FDANews Webinar

PDA's Post Approval Change Innovation for Availability of Medicines Program (PAC iAM^{sm})

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Globalization vs. Nationalization

Companies are globalized

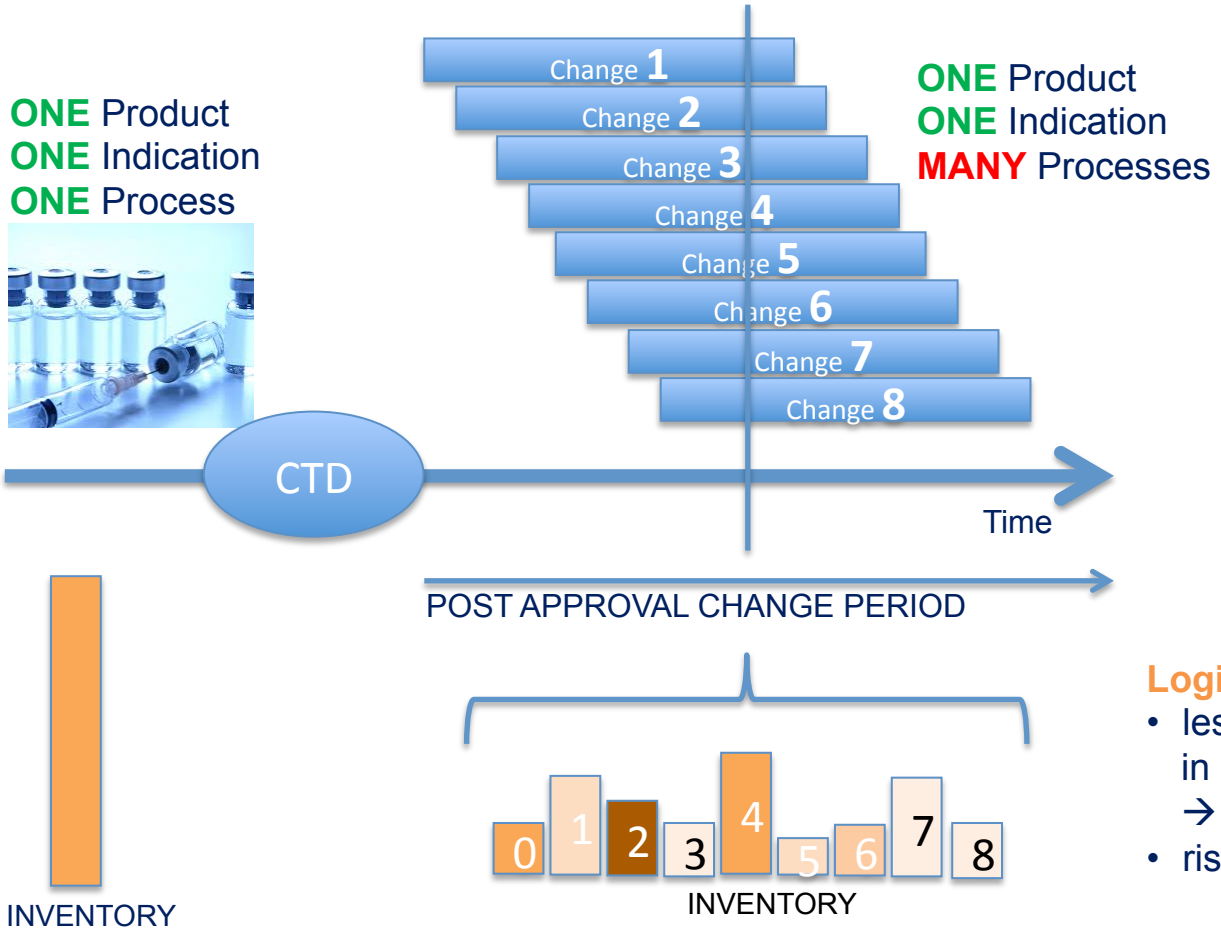
Ideally: one product for one world

Regulatory approvals are nationalized*

Reality: one product with 100+ approvals

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

Post Approval Change, explained



Consequence

Logistics challenge →

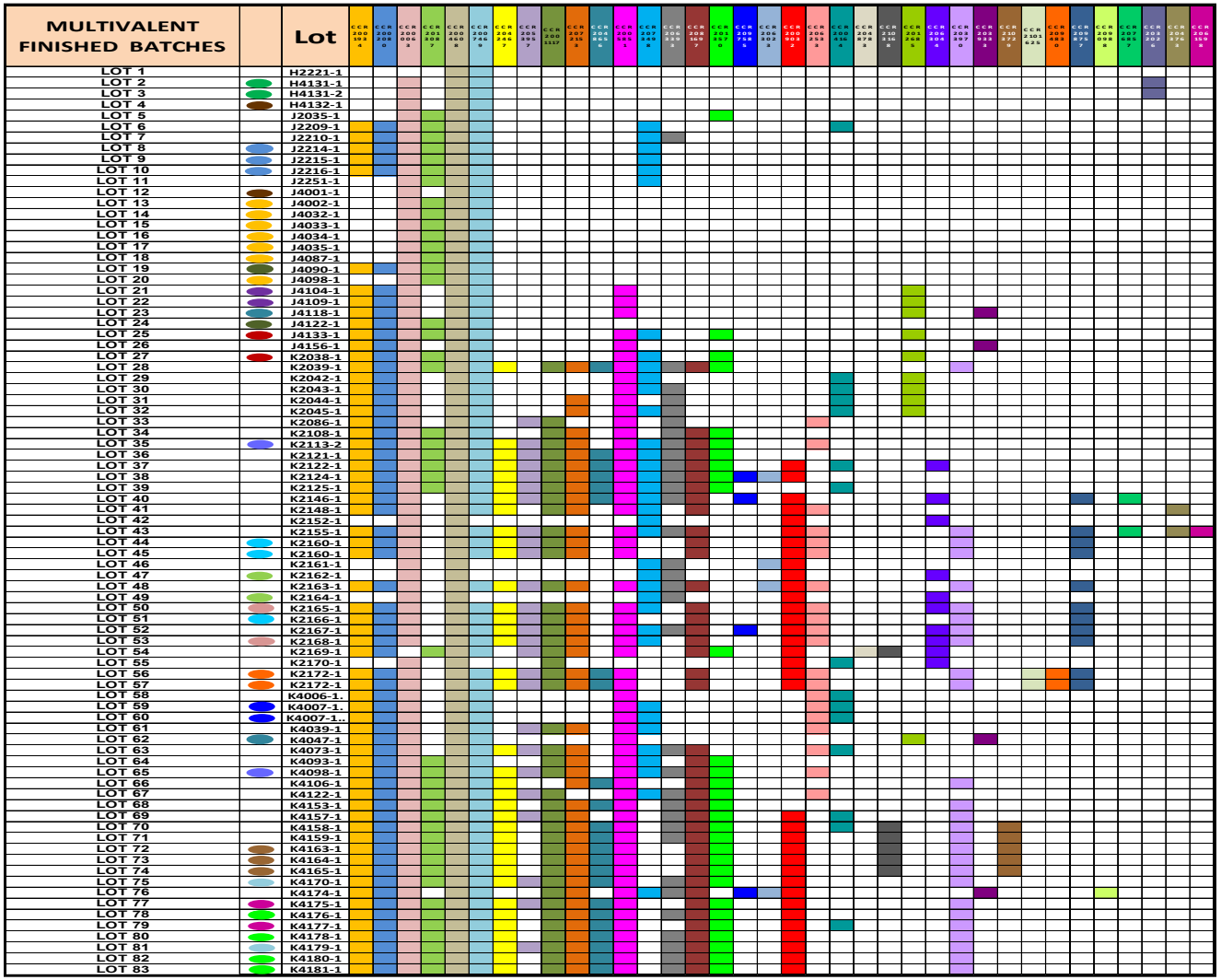
- less ability to act on change in demand for one version → shortage
- risk of errors made

The above is greatly simplified. In actuality, changes are counted in the thousands every year for a full product portfolio.

PAC- a real example

One pentavalent vaccine - one year

83 batches : 55 variations of the same process…



PDA's Contribution

About PDA

- Global organization with >10,000 individual members
- Connecting People, Science and Regulation
- Committed to developing scientifically sound, practical technical information and expertise to advance pharmaceutical and biopharmaceutical manufacturing science and regulation so members can better serve patients.
- www.pda.org
- Website for PAC iAM℠ **pda.org/PAC**

PDA PAC iAM℠ Deliverables

- ✓ Call For Action
- ✓ Points to Consider
  - ✓ Lifecycle Management
  - ✓ Effective PQS for Management of PACs
  - – QRM and Knowledge Management for PACs
- Industry Survey
- Technical Report: Post Approval Change Implementation for Biologics and Pharmaceutical Drugs
- Global Post Approval Change Management Protocol Library of Examples
- Workshops, Trainings, Tools & Templates

