# Q12 Topics and Applicability to Global Markets: Challenges for Global Expansion

CASSS WCBP 2023 Mini-Case

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# ICH Q12 Guidance Introduction

- Finalized in 2019
- Addresses commercial phase of product lifecycle
- Complements guidelines Q8 to Q11

**1.1 Objectives**

This guideline provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner. A harmonised approach regarding technical and regulatory considerations for lifecycle management will benefit

# Q12 Intent and Risk-based Approach

This guideline is also intended to demonstrate how increased product and process knowledge can contribute to a more precise and accurate understanding of which post-approval changes require a regulatory submission as well as the definition of the level of reporting categories for such changes (i.e., a better understanding of risk to product quality). Increased knowledge and effective implementation of the tools and enablers described in this guideline should enhance industry's ability to manage many CMC changes effectively under the company's Pharmaceutical Quality System (PQS) with less need for extensive regulatory oversight prior to implementation. This approach can incentivize continual improvement by providing an opportunity for greater

# Relationship Between Knowledge Management and Change Management

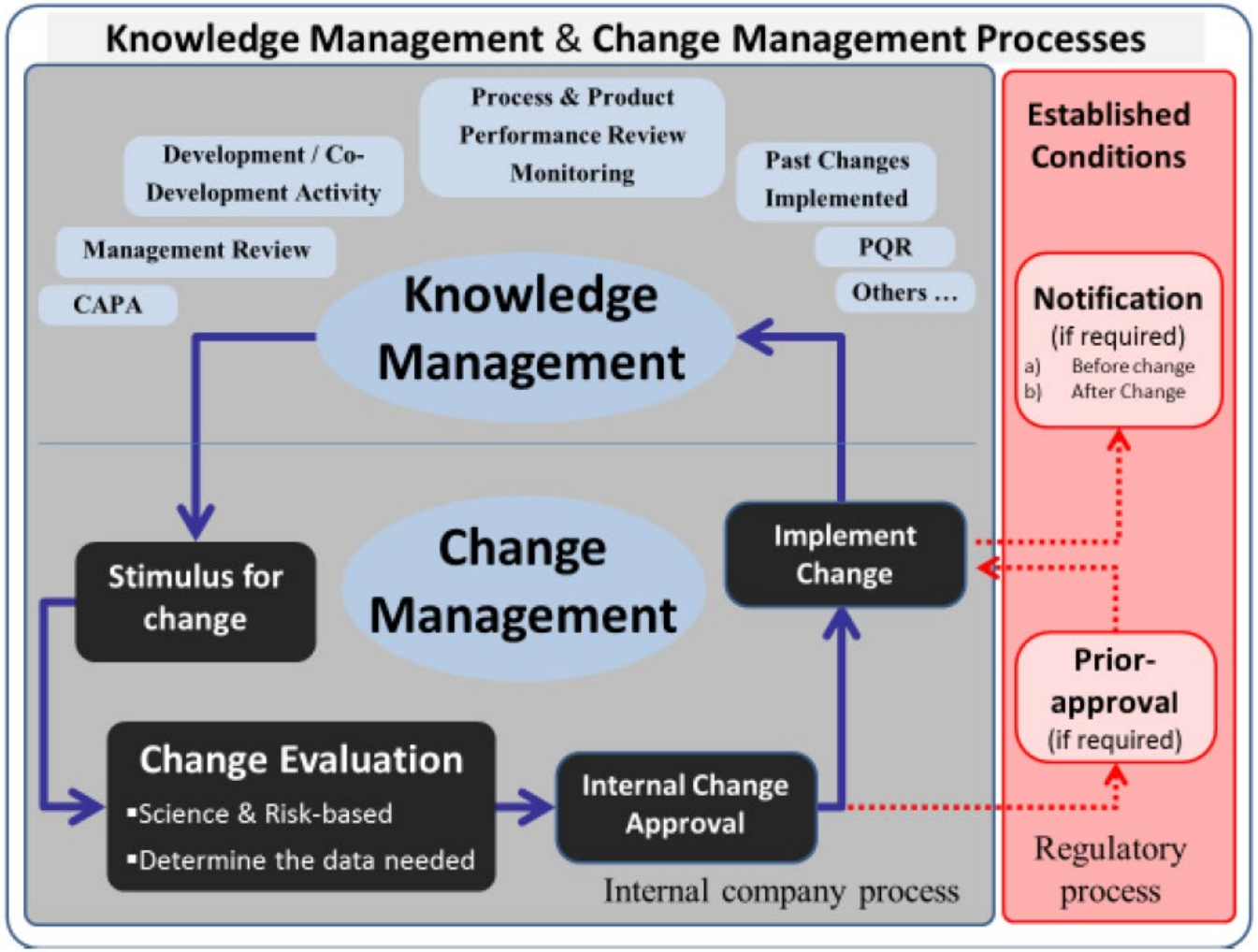
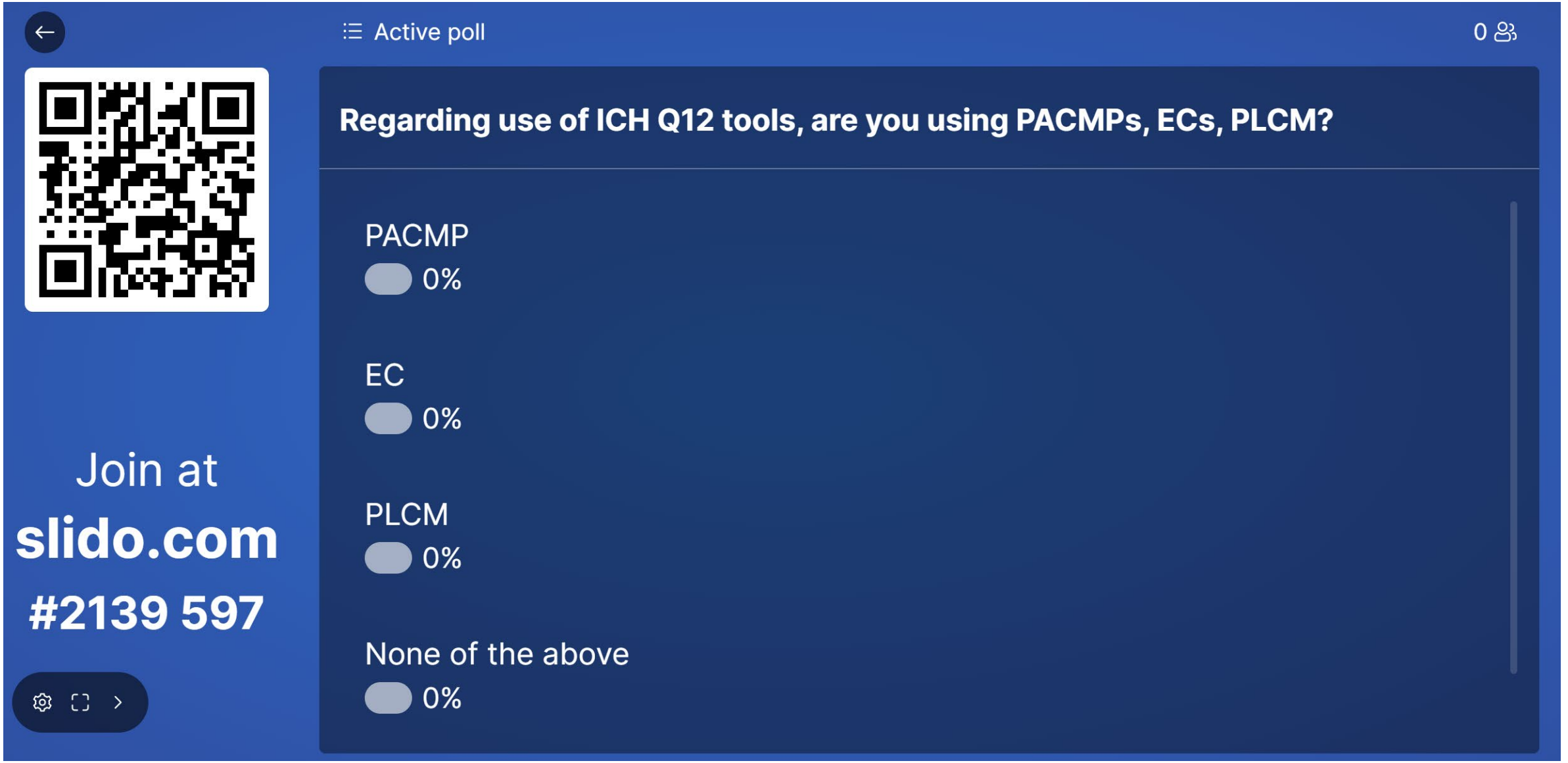



*Figure from ICH Q12*

# However, …

less associated regulatory burden. The extent of this operational and regulatory flexibility and its adequate implementation is subject to the regulatory framework in place, as well as product and process understanding (ICH Q8(R2) and Q11), application of quality risk management principles (ICH Q9), and an effective pharmaceutical quality system (ICH Q10).

