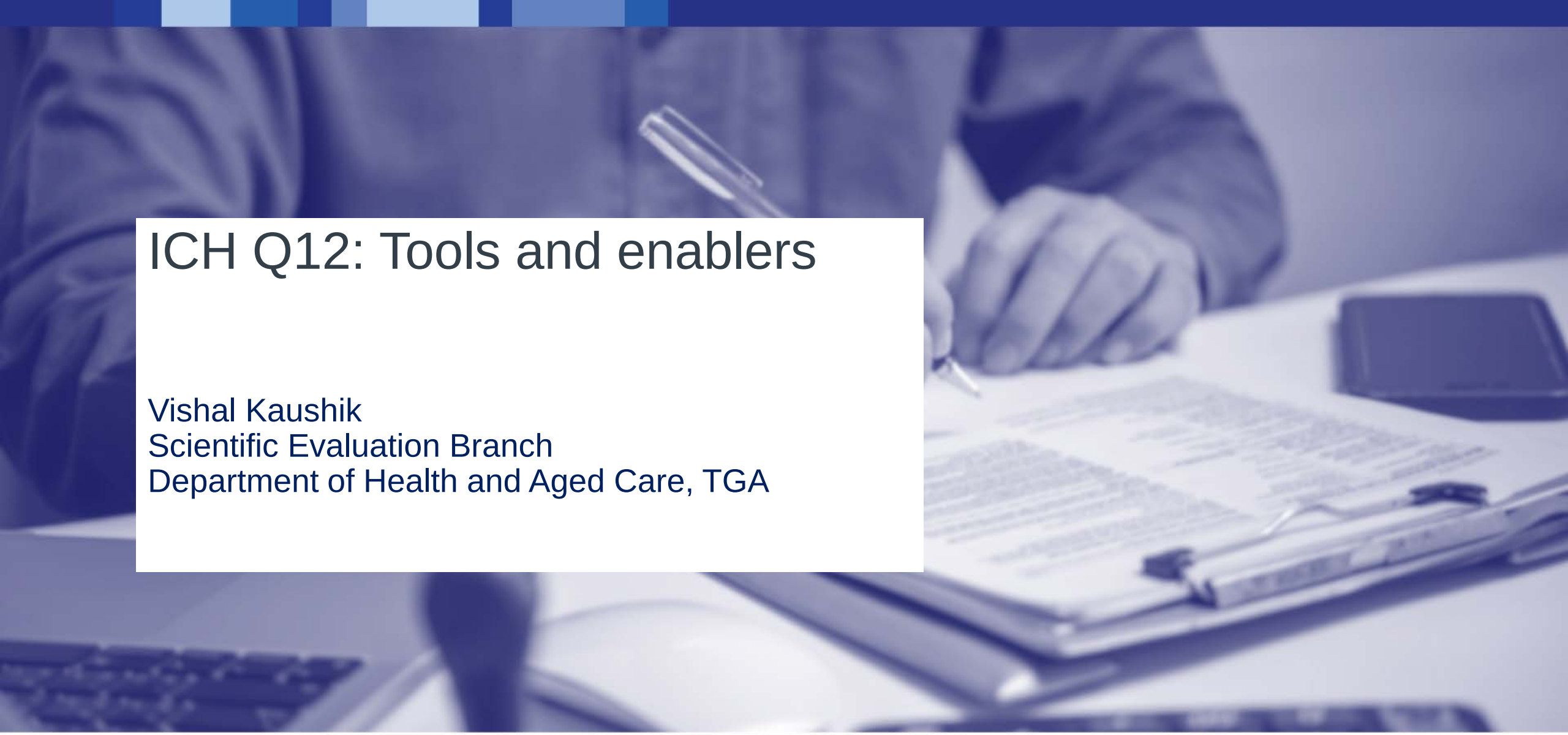

ICH Q12: Tools and enablers

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Overview

- Introduction to ICH Q12
- Global Implementation status
    - Where TGA is up to
- Overview of ICH Q12 Tools and Enabler:
    - Risk Based Categorisation of Changes
    - Post Approval Change Management Protocol (PACMP)
    - Established Conditions (EC)
    - Product Life Cycle Management Document (PLCM)
- Challenges for TGA
- Questions

Introduction- ICH Q12

ICH Q12 guideline provides a framework for managing **post-approval** changes in the chemistry, manufacturing, and controls (CMC) of pharmaceutical products.