The Post Approval Change Paradox

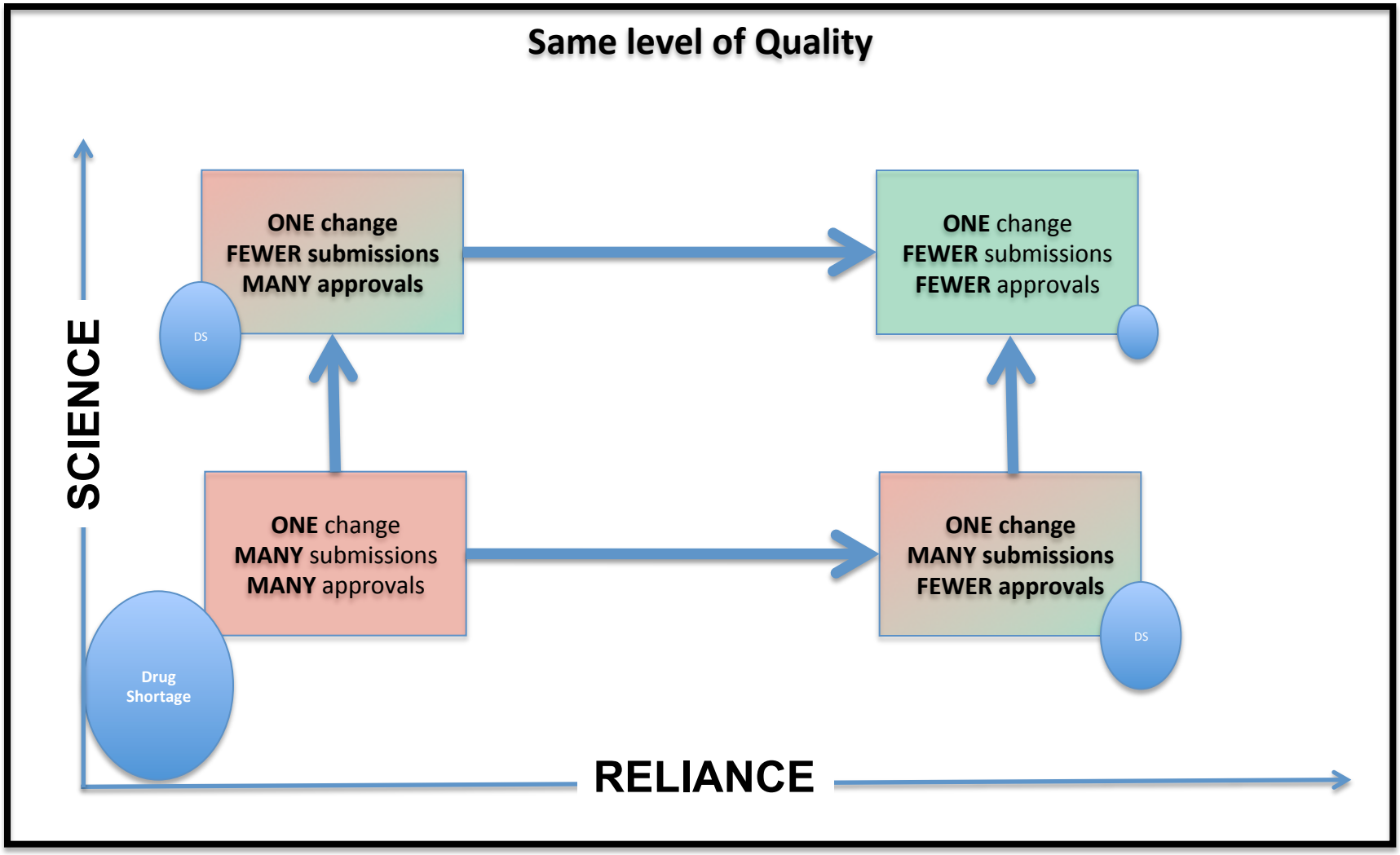
The cGMPs require facilities and processes to be **current**	*yet*	Even simple PACs take **up to 5 years** for global approval to make facility/process current
Improvements are intended to **reduce risks**	*yet*	Long PAC approval timelines **delay risk reduction**
Improvements intended to **assure better availability** of drug products	*yet*	Long PAC approval timelines **hinder availability**
Changes in high tech industries usually happens in **months**	*yet*	In the pharma industry changes are measured in **years**

"Wicked Problem" Characteristics

- Difficult to clearly define
- Many interdependencies and often multi-causal
- Attempts to address the problem often leads to unforeseen consequences
- Often not stable
- Usually no clear solution
- Socially complex
- Rarely is the responsibility of one stakeholder only
- Solutions involve changing behaviors
- Some characterized by chronic policy failure

