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Creating Possible

PACMPs: Best Practices, and Future Opportunities

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Agenda

- Overview of PACMP benefits and global implementation
- ICMRA PACMP Pilot Program Case Study
- ADC Change Case Study
- Opportunities as we move forward!

US and EU History of PACMPs

- The concept of using a pre agreed protocol to facilitate change management has been in place for some time
  - US "Comparability Protocol" - First implemented in 2003
  - EU "Post-approval Change Management Protocol" - First implemented in 2012
- Advent of ICH Q12 brought a much needed harmonization in:
  - Scope
  - Content
  - Expectations
- Similar in principle, but somewhat different in practice
  - Review experience could be different in each region
  - Scope different, particularly around the use of protocols to support addition of new sites

Global Landscape for PACMPs

- ICH Q12 reached Step 4 : 20 November 2019

	PACMP Submission Accepted
Switzerland	Yes
Japan	Yes
China	Yes – Registration testing requirements pose a challenge. CDE consultation is recommended.
Canada	No
Brazil, Mexico, Singapore, Egypt, Turkey, Taiwan, Republic of Korea	No

Gilead ICMRA Pilot Overview

Collaborative Assessments of CMC Submissions

Participating Countries

- US (Lead), EU, GB, Switzerland
- Observing: Brazil, Canada

Scope

PACMP for addition of a manufacturing site for a drug linker intermediate of an ADC product. Site-independent protocol.

Submission Category for Step 1

PAS (US), Type-II (EU, GB, CH)

Reporting Category for Step 2

CBE 30 (US), Type-IB (EU, GB, CH)

Gilead Experience with ICMRA Collaborative Assessment Pilot of a PACMP

- **Step 1 Submission:**
  - Harmonized Assessment Timeline: 4 months (120 days)
  - PACMP submitted in parallel to lead and participating Regulatory Authorities (RAs) via respective submission portals, with same content (Sep 2023)
- **Harmonized Feedback:**
  - Received a harmonized list of questions (common requests) with region-specific comments issued in a parallel by all lead and participating RAs on the same day (Nov 2023, 2 IRs)
  - Responses submitted in parallel to each RA through respective portals by the requested deadlines
- **Approval and Data Requirement:**
  - FDA and Swissmedic granted approvals on the same day, with MHRA and EMA approvals following within the next couple of days (Jan 2024)
  - Overall data requirements were aligned across all RAs, with additional data requested by the FDA to be provided via an annual report
- **Step-2 CBE-30/Type 1B** will not be included in the collaborative review process as part of the ICMRA pilot. However, all lead and participating Regulatory Authorities commit to engaging with each other and share information during the assessment of the Step-2 submission

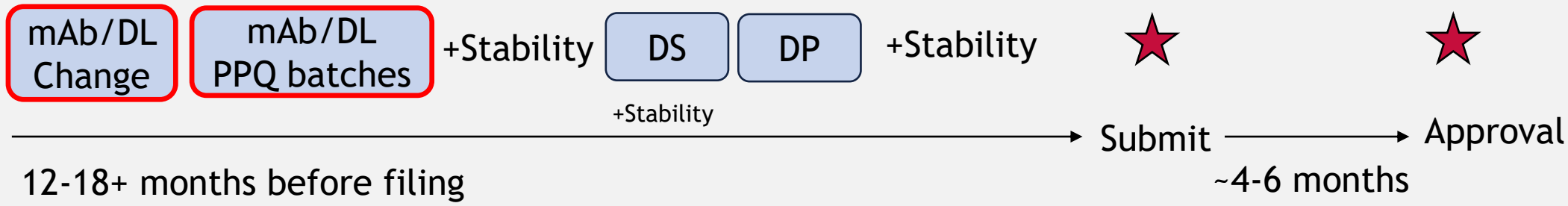
ICMRA Collaborative Assessment Pilot of a PACMP

