# The criticality of efficient CMC changes through the product lifecycle

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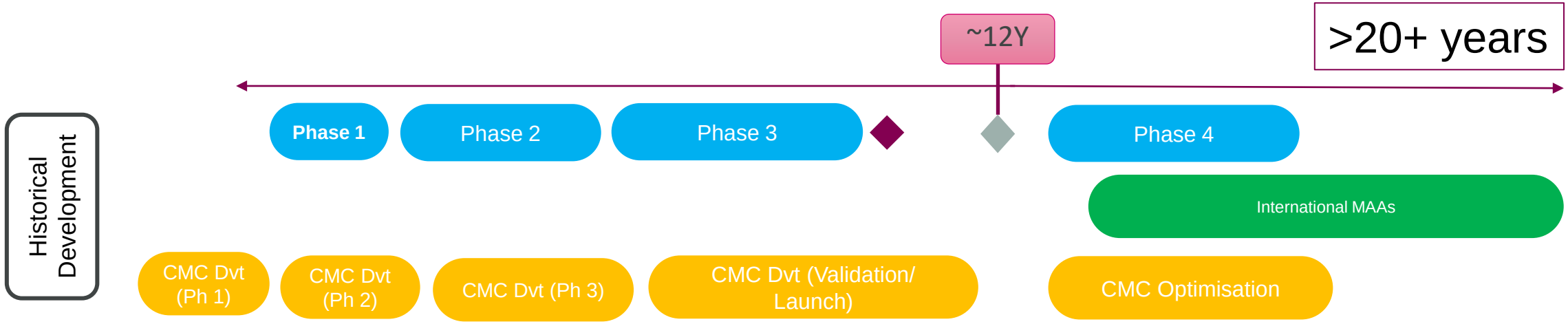
# Traditional development

