Opportunities and Challenges with Implementation of Q12

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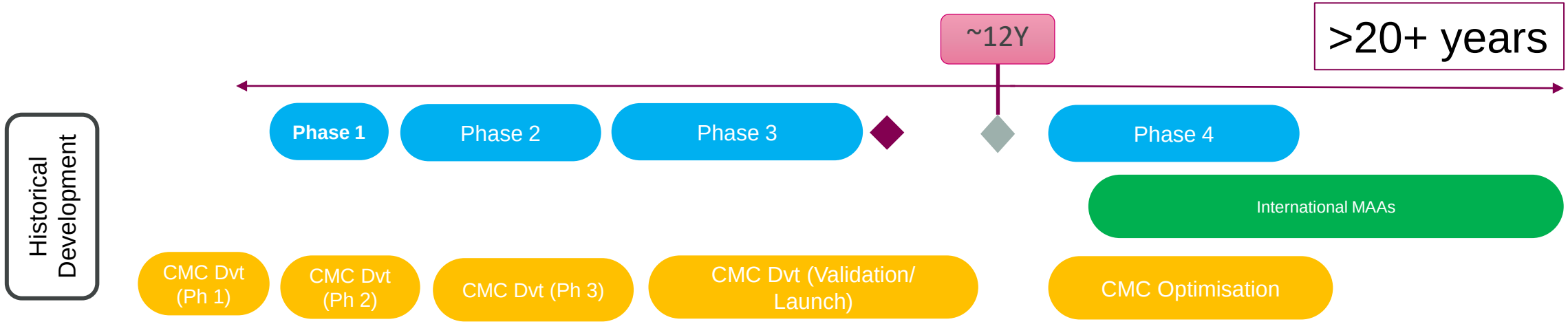
Traditional development

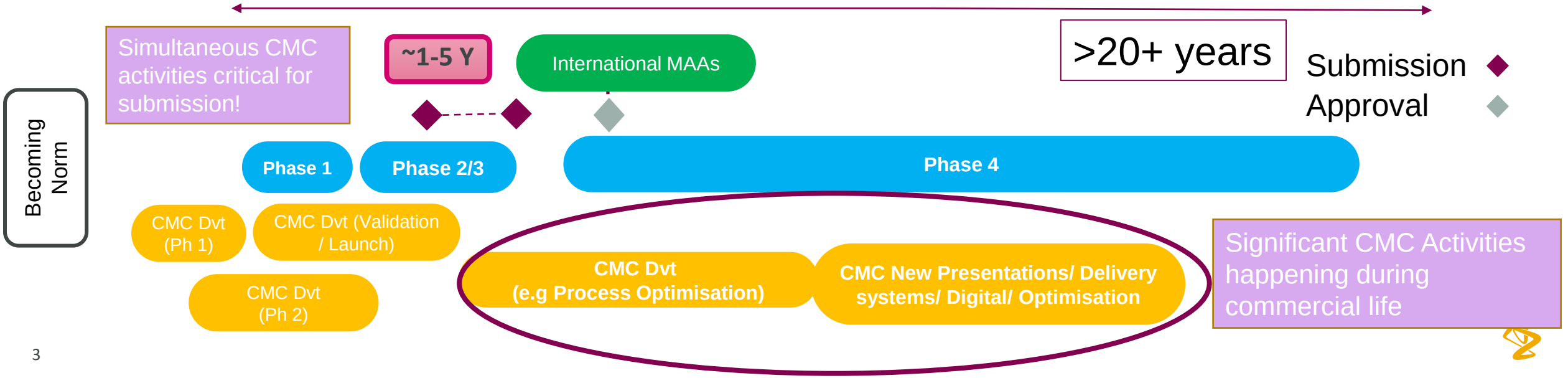
Submission ◆
Approval ◆

- Three distinct phases of clinical development (>12 years to NDA approval)
  - Clinical studies in China often after US approval
- Limited large Ph4 clinical studies
- Registrations in International markets slowly over many years
- Ten+ years for development of the commercial manufacturing process
  - Many CMC changes introduced at the start of next phase of clinical development
- Identification and transfer to commercial facility ahead of potential launch
- Phase 3 supply manufactured in commercial facility
- Commercial process optimisation more limited in scope given long development timelines