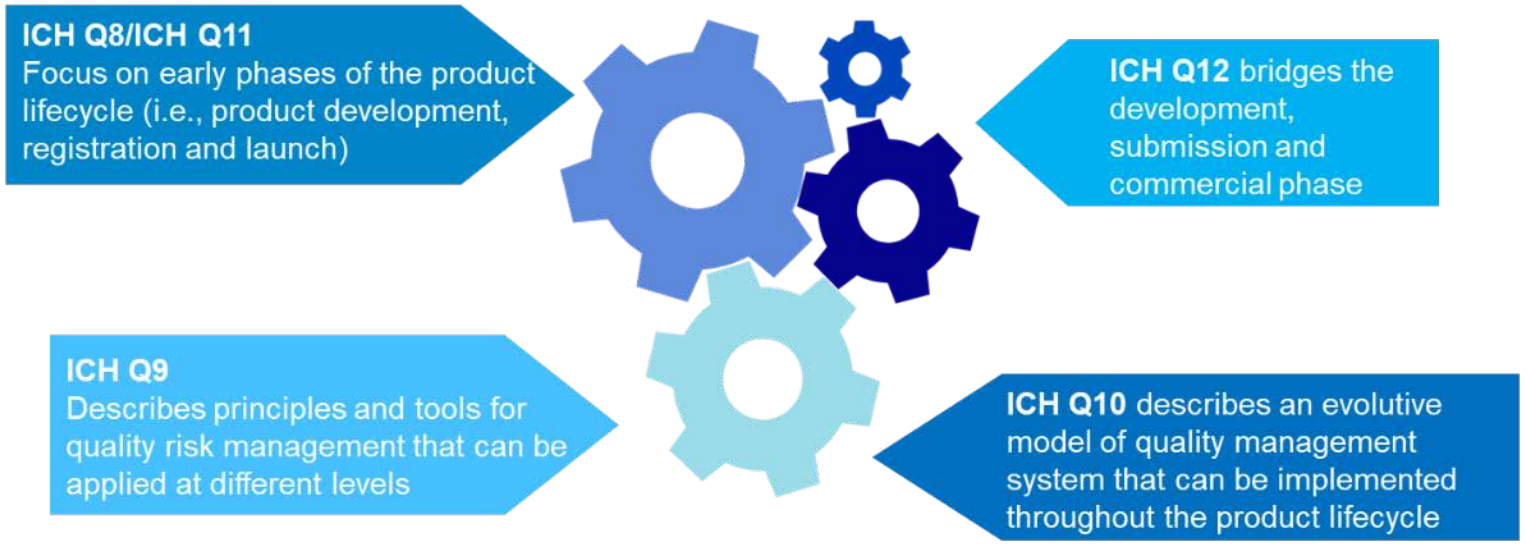
Objective

- To provide a globally harmonised framework for implementation of CMC changes.
- To help implementation of these changes in more predictable and efficient manner.

Scope

- Pharmaceutical drug substances and products (both chemical and biological)
- Drug-device combination products that meet the definition of a pharmaceutical or biological product.

Product lifecycle management



- ICH Q12 addresses the **commercial phase** of the product life cycle
- It utilizes the idea that the product development is an ongoing process and continues beyond registration
- It also establishes that with increased product and process knowledge the risk associated with post- approval CMC changes can be reduced and the changes can be managed more efficiently

The extent of operational and regulatory **flexibility** is subject to **product and process understanding** (ICH Q8 and Q11), application of **risk management principles** (ICH Q9), and an **effective pharmaceutical quality system** (ICH Q10).