	Step 1: Submission of a PACMP	Step 2: Reporting of Implementation In Accordance with Approved PACMP
Submission Content	• Description of proposed changes and associated risk assessment • Summary of manufacturing and control strategy • Comparability study plan • GMP status of proposed manufacturing site • Proposed reporting category for Step-2 implementing submission	• Results from process validation batches • Comparability study results • Confirmation that the proposed manufacturing site has an acceptable recommendation from the most recent cGMP inspection • Update relevant sections of the dossier
Reporting Category (US/ EU/GB/CH)	PAS / Type II	CBE-30 / Type 1B
Harmonized Assessment Timeline	4 months (120 days)	N/A (not as part of ICMRA pilot)

Ongoing discussions about submitting this PACMP in other markets

Front loading in the preapproval space, enables further efficiency in the post approval space

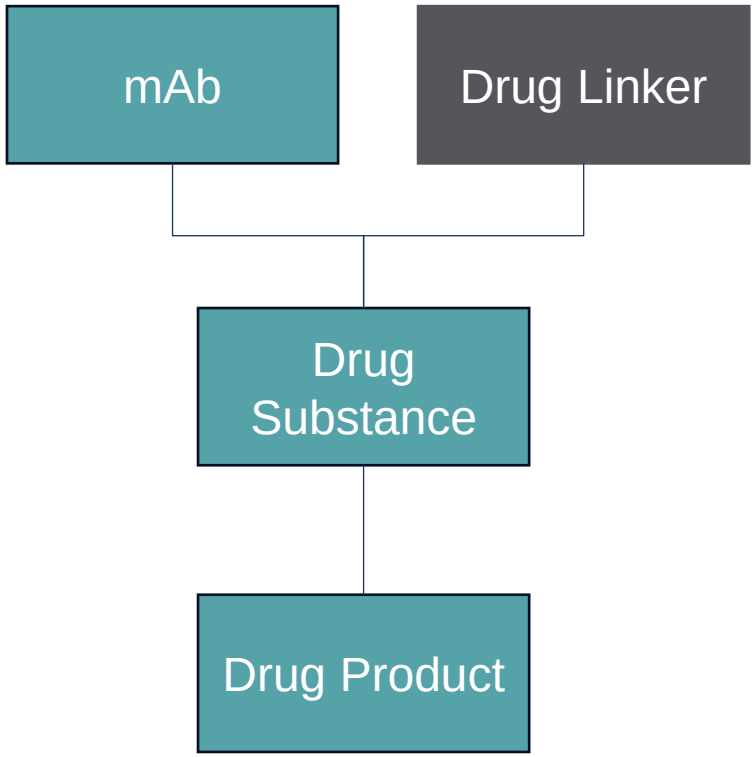
NORMAL SUBMISSION PATHWAY (ADC)



2-STEP APPROACH WITH A PACMP

PACMP as a regulatory tool provides predictability and transparency in terms of the requirements and studies needed to implement a change.

Case Study#2: Single Post Approval Submission for an ADC Product



- Process improvements made at mAb, DS, and DP nodes.
- The post-approval change submitted as a single end-to-end submission covering all changes.

How do we de-risk this PAS with a large amount of data and scope, and a very high level of complexity?

Use of PACMP to Provide Transparency to HA in Advance of Complex Post-Approval Changes

	PACMP	Post-Approval Submission
Submission Content	• Detailed description of proposed changes and associated risk assessment • List of process characterization/validation studies to be performed • Comparability protocol for each node (mAb, DS, and DP) • Summary of control strategy	• Results from process characterization/validation studies • Comparability study results • Release and Stability data
Reporting Category (US/EU)	PAS / Type II	PAS / Type II (No downgrade proposed as part of PACMP)
Submission Timing	6-9 months prior to PAS submission	NA

Although no request for downgrade of reporting category or accelerated review, the benefits of the PACMP submission in advance of a complex PAS include:

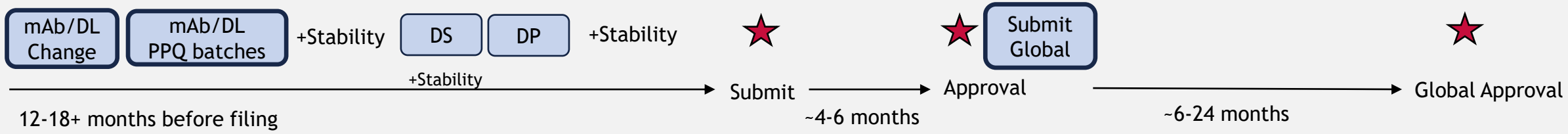
- Provide HA with transparency to the scope of changes
- Opportunity to receive feedback on the submission strategy and proposed data package
- Early HA feedback increases probability of a smooth review and mitigation of unforeseen and/or numerous requests

Opportunities as we move forward!

- PACMPs are most commonly used for manufacturing site changes……There are no constraints on type of changes that can be submitted via PACMPs.
- Multiple changes can be bundled into the same PACMP.
- Even though most time benefit comes from downgrade of changes from PAS/Type II to CBE 30/Type 1B, we should explore submitting PACMP to downgrade from CBE30/Type 1B to AR/Type 1A.
- Proposing PACMPs at the time of BLA/MAA has significant benefit for post approval lifecycle management.
- How do we expand the use of PACMPs? Can we use reliance for PACMPs?

PACMP and Reliance

NORMAL SUBMISSION PATHWAY



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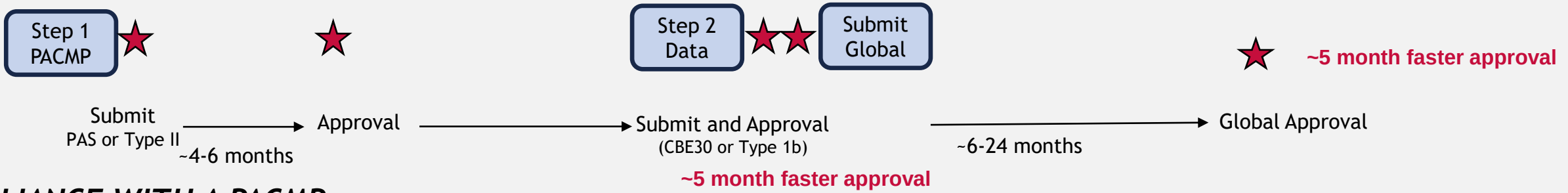
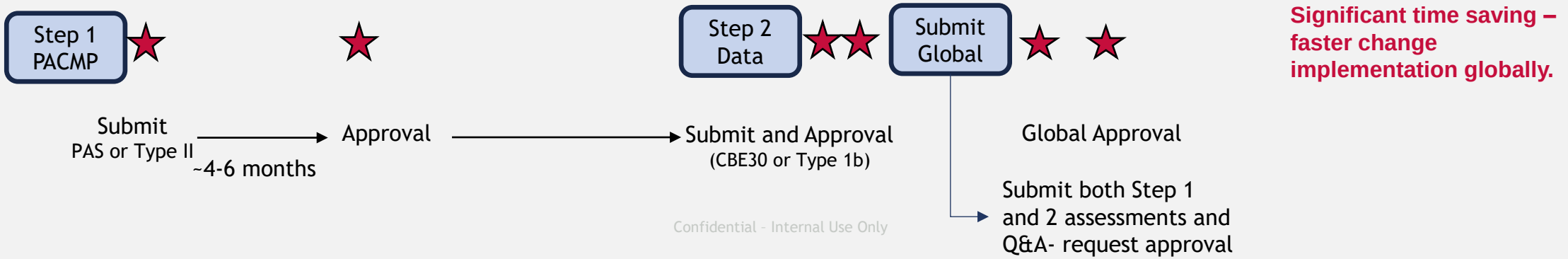


RELIANCE WITH A PACMP



Thank you!

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