How is Product Lifecycle Changing

- Clinical development is accelerating as targeted therapies and disease understanding grows
  - Less than 5 Years becoming routine in oncology – **Covid therapies less than 1Y!**
- Oncology business strategy is to design for registration based on extended Ph1 or Ph2 studies
- Ph 4 clinical development linked to common mechanism of action (Imfinzi >240 Clinical Trials)
- CMC development timeline shortened, lots of simultaneous activities
- Change is critical within the clinical development phase
  - To ensure continued supply to clinical studies that could be registrational
- Significant change expected in launch to commercial phase and there after



The Challenge: Diverse global regulatory environment for post-approval changes

Example of a single change: introduce a new filling site

Total expected approval lead time for a world wide approval

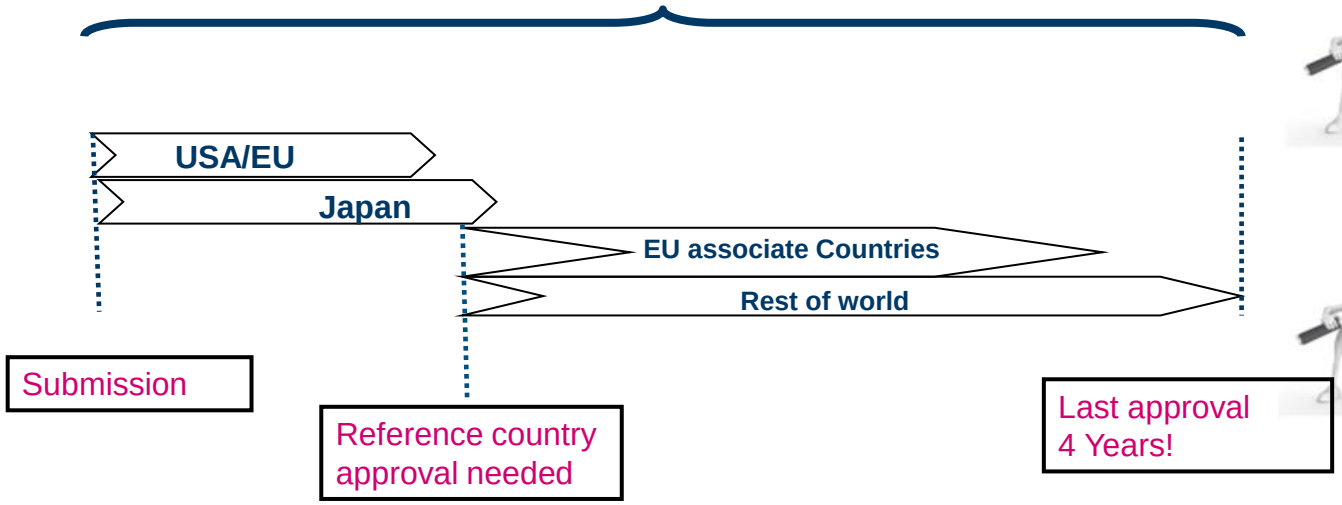
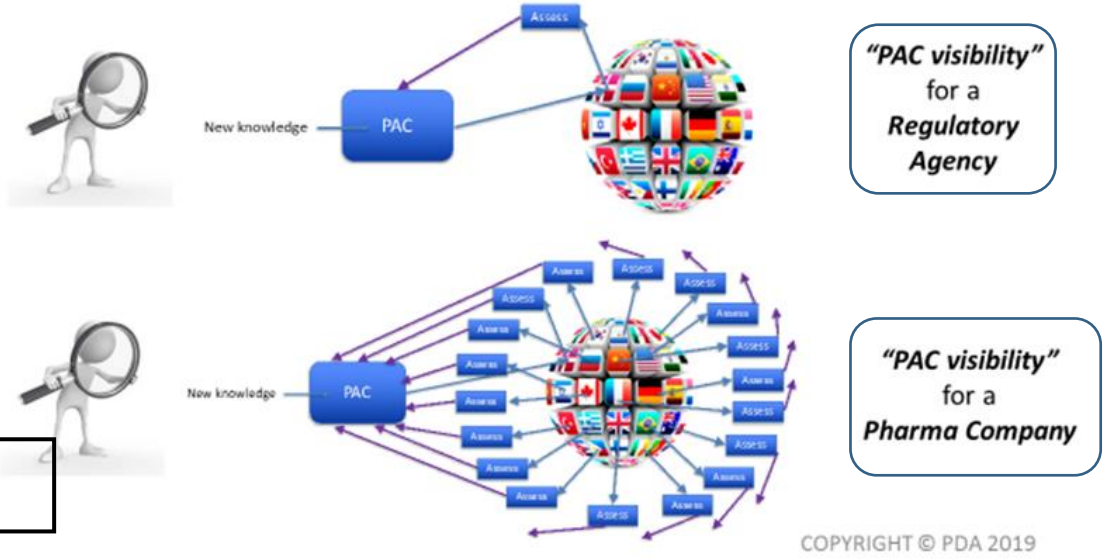