Global implementation status

- **United States** the FDA has been most successful in implementing ICH Q12 – existing framework aligned well with the guideline.
- **EU** has implemented parts of the guidelines, but further legislative amendments are required before complete adoption is possible.
- **Japan** is in advanced stage of implementation after amendment to PMD Act: Still, challenges are there before full adherence to ICH Q12 is achieved.
- **China** officially announced implementation of ICH Q12 in August 2024
- **Globally** the adoption is slow due to misalignment with local regulatory framework and need for supportive legal basis

Where we are up to…

2022 consultation – In early 2022, the TGA consulted with stakeholders to assess interest in adopting ICH Q12. The response was overwhelmingly positive, indicating strong support for its implementation.

Minor variations reform – Initiated in 2023 a review of the current framework , examining existing codes, processes, and deficiencies.
Also aiming to assess alignment of current framework with ICH Q12 requirements

Current status of adoption…

- Conducting a gap analysis of internal processes
- Benchmarking processes from other regulators
- Considering collaborative assessment pathways

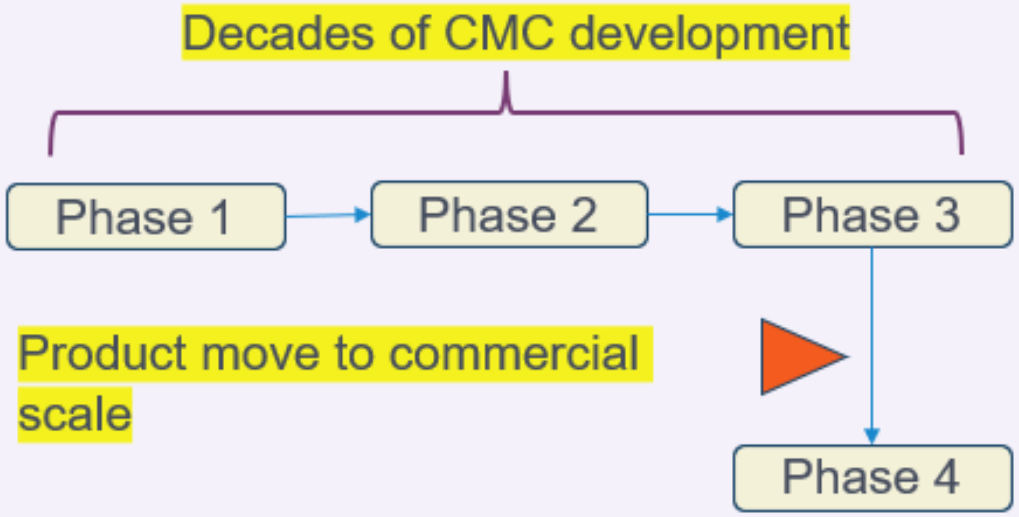
(Flexible) Risk based categorisation of CMC changes

Flexible risk based categorisation

- Enhances innovation and facilitate continuous improvement throughout the product lifecycle.
- Acknowledges that product development continues beyond registration
- Enables the use of other tools of ICH Q12
- Does not affect the principles of risk-based categorisation

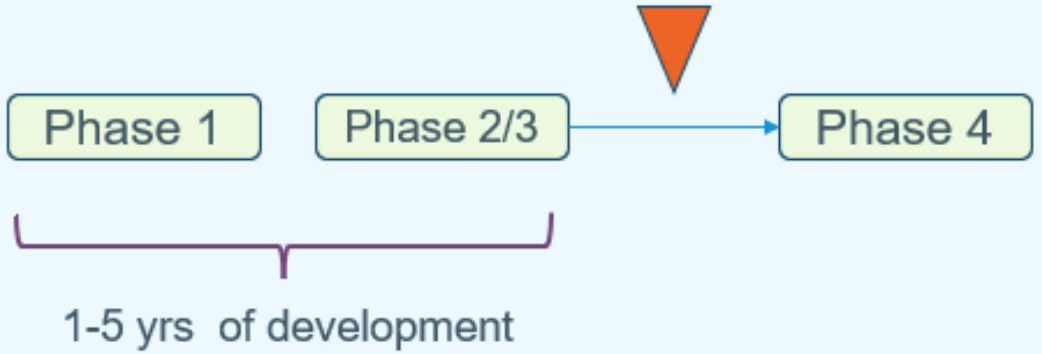
Changing product life cycle

Traditionally- Product Development takes ~ 20 years before commercialization, providing sufficient time for manufacturing process optimization.



