem
- Influenced ICMRA to initiate PQKMS and PIC/S to publish the CM Recommendation Paper

The work continues with a systems thinking approach

If senior Quality and Regulatory CMC Industry leaders come together to create one global standardized PAC approach & template, we can achieve even more.

It is up to us