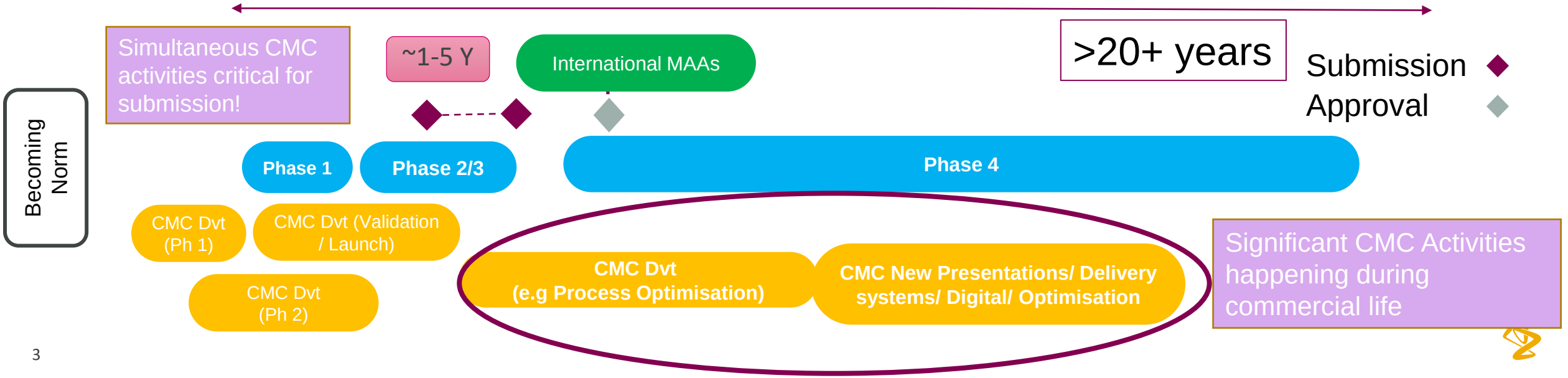
Submission ◆
Approval ◆

- 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

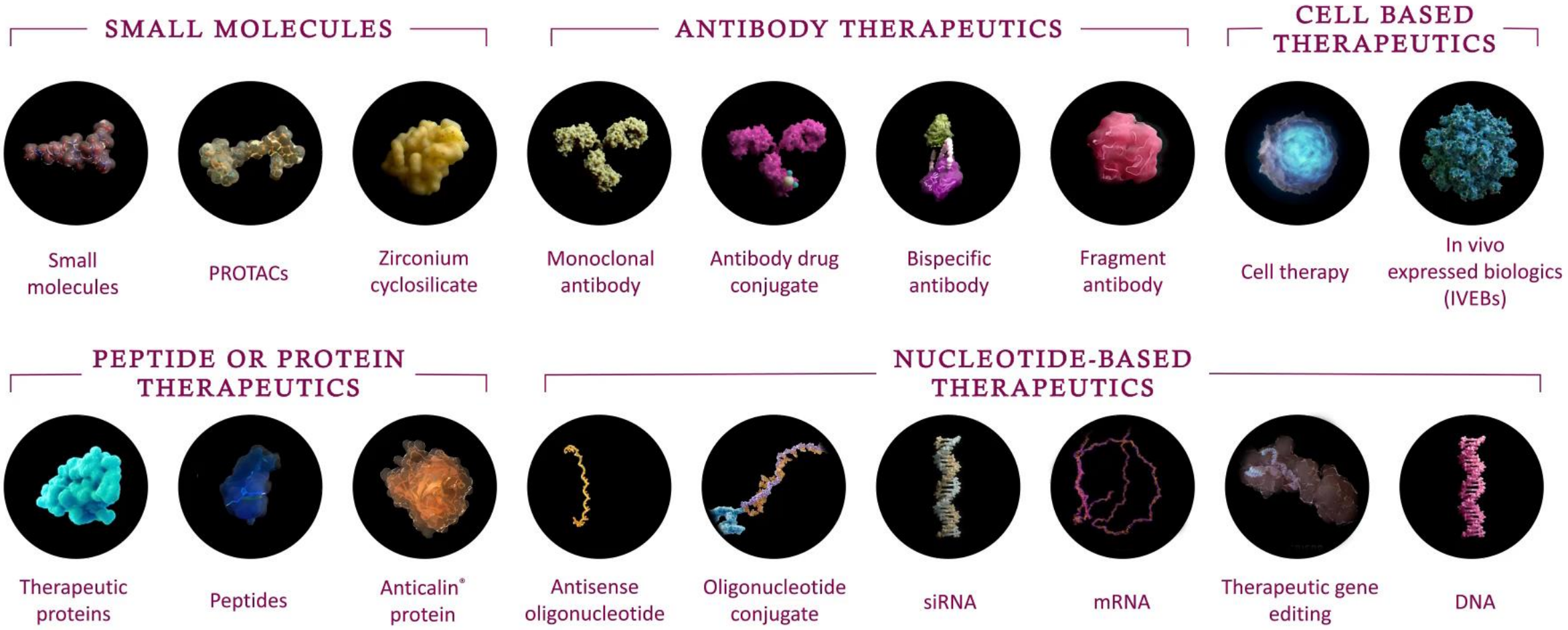


# How is Product Lifecycle Changing

- 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
  - **Strategy would be to include China in these multiregional clinical studies**
- Significant change expected in launch to commercial phase and after



# 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 will become even more critical
- CMC Regulatory frameworks need to be ready to support rapid acceleration!