Source: Vinther, A., Drug Shortage is a "Wicked Problem ", PDA Letter May 2016

Industry and Regulators Working Together



Established Conditions, explained

- Legally binding information (or approved matters) considered necessary to assure product quality
- Contained in a regulatory submission, submitted by the applicant, and approved, as necessary, by the regulatory authority.
- May be specifically proposed in a submission or they may be implicit based on existing regulation and guidance.
- Any change to Established Conditions necessitates a submission to the regulatory authority

Focus & Contribution from PDA

- Dialog on convergence of health authorities on "global" set of Established Conditions (via ICH and WHO) per product
- Increased product/process understanding and risk management to help shift Established Conditions changes from "tell & do" to "do & tell"

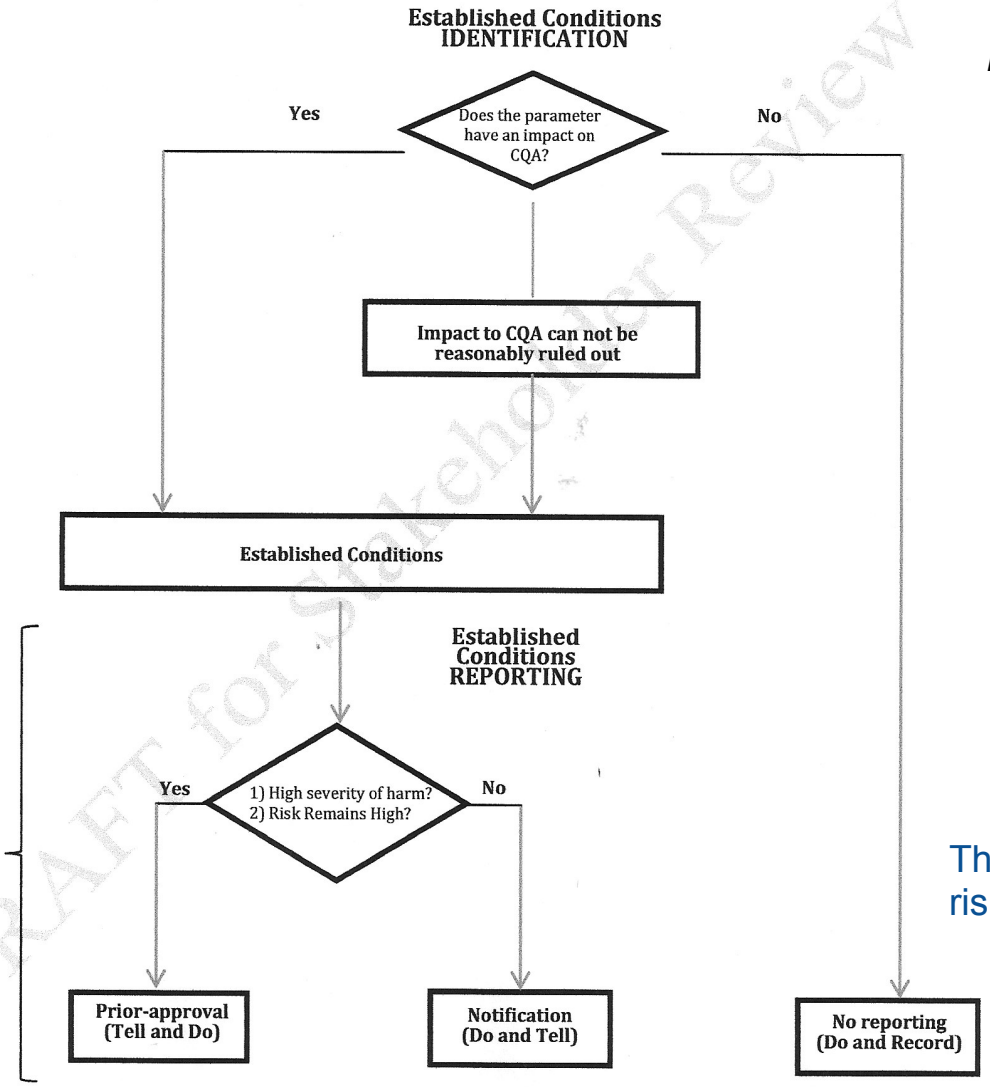
Reporting Categorization of Changes

- **Prior-approval**: Changes with sufficient risk; require regulatory authority review and approval.
- **Notification:** Moderate to low risk changes may not require prior approval; generally require less information to support the change. Communicated to regulatory authority formally within a defined time period after implementation.
- The lowest risk changes are only managed and documented within the PQS and not reported; may be assessed on inspection.