Figure 2: PAC Regulatory Complexity – Seen From Different Angles

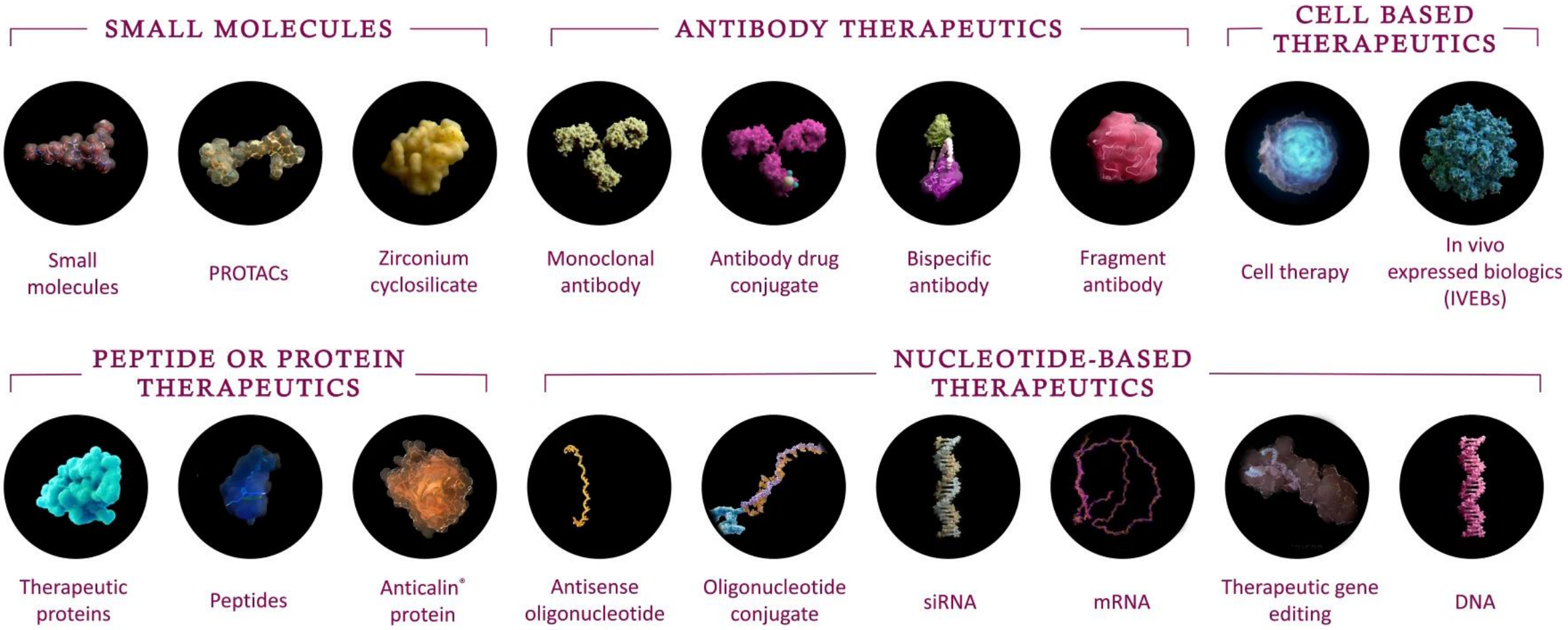


A. Vinther and E. Ramnarine, PDA Journal of Pharmaceutical Science and Technology, 2019

Result:

- For a new filling site, long and different approval time lines => some countries will have to be supplied from the old filling factory for four years.
- Company must produce the same product manufactured in different facilities

Large variety of product types