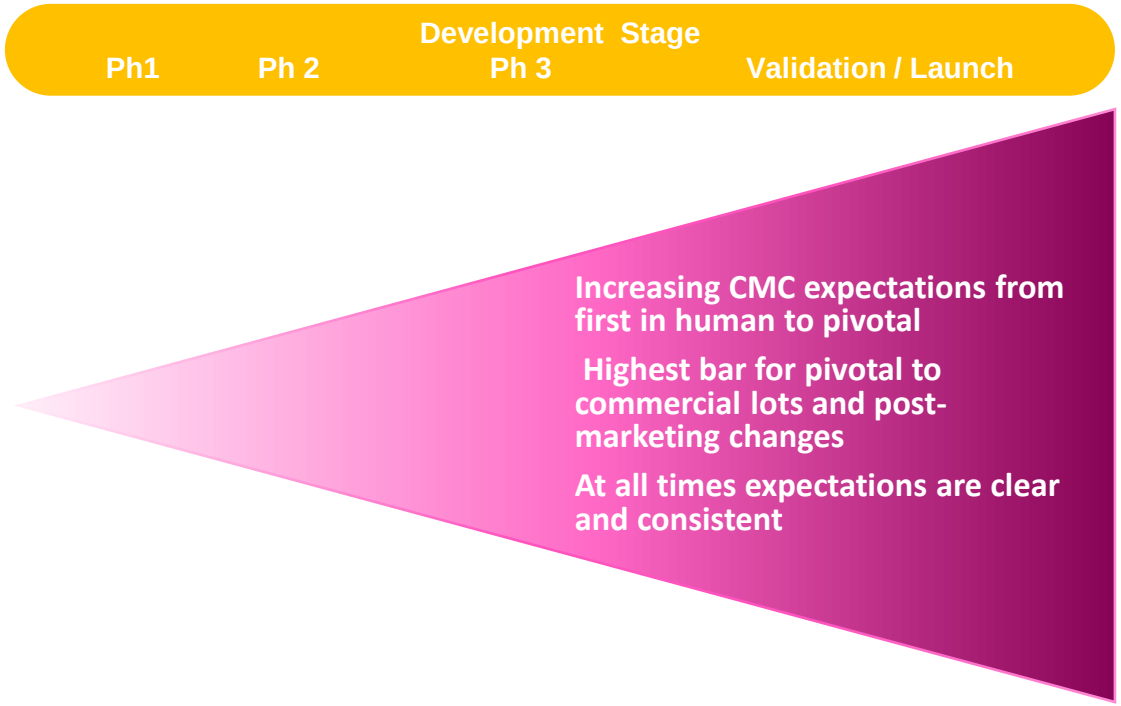
**Otherwise, Patients will wait!**

# CMC change is constant throughout clinical development

## Rapid implementation is crucial to maintaining study timelines

| Change | US |
|---|---|
| Process changes | 30 days |
| Manufacturing site addition | 30 days |
| Shelf-life extension | N/A |
| Raw material source | AR |
| Analytical method changes | 30 days |
| Formulation changes | 30 days |
| Pool to single clone | 30 days |

## CMC information to support a change should be risk based and phase appropriate



# Case Study: New drug product site between registration trial and commercial application

**Case Study**

- Biologic product with complex supply chain
- Interim clinical data showing significant clinical benefit
- DP Site A: very constrained (clinical facility), unsuitable for commercial supply
- DP Site B: proposed commercial site with significant increase in scale
- No change in formulation, process or primary container closure

**Analysis of the Change**

- **Data to support the change based on science and risk analysis**
- Example of comparability data in table below
- Same shelf life and storage conditions for Pre-change & post-change lots based on comparable stability data

| Data comparison category | Pre-change lots | Post-change lots |
|---|---|---|
| Release testing | Historical data set | 3 PPQ lots |
| Analytical Profile Comparison | 3 lots | 3 PPQ lots |
| Extended characterization | 3 lots | 3 PPQ lots |
| Stability profile comparison (accelerated and/or stress) | 3 lots | 3 PPQ lots |
| Long term stability (3 months) | N/A | 3 PPQ lots |