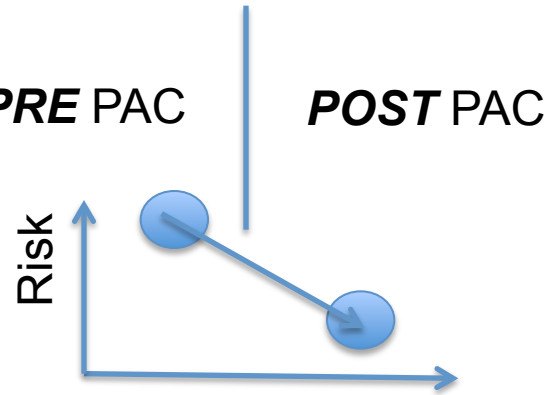
Focus & Contribution from PDA

- How to apply QRM for effective change categorization
- Focus risk scope as: impact to product quality, efficacy, and/or patient safety
- Global alignment on PAC categorization
- Allow more changes in the PQS based on risk level; reduce number of prior approval changes
- Changing the mindset to allow faster implementation when PACs result in lower risk

Established Conditions & Reporting Categories explained



If…..



Then…..

Implement change as 'Do & Tell' even for Established Conditions

The company must have an effective PQS (including risk and knowledge management) for managing PACs

Changes to Established Conditions, Example

Change in a starting raw material (can impact a CQA)

COMPANY A

Extensive documented data/ understanding of raw material attributes and impact to CQA

Risk Assessment

High risk

Prior Approval
"Tell and Do"

COMPANY B

Extensive documented data/ understanding of raw material attributes and impact to CQA

Risk Assessment

Moderate/low risk

Notification
"Do and Tell"

COMPANY C

Limited data/understanding of raw material attributes and impact to CQA

No Risk Assessment

Prior Approval
"Tell and Do"

The same PAC will have different regulatory flexibility depending on knowledge and risk as well as whether or not the Company has an effective PQS for managing PACs

Pharmaceutical Quality System Effectiveness for Managing Post Approval Changes

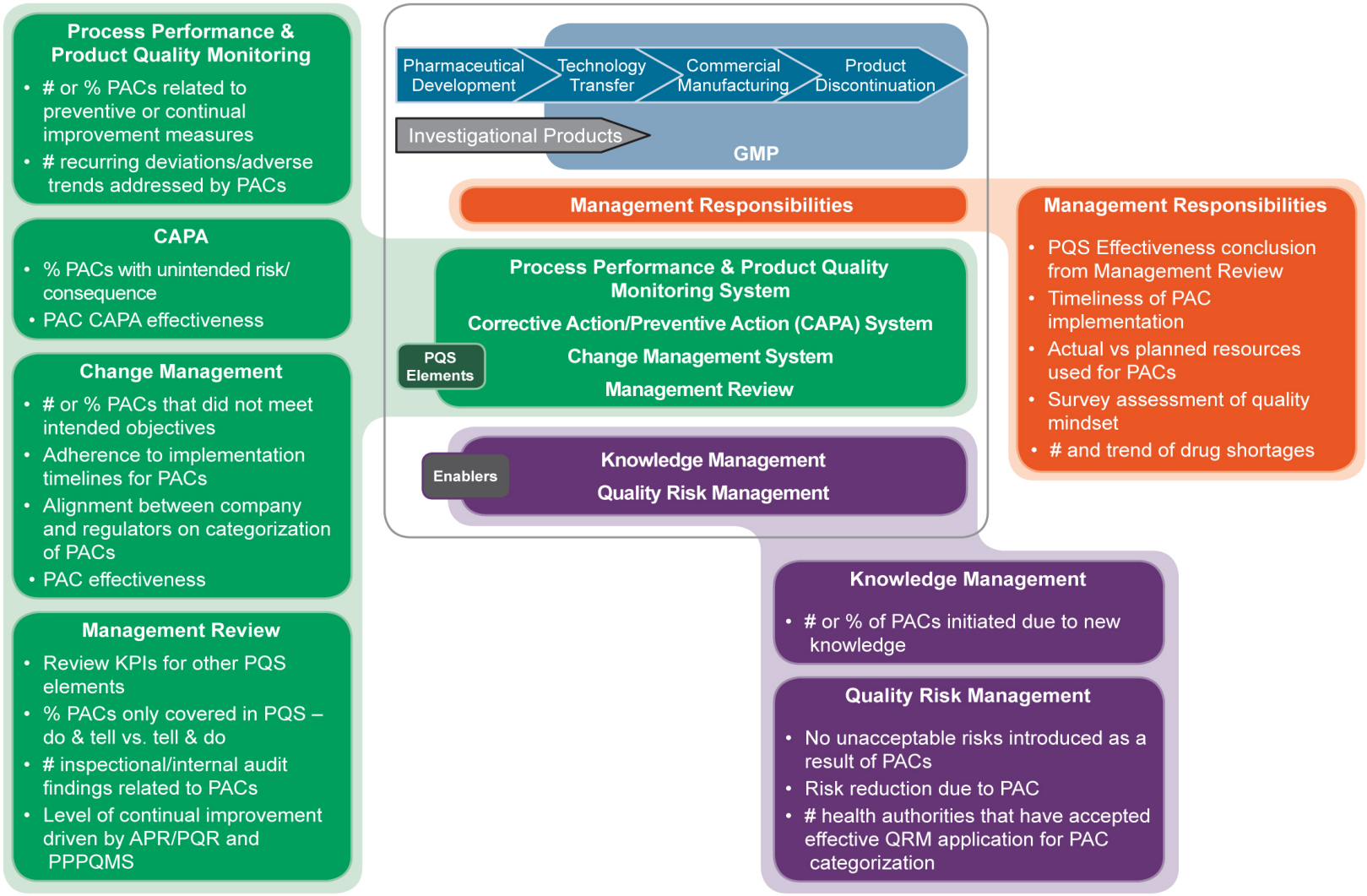
- Firms that have implemented an effective PQS per Q10 and regional GMPs, provide confidence to the regulatory authority that changes are supported by data obtained through application of patient-centric, risk-based principles. As a result, regulatory authorities can allow more post-approval changes to be managed under the PQS, without requiring prior review and approval by the regulatory authority.
- Building an effective PQS is the responsibility of a firm and it is not the intent to require by default a specific inspection assessing the state of the PQS before the firm can use the post-approval change benefits described in the guideline.
- If the PQS is found not to be effective, it may result in restrictions on the ability to make changes with downgraded notification to regulatory authorities.