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# Topics Discussed in Q12

- Established Conditions (ECs)
- Post-Approval Change Management Protocol (PACMP)
- Product Lifecycle Management (PLCM)
- Pharmaceutical Quality System (PQS)
- Change management and regulatory process
  - Includes discussion about supply, global implementation

# Established Conditions (ECs)

### 3.2 ECs in the Regulatory Submission

#### 3.2.1 ECs Definition

ECs are legally binding information considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority.

- Dossiers contain a combination of ECs and supportive information. Knowledge gained throughout product lifecycle is basis for identifying what is an EC and what is supportive information
- ECs can be identified for the manufacturing process and analytical methods

# Identification of ECs for the Manufacturing Process

- Q12 outlines several approaches for determination of ECs
- Increased amount of product and process knowledge can lead to fewer ECs or ECs with wider ranges

**Figure 1: Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters**

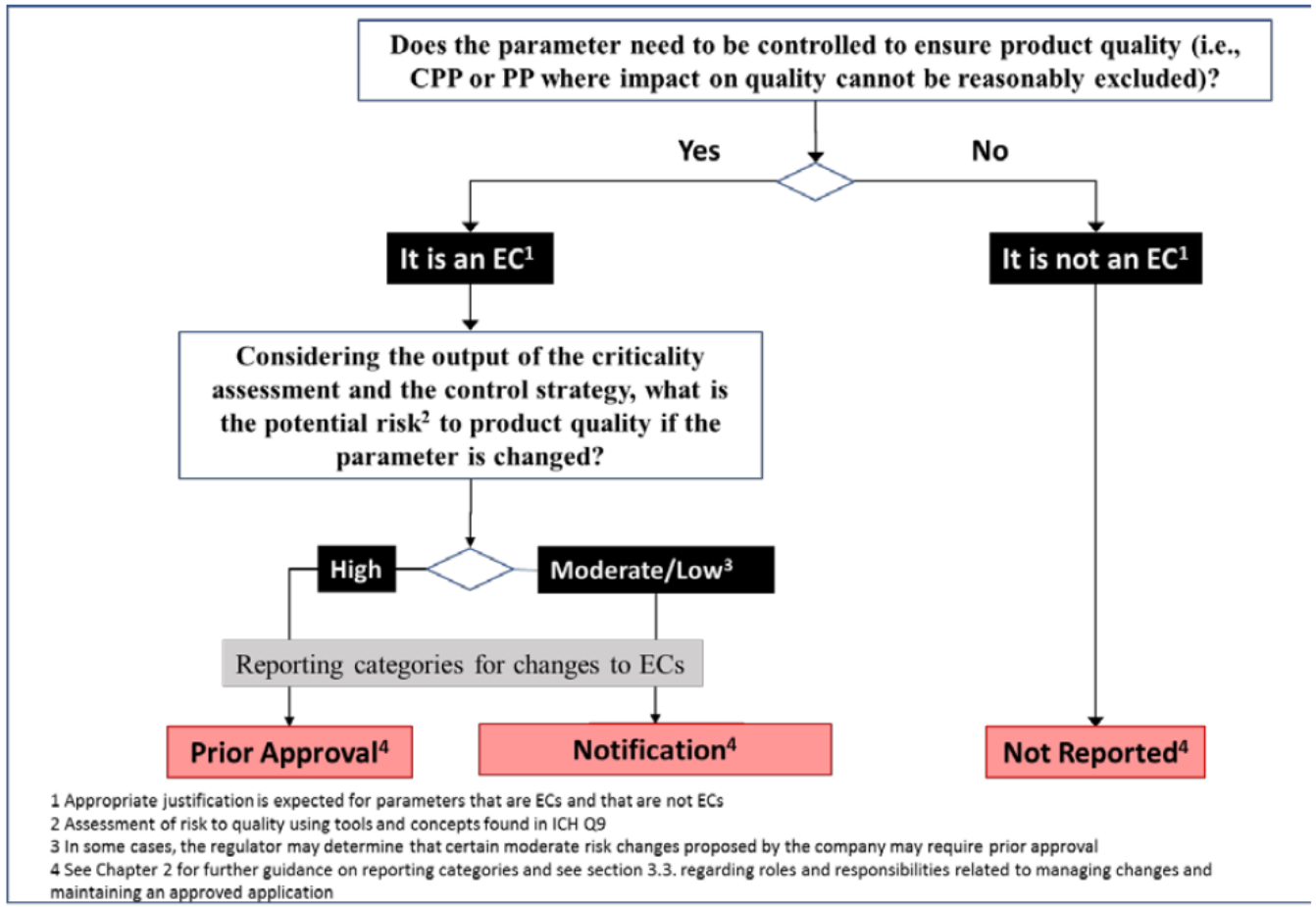



*Figure from ICH Q12*

# Case Study 1: Identification of ECs for CE-SDS (*adapted from ICH Q12 Annex IC)*

| | **All information listed are ECs** | **Reporting Example** |
|---|---|---|
| Method | Measurement of Purity: Determination of charged variants of active substance by capillary electrophoresis (non-reduced) and corrected relative area% | Notification Moderate (“NM”; CBE 30, Type IB, MCN, etc.) |
| Test solutions | *Illustropin* RS (1 mg/mL in water) | Notification Low (“NL”; CBE 0, AR, Type IA, MCN, etc.) |
| Equipment | • Suitable Capillary Electrophoresis system<br>• Suitable spectrophotometric detector<br>• Capillary: uncoated fused silica capillary diameter 50 um and effective length at least 70 cm | |
| Condition | • Chemicals (Pharmacopoeial quality)<br>• Instrument parameters<br>• Sample Analysis<br>• System conditioning | NL |
| System Suitability | System Suitability Criteria | NL |
| Acceptance Criteria | Deamidated forms: maximum 5.0 per cent; Any other impurity: for each impurity, maximum 2.0 per cent; Total: maximum 10.0 per cent. | Widening: NM Narrowing: NL |

# Conditions that must be met in order to implement the change at the corresponding reporting category

- No change in the limits/acceptance criteria outside the approved limits for the approved assays used at release/ stability.
- Method of analysis is the same and is based on the same analytical technique or principle and no new impurities are detected
- The modified analytical procedure maintains or improves performance parameters of the method
- The change does not concern potency-testing
- No changes made to the test method
- The transfer is within a facility approved in the current marketing authorization for performance of other tests