Great for Patients

Terrifying for CMC

Implications For CMC

- Speed of clinical development will continue to accelerate, especially with the impact of COVID-19

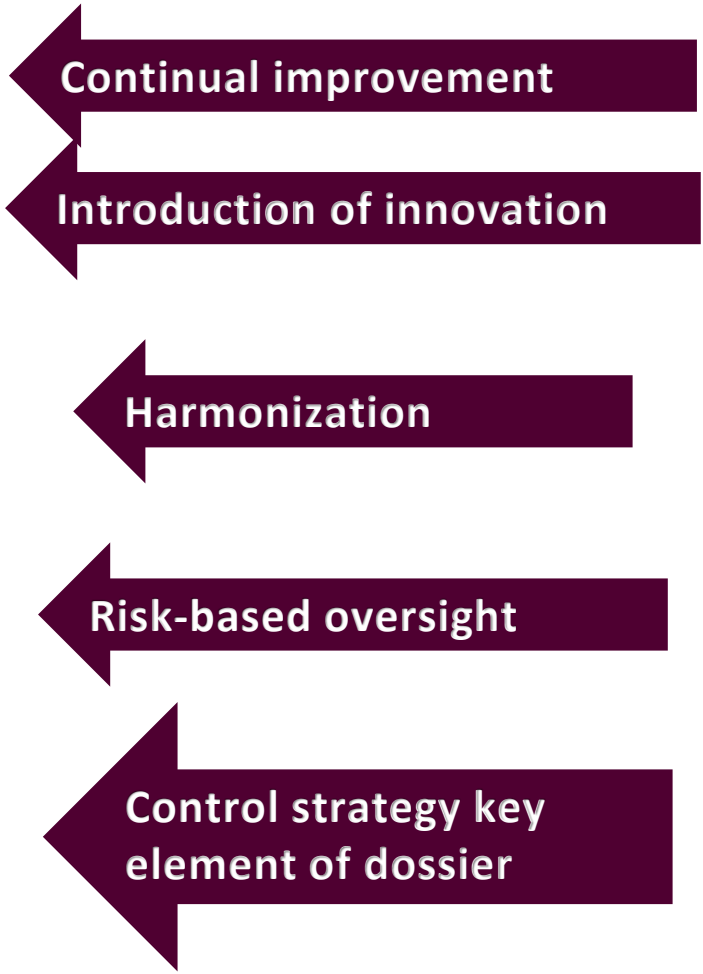
- CMC and supply chain development/commercialisation cannot be left behind
- Rapid implementation of CMC Change across the lifecycle is becoming even more critical
- CMC Regulatory frameworks need to be ready to support rapid acceleration!

Otherwise, Patients will wait!