Contemporary Product Development approach is squeezed to <5 years and in some cases <1 year (COVID 19 vaccination development)

- Most of the process optimization happens after registration
- CMC changes are frequent throughout PLC
- Efficient and harmonised CMC management is vital



Significant CMC activity and process optimization happens after registration

Risk based categorisation

Risk level	ICH Q12		FDA	TGA	
	Categories	Reporting obligation		Categories	Reporting obligations
High	PA	Prior Approval	PAS (6 /10 months)	Cat-3 (45 days)	**Prior Approval** – with extensive evaluation.
Moderate	NM	Tell, Wait and Do	CBE 30 30 days	SAR (45 days)	**Prior Approval** – with evaluation.
Low	NL	Tell and Do	CBE 0 (immediately effected)	Notification	**Tell and Do** -No evaluation No timeframes
Lowest	NR	Do and Tell	Annual Report	Managed within PQS	Reported after implementation

We have relatively rigid system with most reportable changes included in Appendix 1 and notifiable changes included in regulations.

There is not much middle ground between notification and prior approval- we may look in to reducing timeframe and approval requirement for SAR to align it with other regions.

Post Approval Change Management Protocol

Post Approval Change Management Protocol (PACMP)

- A regulatory tool designed to streamline the process of implementing post approval changes.
- Prospective plan for managing future changes, throughout PLC.
- Voluntary and can be submitted any time after registration

Post Approval Change Management Protocol (PACMP)

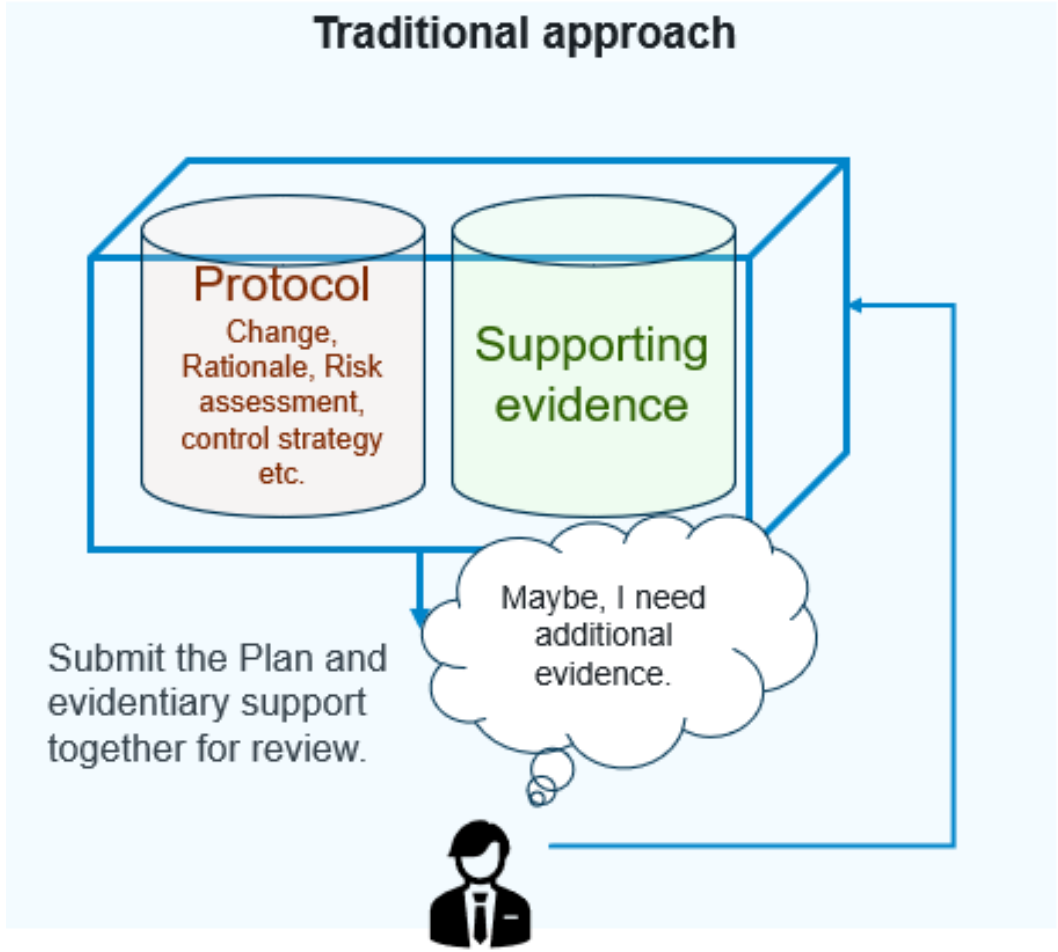
The PACMPs are implemented in two steps:

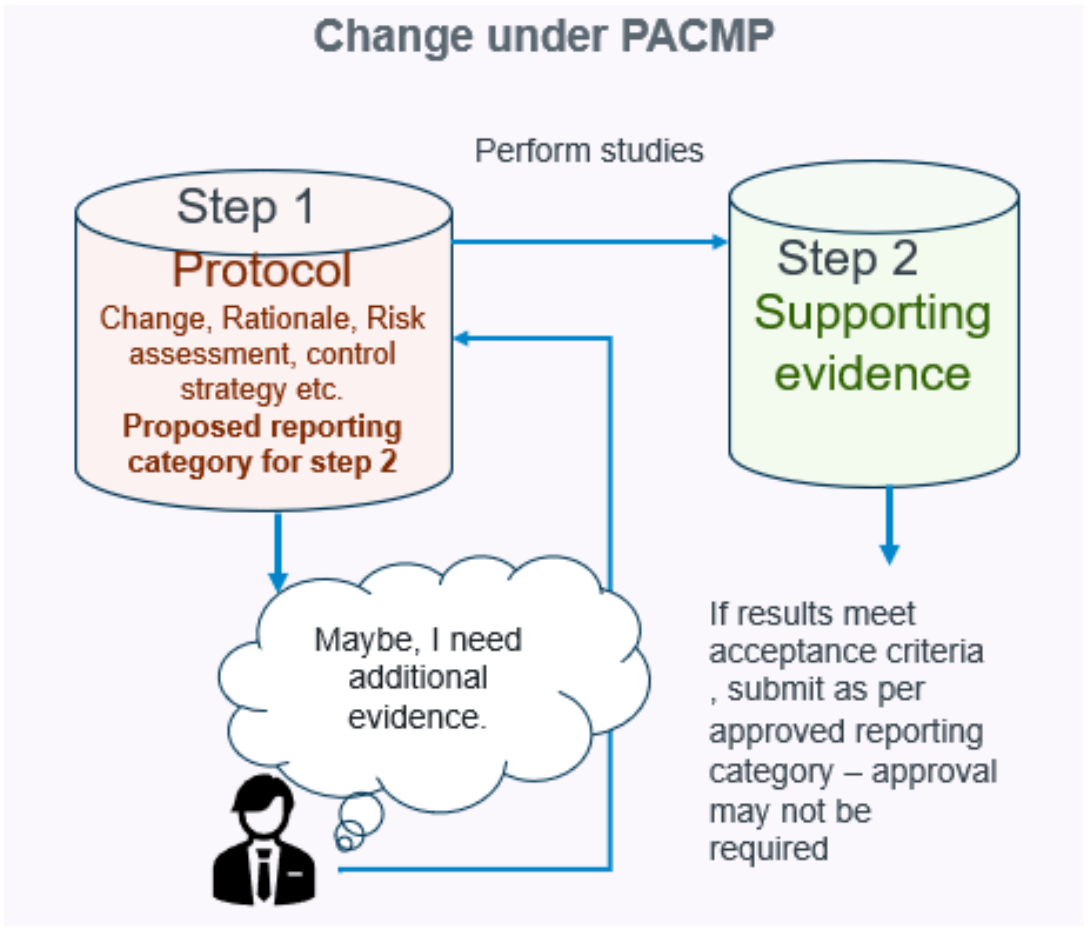
Step 1: Submission of a detailed protocol outlining the proposed changes, rationale, risk management strategies, and acceptance criteria.