Focus & Contribution from PDA

- Stronger adoption of ICH Q10 Annex 1 - when companies can demonstrate an effective PQS and product and process understanding, including the use of QRM they "gain the opportunity to optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement"
- Develop requirements and KPIs of key PQS elements that are essential for effective PAC management – PDA PtC on PQS Effectiveness for PAC Management

- Implementation of an effective PQS is essential for a company to achieve product realization, establish and maintain a state of control, and facilitate continual improvement
- When changes are made during the commercial life of a product, an effective PQS, product and process understanding, and use of quality risk management should ensure that product quality, patient safety, and adequate supply to patients are maintained
  - This, according to ICH Q10 – Annex 1, should provide companies the opportunity to manage post-approval changes (PAC) with reduced regulatory oversight
- **The Points to Consider paper is a step-by-step guide for implementing an effective PQS for managing PACs** – and is a direct continuation of ICH Q10
- Objective is to advice companies and regulators to take advantage of ICH Q10, Annex 1
- Focuses on
  - Management Responsibilities
  - PQS Elements: Process Performance and Product Quality Monitoring System, CAPA System, Change Management System, Management review of process and product quality
  - Enablers: QRM & Knowledge Management
  - Quality Culture

KPIs to Demonstrate Effectiveness of the PQS for PACs



Product Specific Lifecycle Management Strategy (PSLCM)

Objectives of LCM

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

Elements of Lifecycle Management

- Product Established Conditions (EC) incl. Control Strategy Summary
- Planned Post-Approval Changes
- Summary of how product lifecycle will be managed in the PQS
  - Managing Product & Process Knowledge During the Commercial Lifecycle
    - *Product & Process Monitoring*
    - *Annual Product Review (APR)*
    - *Post-marketing Surveillance and Pharmacovigilance*
  - Control System Management
  - Managing PACs in the PQS