HUGE NEED FOR Q12 TO BE SUCCESSFUL

ICH Q12 a Great Opportunity For Patients and Industry

- Provides a **risk based framework** to facilitate the management of post-approval CMC changes in a more **predictable and efficient manner**
- Includes **harmonized** regulatory tools and enablers with associated guiding principles
- Outlines how increased **product and process knowledge** can contribute to understanding of **which post-approval changes** require regulatory **submission**
- Reiterates how an **effective pharmaceutical quality system** is essential in the management of **changes during the product lifecycle**



ICH Q12

Key tools

- Categorization of Post-Approval CMC Changes
- Established Conditions (ECs)
- Post-Approval Change Management Protocol (PACMP)
- Product Lifecycle Management (PLCM) Document

Pharmaceutical Quality System (PQS) and Change Management

Relationship Between Regulatory Assessment and Inspection

New Concept - Established Conditions (ECs)

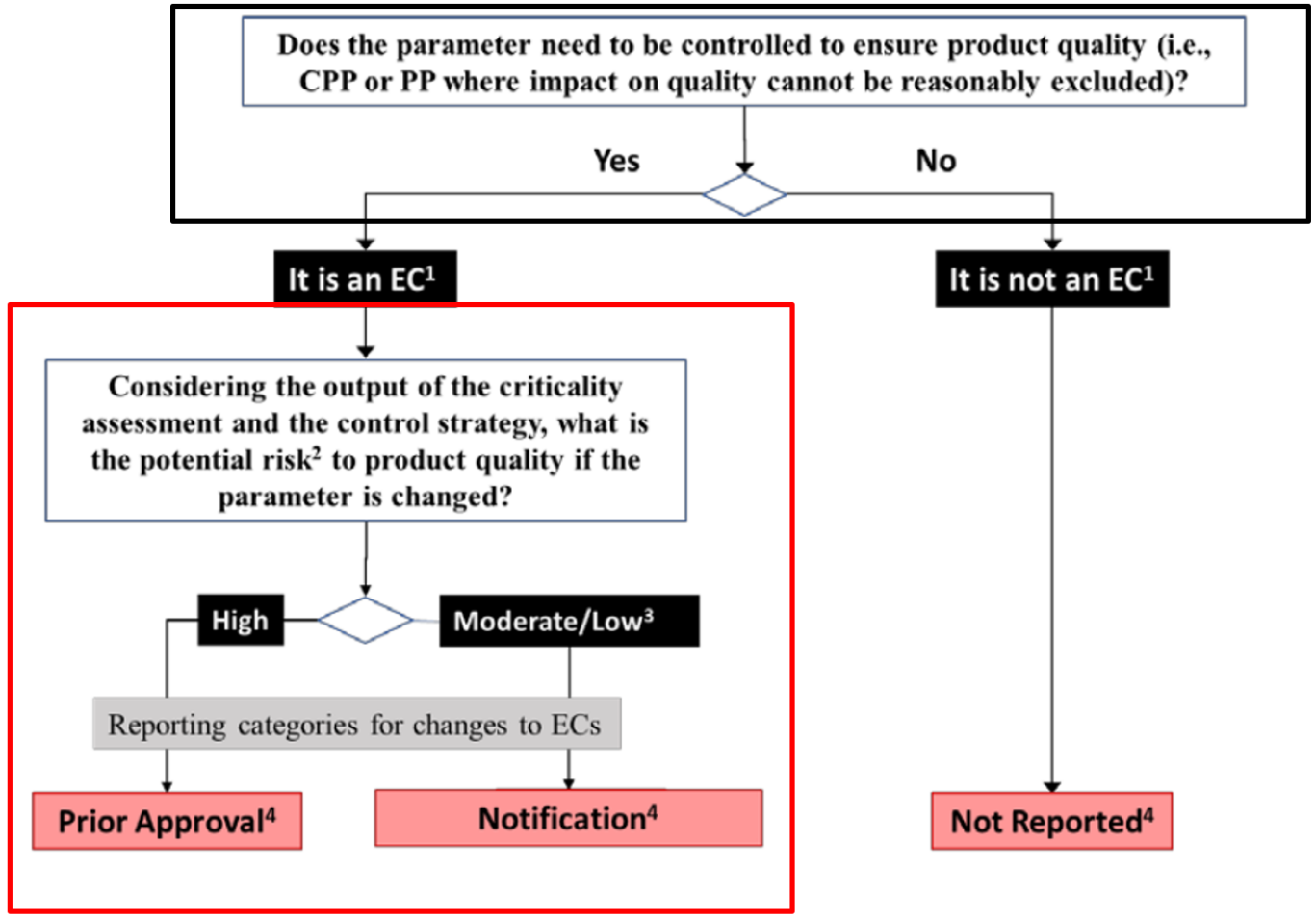
- **Allows regulatory change control to focus on factors important for control of Product Quality**
  - **Enabling more rapid improvements to be conducted and managed only through the PQS with inspectional oversight**