# Mechanisms to Accelerate PACs

# 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**

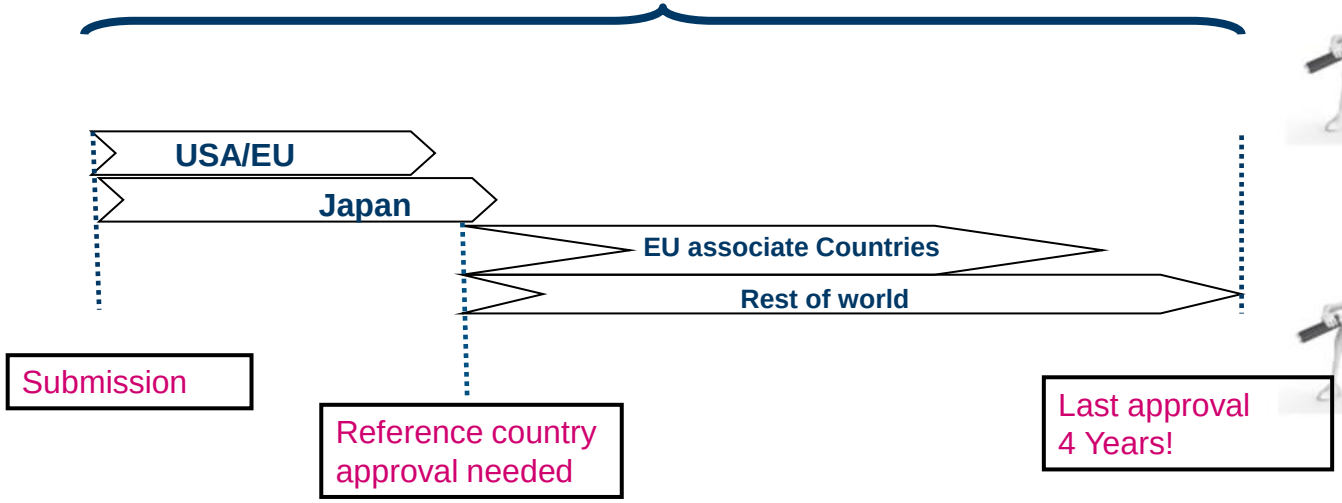
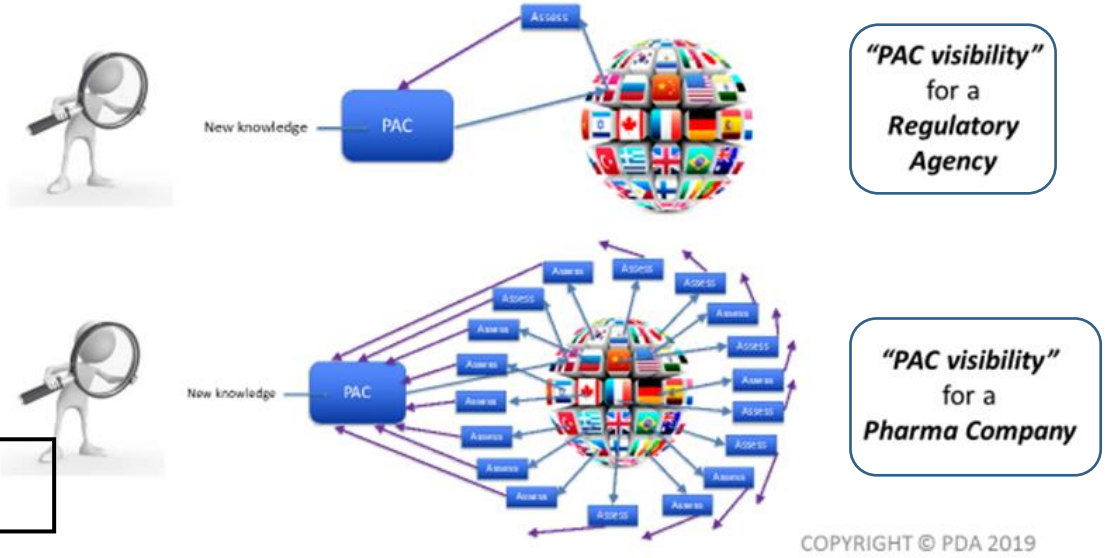