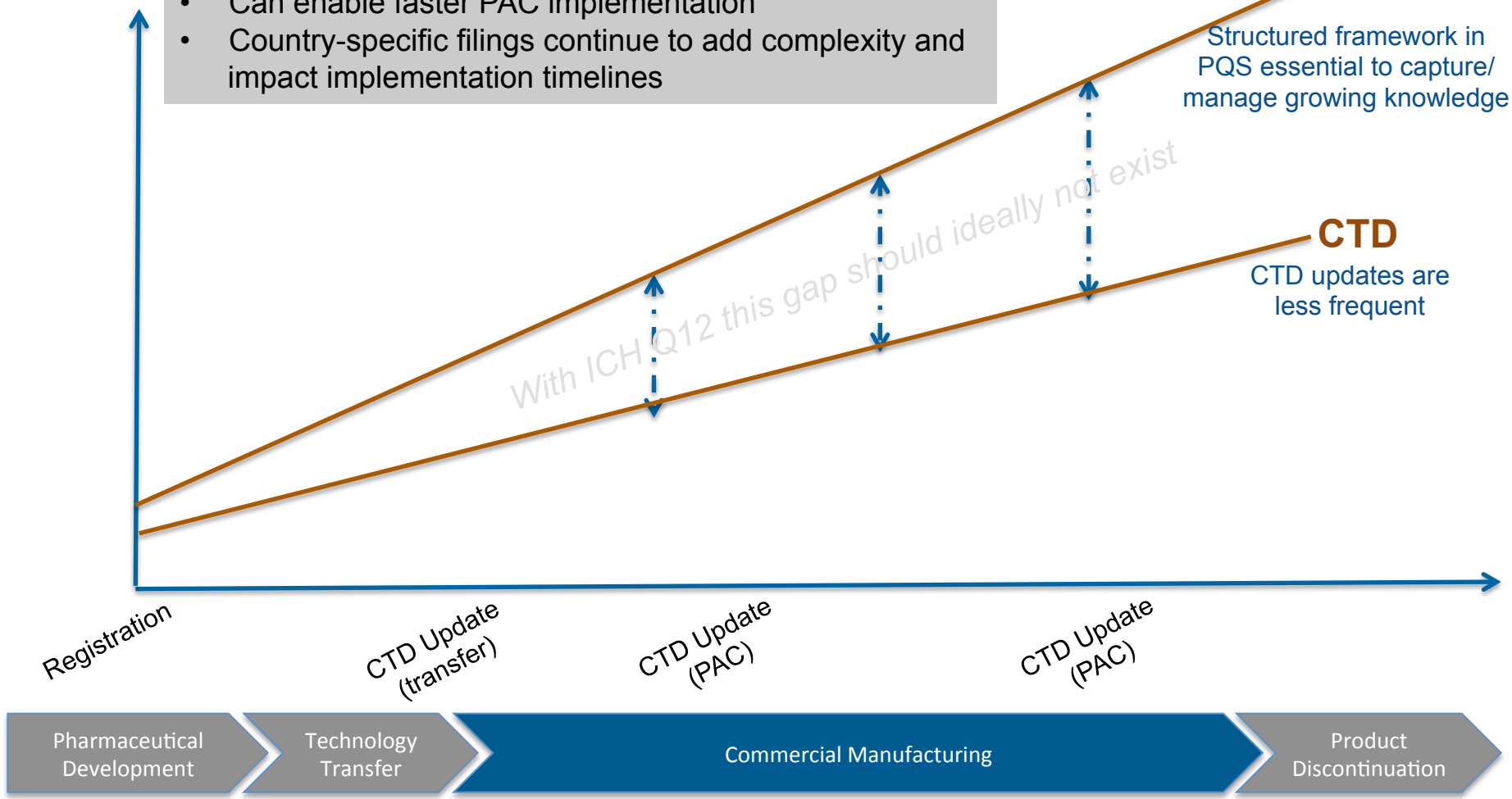
Focus & Contribution from PDA

- Expand LCM discussion from managing PACs to a much broader conversation about LCM elements and the importance of Knowledge Management