ICH Q12

1. **Identify Establish Conditions**

2. **Assign Reporting Category**

2a. Identify impacted CQAs for each process step
2b. Evaluate the impact of the process step on each identified CQA and assess the potential risk to product quality against the **overall Control Strategy** if the process step fails
2c. Pinpoint the most impacted CQA and determine the **maximum risk** associated with the process step
2d. Assess each Establish Condition within the process step and assign reporting category based on potential risk (*very low, low, moderate, high*) to product quality relative to the **maximum risk**



Established Conditions (ECs)

Cation Exchange Chromatography Example

Parameter, Output, or MC	EC/NR	Justification
Unit Operation & Sequence of Steps	EC PA	Unit operation and sequence of step are EC
cation exchange chromatography resin	EC PA	Change of material can lead to adverse effects on separation and product quality.
0.5/0.2µm Filters	NR	Equivalent alternative can be used
Elution buffer (pH x-y) Elution buffer conductivity (x-y mS/cm at 25°C)	EC NM	Statistically significant impact on CQA (aggregate). Ranges explored and impacts understood from process characterisation studies. CQA readily monitored in process step and controlled in DS spec.
Protein load (≤ x g protein/L resin)	EC NL	Impact on CQA cannot be excluded but not impact observed within studied range
Process Temperature (15-25°C) Column bed height (x-y cm) Flow rate (linear velocity) (≤ x cm/hr)	NR	Impact on product quality can be reasonably excluded.
Step yield (≥ x%) CEX product pH (pH x-y) CEX product conductivity (x-y mS/cm at 25°C)	NR	Performance attribute assesses only process performance; no impact on following unit op or product quality

Benefits of Identifying ECs from Pilot

- Clarified changes that need to be communicated to HA
- Enables better understanding between sponsor and HA using science and risk based decisions
- More process improvements have been made through PQS only, as described in Q10
- ECs & PLCM can help drive consistency within a Health Authority and across different HAs
- Opportunity to replace/amend regional documents (MTP China, CPID Can etc) with PLCM
- Ultimately will enable more simultaneous NDA submissions to multiple countries

FDA Pilot Program Experience

- Three rounds of questions, plus one telecon
- FDA focused on how does the PQS support change management?
  - if you do x, how will we know? How do you know doing x doesn't result in something unexpected
  - Are your analytical methods capable of picking up changes you haven't foreseen?
  - **Illustrated importance of inspectors & assessors communication in implementation of Q12**
- No request to document PQS aspects in Module 3
- Agreed to almost all AZ proposals

- Subsequently implemented accelerated PLCM & PQS changes
  - Requires "Flavour Management" of US Supply – manageable for some products
  - Slower implementation in other regions
  - Different process for change management assessment and regulatory compliance

How quickly can a PACMP enable addition of DS Site critical for supply? (COVID Vaccine) - **7 calendar days!**