**Figure 2: PAC Regulatory Complexity – Seen From Different Angles**




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

# ICH Q12

## Key tools

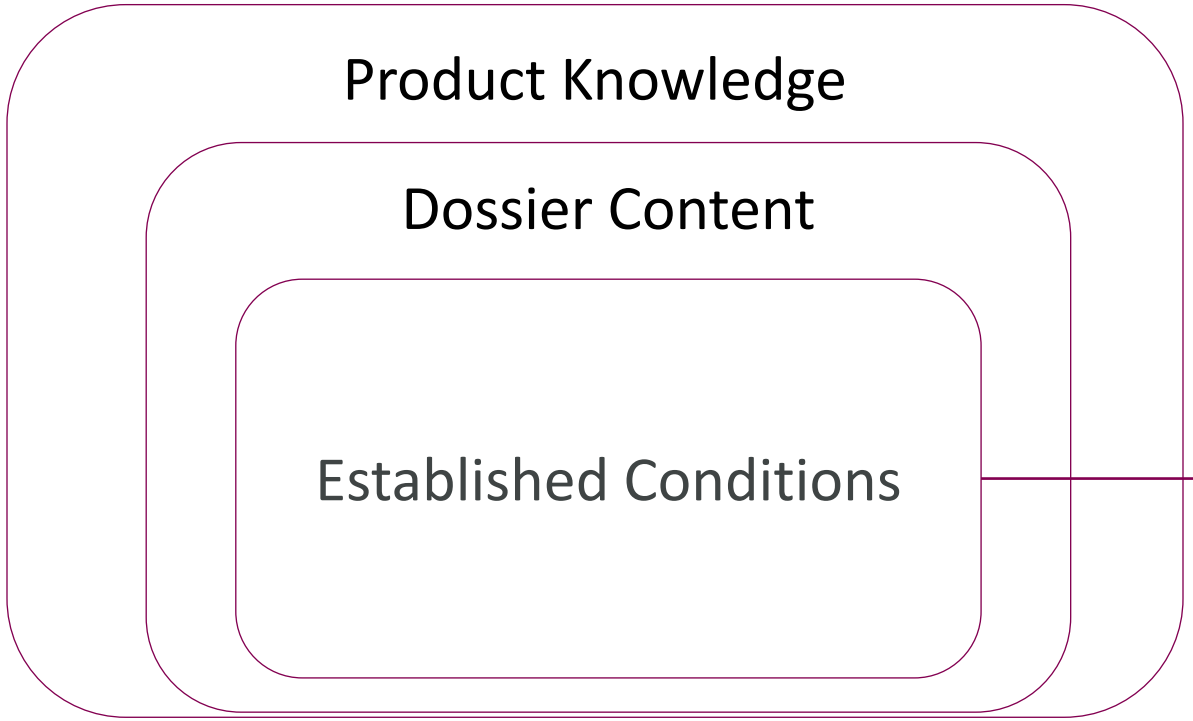
- Categorization of Post-Approval CMC Changes
- Established Conditions (ECs)
- Post-Approval Change Management Protocol (PACMP)
- Product Lifecycle Management (PLCM) Document