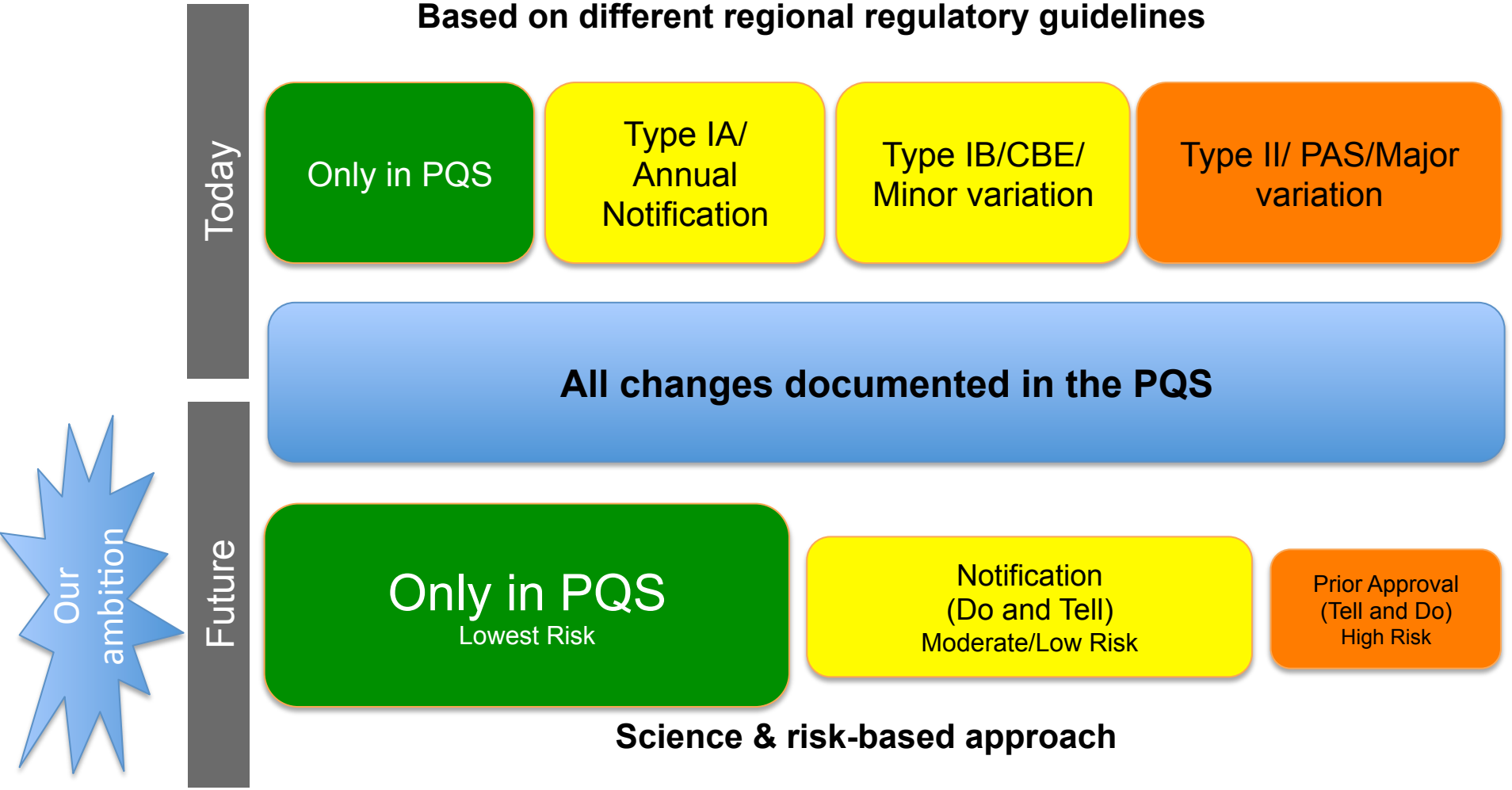
Note: Additional elements to consider
Supply strategy
Drug shortage prevention plan

Role of Knowledge Management in LCM and PAC Management

- ↑ knowledge should enable risk reduction, continual improvement & possible reduction in filing category
- Can enable faster PAC implementation
- Country-specific filings continue to add complexity and impact implementation timelines



Moving to Science & Risk-Based PAC Management



PDA Deliverables and PAC iAM Website

Mission: Identify, assess and address current barriers to implementation of PACs that are intended to ensure continued operations, drive innovation and continual improvement

- ✓ Website for PAC iAM℠ **pda.org/PAC**
- ✓ Call For Action PDA Letter January 2016
- ✓ Points to Consider PDA Journal
  - ✓ Lifecycle Management
  - ✓ Effective PQS for Management of PACs
  - – QRM and Knowledge Management for PACs
- ✓ PDA PAC iAM Survey Open until Feb 16th
- Technical Report: Post Approval Change Implementation for Biologics and Pharmaceutical Drugs
- Global Post Approval Change Management Protocol Library of Examples
- Workshops, Trainings, Tools & Templates
  - PDA EU Annual Meeting June 13-14, Berlin
  - PAC Workshop Sept 13-14, Wash D.C.
- Drug Shortages (TR68): Enable reduction of drug shortages resulting from PAC complexity pda.org/drugshortage
- Manufacturing Science & Operations Program & Aging Facilities: Expedite PACs related to implementation of new technologies and facility upgrades

PDA PAC iAM℠ Task Force

- **Anders Vinther, Sanofi Pasteur (co-lead)**
- **Emma Ramnarine, Roche/Genentech (co-lead)**
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- Kara Follman, Pfizer
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- Barbara Jengtes, PhACT GmBH
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- **Website for PAC iAM ℠ pda.org/PAC**