Strategy

- No significant changes to DS manufacturing process, batch size, or process controls, and the container closure.
- Materials used in the DS manufacturing process equivalent
- No changes to the specifications for either DS or DP
- No changes to DS release or stability testing procedures or DS control sites.
- No change to approved DS release site or DP manufacturing or controls

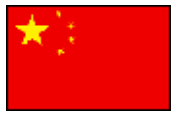
Results

- Analytical methods for in-process controls transferred and validated
- Manufacturing process validated in accordance with proposed validation protocol
- DS (3 Bxs) & DP (1 Bx) assessed against comparability protocol (release and characterisation data)
- Site inspected ahead of submission of the executed PACMP

Implementation

- Submitted as Type IB in EU - **Approved in 7 calendar days!**
- Shelf life and storage conditions for existing sites applied to new site
- DS (3 Bxs) on long term stability, data to be reported after implementation

Progress on implementation

REGION	IMPLEMENTATION STATUS	COMMENTS
	Published	Accepting all examples of ICH Q12 tools.
	On Hold	Review of Variations Regulation needed to allow implementation of ECs & PLCM
	On Hold	Currently not prepared to entertain applications with ECs identified with anticipated reportability in a PCLM.
	Adapting Local Regulations	PMDA is in the process of reviewing regulation to determine how a notification reporting category can be introduced for low-risk changes
	Considering Pilot	Conducted training program with Industry support. Considering a pilot program
	Considering Pilot	Preparing training program with Industry support. Considering a pilot program
	Considering Pilot	Considering a pilot program

Survey Data

Is it possible to have same ECs Globally?

IQ Working group on Specification harmonization to investigate low acceptance rate

IQ Survey on Control Strategy acceptance BLA/MAA (US/EU/HC/JP)

Country	Submissions	S.2.2 Accepted	S.2.3 Accepted	S.2.4 Accepted	S.4.1 Accepted	S.7 Accepted	P.3.2 Accepted	P.3.3 Accepted	P.3.4 Accepted	P.5.1 Accepted	P.8 Accepted	Likelihood of core Accepted
HA1	14	93%	93%	93%	57%	79%	86%	79%	71%	29%	71%	75%
HA2	11	45%	45%	45%	64%	91%	64%	45%	73%	18%	82%	57%
HA3	15	47%	13%	27%	27%	87%	60%	33%	60%	27%	60%	44%
HA4	14	86%	57%	93%	79%	71%	71%	29%	57%	50%	71%	66%
	54	68%	52%	64%	57%	82%	70%	46%	65%	31%	71%	61%

Deep Dive needed to understand difference in acceptance rates between regions

Deep Dive needed to understand overall low acceptance rate

Further Harmonisation Required….

- Q12 Key principles that will help!
  - Control Strategy focused on factors important for control of Product Quality
  - Change classifications based on risk not fixed levels (e.g. Design Space etc)
  - Increase proportion of PAC managed only within the PQS
- Other areas of harmonisation
  - Q1 – Need to harmonise and reduce post-approval stability requirements
  - Q6A/B – Focus on clinical relevance
  - M4Q – Risk Based QoS introducing clinical risk benefit perspective
  - Remove regional dossier formats and standardise on PLCM structure for ECs across ICH and beyond

Is Q12 Sufficient to Resolve the Problem?

Real-Time Post Approval Changes (PAC)…..
…How Do We Get From YEARS to WEEKS for PACs?