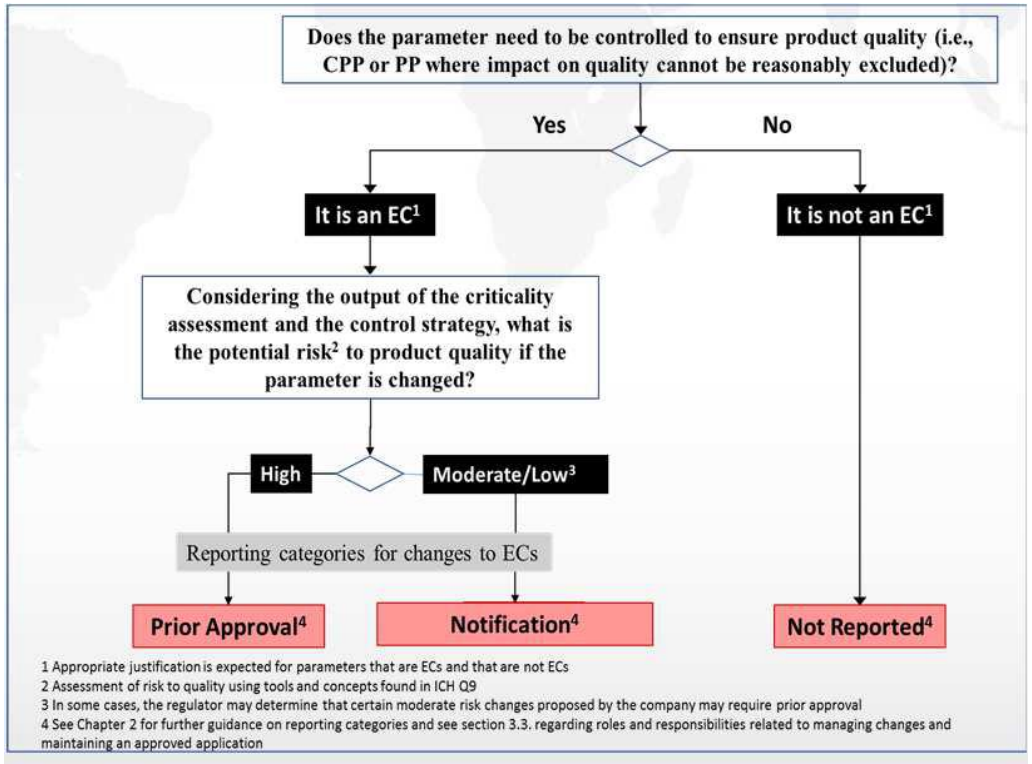
Pharmaceutical Quality System (PQS) and Change Management

Relationship Between Regulatory Assessment and Inspection

# New Concept - Established Conditions (ECs)

- Established Conditions are legally binding information considered necessary to assure product quality
  - Scientific understanding is central to establishing ECs
- Change reporting category for ECs becomes a risk-based evaluation of the impact on product quality
- Negotiated up-front with the agency
- **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**



# Established Conditions (ECs)

## Cation Exchange Chromatography Example

| Parameter, Output, or MC | EC/NR | Justification |
|---|---|---|
| Unit Operation & Sequence of Steps | EC<br>PA | Unit operation and sequence of step are EC |
| cation exchange chromatography resin | EC<br>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)<br><br>Elution buffer conductivity (x-y mS/cm at 25°C) | EC<br><br>NM | Statistically significant impact on CQA (aggregate).<br>Ranges explored and impacts understood from process characterisation studies.<br>CQA readily monitored in process step and controlled in DS spec. |
| Protein load (≤ x g protein/L resin) | EC<br>NL | Impact on CQA cannot be excluded but not impact observed within studied range |
| Process Temperature (15-25°C)<br>Column bed height (x-y cm)<br>Flow rate (linear velocity) (≤ x cm/hr) | NR | Impact on product quality can be reasonably excluded. |
| Step yield (≥ x%)<br>CEX product pH (pH x-y)<br>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 amend or replace MTP document with ECs/PLCM in China?
- 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?
- Agency were very interested in 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?
  - Lots of reference back to PQS
  - Illustrated the importance of interactions between inspectors and assessors in implementation of Q12
- No request to document PQS aspects in Module 3
- Agreed to almost all AZ proposals
- Final approval received 20th December with no Post Marketing Commitments