Step 2: Execution of the changes as per the approved protocol, with results reported to regulatory authorities (risk category is typically reduced by at least 1 level from its default level)

- Provides transparency and predictability in terms of requirements and studies needed to implement the change.

How PACMPs works in practice





Established Conditions (EC)

Specific elements in the product registration that are considered necessary to assure product quality.

Legally binding information, consequently, any change to this information requires communication with the regulatory authority.

Established Conditions (EC)

Implicit ECs: These are the elements of product registration information that are considered critical but are not identified as ECs by the sponsor.

- The variation in these elements are managed according to default regulatory expectation.

Explicit ECs: These are the elements that have been specifically identified as ECs by the sponsor.

- Explicit ECs have 2 components – the identified EC and its proposed reporting category.
- It is voluntary but if identified, must be justified by the sponsor and approved by the regulator.
- Identifying explicit EC is appropriate when the EC or proposed reporting category is different from the default regulatory guidance.

How ECs work in practice

- Identify ECs - using either of the three recommended methods:
  - Ø Parameter (input) based (minimal approach)
  - Ø Parameter (input) based (Enhanced approach)
  - Ø Performance (output) based
- Assign a risk-based reporting category to the EC (PA, NM, ML)
- Submit the EC for approval– identified EC, justification, risk assessment & risk category, regulatory commitments (if changed), supporting data (that will be generated), proposed reporting category and any other relevant information.
- If amendment is required to an approved EC – Must be pre approved.

Product Life-Cycle Management Document (PLCM)

PLCM serves as a central repository that outlines how a product will be managed throughout its commercial lifecycle.

Key Elements: It captures the ECs and their associated reporting categories.
It contains any regulatory commitments in relation to the CMC changes and references to any Post-Approval Change Management Protocols (PACMPs).

How PLCM document may work in practice

Central repository (can be a table in eCTD) containing:

- ECs and PACMPs , their associated regulatory commitments
- Changes implemented and commitments fulfilled

Submission

- At the time of registration or at any time after registration.
- Resubmit when changes are made to information included in the PLCM
- It should also be updated when approve regulatory commitments are completed

Use of PLCM

- Helps in tracking and managing changes made to a product.
- Provides snapshot of changes and regulatory commitments at the time of GMP inspection.

Challenges for TGA

1. **Regulatory Framework Limitations**: Existing legal frameworks may not fully support the flexible approaches outlined in ICH Q12.
2. **Lack of Clarity and Consistency**: Inconsistency in submissions across all products and within the same products (EC and PACMP) may pose a problem for TGA.
3. **Consistency Across Regions**: Achieving harmonisation across different regulatory jurisdictions can be difficult.
4. **Training and Expertise**: May require extensive training to effectively implement risk-based assessments

Challenges for TGA

5. **Data Management and Evaluation**: The need for robust data management systems to support risk assessments and track changes can be a significant challenge (**PQKMS**).
6. **Resource Allocation**: Implementing a flexible approach may require additional resources, including personnel and technology.
7. **IT Solutions**: a several existing IT workflows may be impacted, and new IT solutions may be needed which can take a long time and will be resource intensive.

Questions?

Scan the QR code with your device to submit a question.