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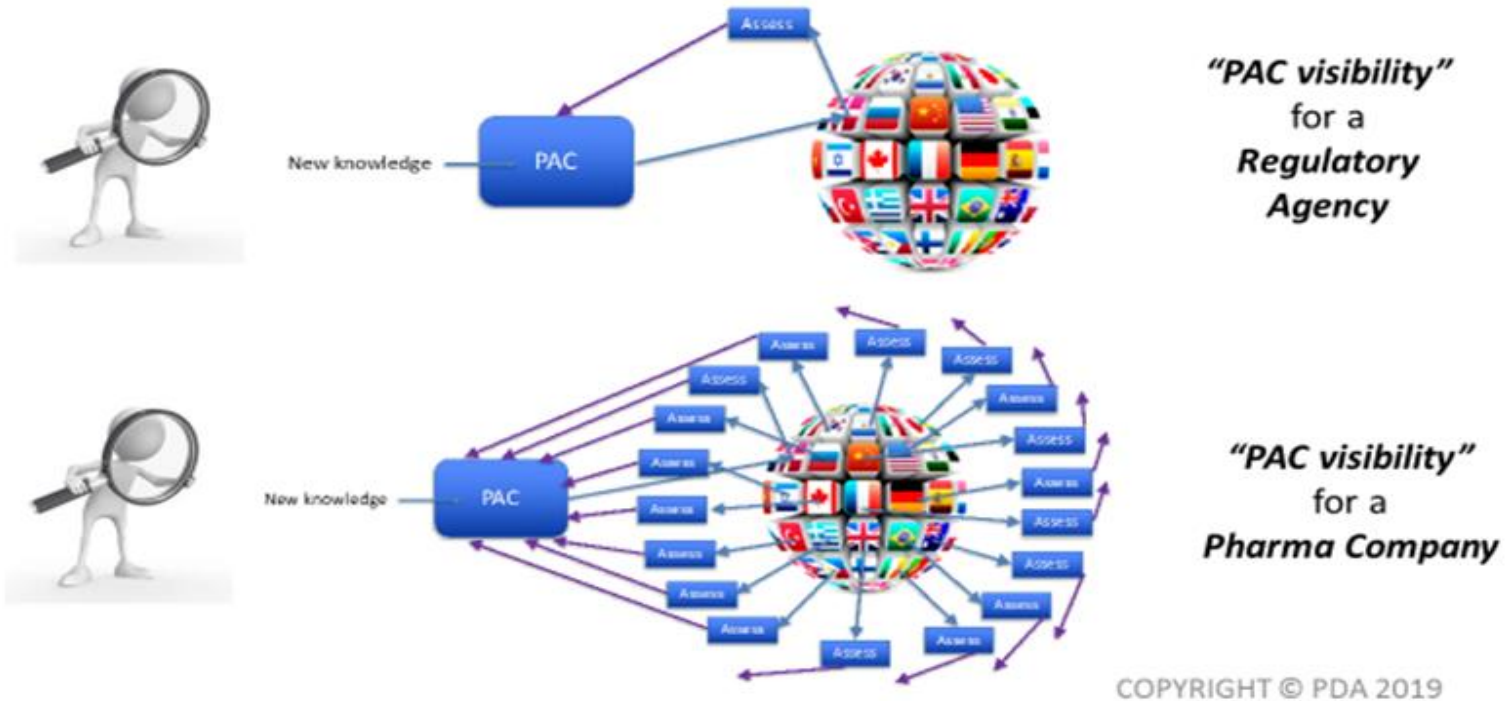
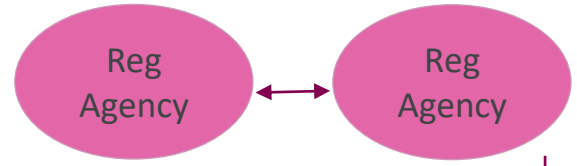


A. Vinther and E. Ramnarine, PDA Journal of Pharmaceutical Science and Technology, 2019 - **One Voice of Quality**



- **Work Sharing**
- **Reliance**
- **Recognition**
- **Follow WHO guidelines**
- **FDA Reflection Paper,** Enhancing Regulator and Manufacturer Agility, ICH MC 12/2020

Acknowledgements

- Stuart Finnie AZ
- Jane Duncan AZ
- Greg Rullo AZ
- IQ Control Strategy Harmonisation Metrics Team