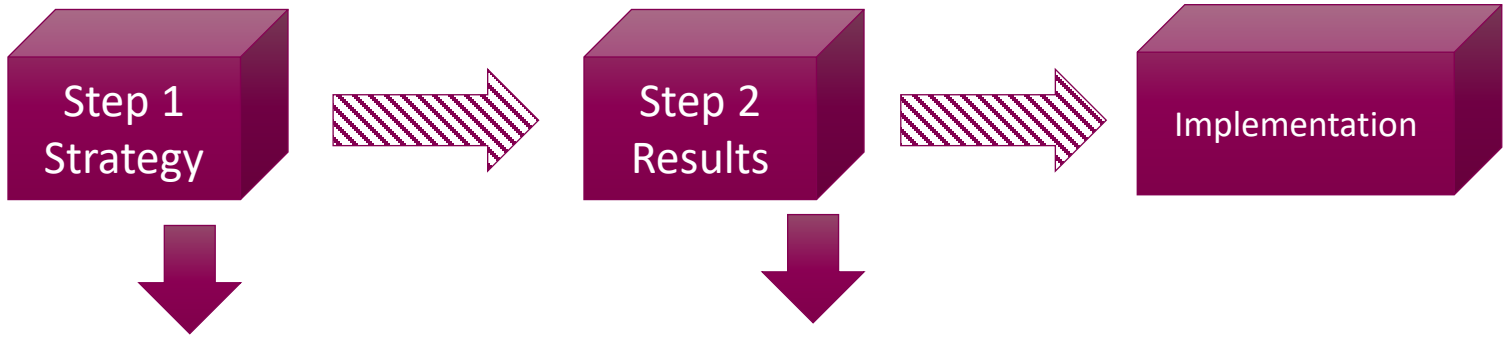
- Support for FDA review team by FDA EWG representatives was KEY

# How to accelerate Post Approval Changes (PAC) PACMP

- An increasing number of major changes will be critical in early commercial phase as well as later
- Supply chain expansion
  - Multiple drug substance & drug product sites to supply single region becoming more common
    - To manage rapid expansion and mitigate shortage
- PACMP critical tool for rapid implementation of sites
  - Requires tiered, risk based classification system (Q12)
  - Now being used in US, EU, JP, *Can*
  - Agreement on acceptance criteria and implementation up front
  - If critical for supply; confirmation of GMP status or site inspection could be done upfront
  - Accelerates the execution and regulatory review!

# Post-Approval Change Management Protocol (PACMP)

- Need to expand the use of PACMPs
- Need to be able to be re-used over the product life
- Modification of a PACMP by **notification**
- e.g for replacement or revision of a test, study or acceptance criterion, should provide the same or greater capability for product quality




| Component | Step 1 registration of protocol | Step 2 change implementation |
|---|---|---|
| Overall Strategy Scope & Limitations | Defined scope and limitations | Demonstrate requirements of scope met, including process changes associated with transfer |
| QRM | Description of QRM program and approach to site transfer risk assessment | Documented risk control strategy and executed risk management report summary |
| Comparability & Stability | Comparability plan, real-time stability commitments and acceptance criteria (product-specific) | Data demonstrating that acceptance criteria are met |
| Process Validation | Overview of validation program | Summary of facility/equipment differences and applicable validation; validation summary data support the process, facility/equipment, and method transfer |
| Site risk | Description of site inspection risk assessment | Outcome of site inspection risk assessment defines actual change submission requirements |

# How quickly can a PACMP enable addition of DS Site critical for supply? (COVID Vaccine)

## 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

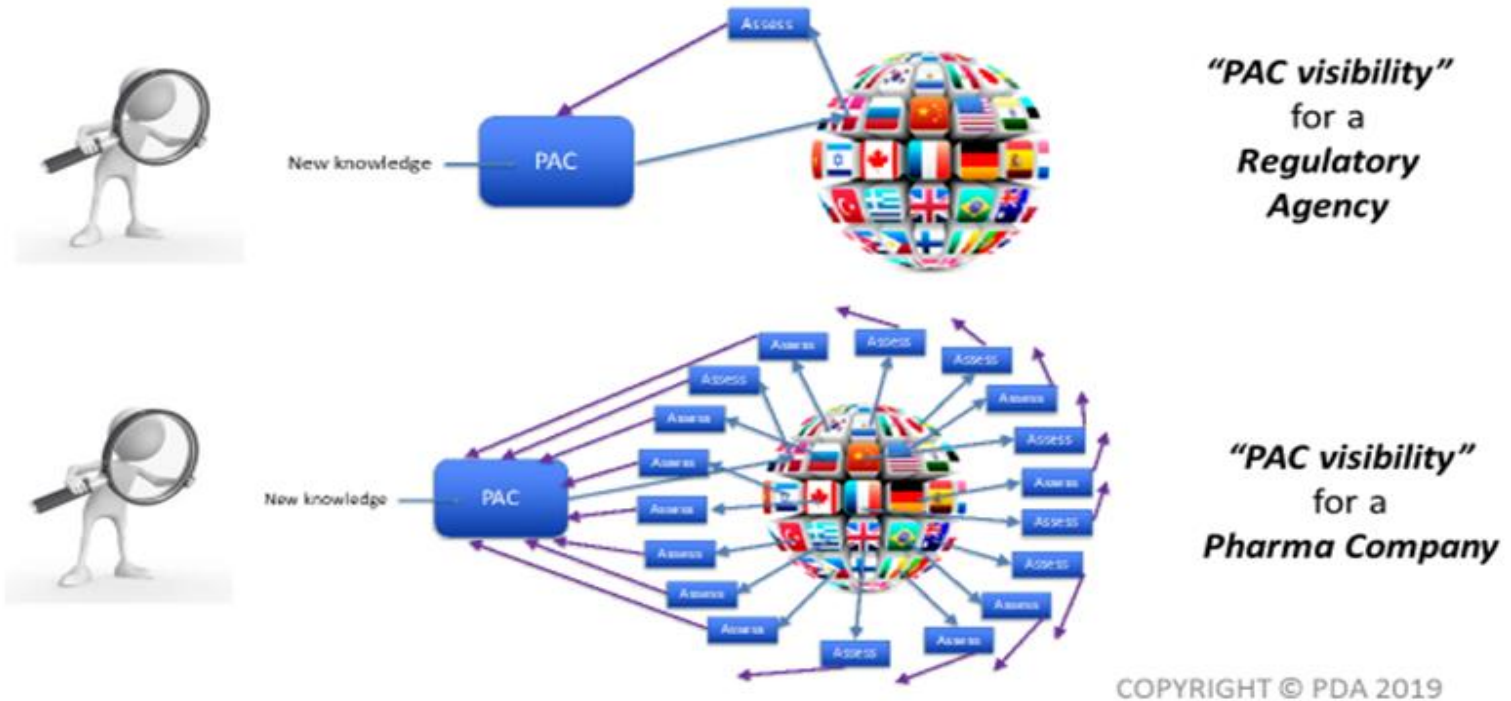
## Implementation

- 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

# Is Q12 Sufficient to Resolve the Problem?

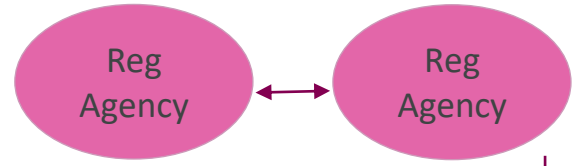
## Real-Time Post Approval Changes (PAC)…..
## …How Do We Get From YEARS to WEEKS for PACs?

**Figure 2: PAC Regulatory Complexity – Seen From Different Angles**






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




- **Work Sharing**
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# Acknowledgements


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