- The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, change in total impurity limits)

# Example Supporting Data

- Updated drug substance specifications and JOS.
- Copies or summaries of analytical procedures if new analytical procedures are used.
- Validation/qualification results if new analytical procedures are used.
- Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.
- Documented evidence that consistency of quality is maintained.
- Information demonstrating technology transfer qualification for the non-pharmacopoeial assay or verification for the pharmacopoeial assay.

# PACMP

- Post-Approval Change Management Protocol (PACMP) (Chapter 4)

  The PACMP is a regulatory tool that provides predictability regarding the information required to support a CMC change and the type of regulatory submission based on prior agreement between the MAH and regulatory authority. Such a mechanism enables planning and implementation of future changes to ECs in an efficient and predictable manner.

- 1+ changes associated with a single product
  - Can be used repeatedly to make a specified type of CMC change over the lifecycle of a product, applying the same principles. Need to provide justification.
  - Example: WCB protocol, WRS protocol, filter changes
- Broader protocol, can be across products
  - Example: Transfer of multiple products to a new facility

# Elements of a PACMP

- Detailed description and rationale of change (table format recommended)
- Lists of tests and studies to be performed based on risk assessment
- Discussion regarding the suitability of the approved control strategy
- Any other conditions to be met, such as confirmation that certain process qualification steps will be completed before implementation
- Supportive data to allow for risk mitigation where applicable
- Proposed reporting category
- Confirmation that ongoing verification will be performed under the PQS

# Case Studies

- Case Study 1: Identification of ECs for CE-SDS *(adapted from ICH Q12 Annex IC)*
- Case Study 2: Site transfer variations PACMP *(adapted from Jagga et al, Regulatory Rapporteur, Vol. 18 No. 6 June 2021)*

# Case Study 2: Site Transfer Variations

*(adapted from Jagga et al, Regulatory Rapporteur, Vol. 18 No. 6 June 2021)*

- Step 1: PACMP
  - Introduction and scope
  - Detailed description of change
  - Risk assessment
  - Development and characterization data
  - Process comparison and control strategy
  - Process validation strategy
  - Comparability Plan
  - Commmitments and implementation timeline
- Step 2: Submit results along with the variation package
  - By leveraging PACMP, can submit under minor variations (according to categorization in approved PACMP) instead of under major variations

# Comparison of ICH Q12 PACMP management against traditional approaches for site transfer variations

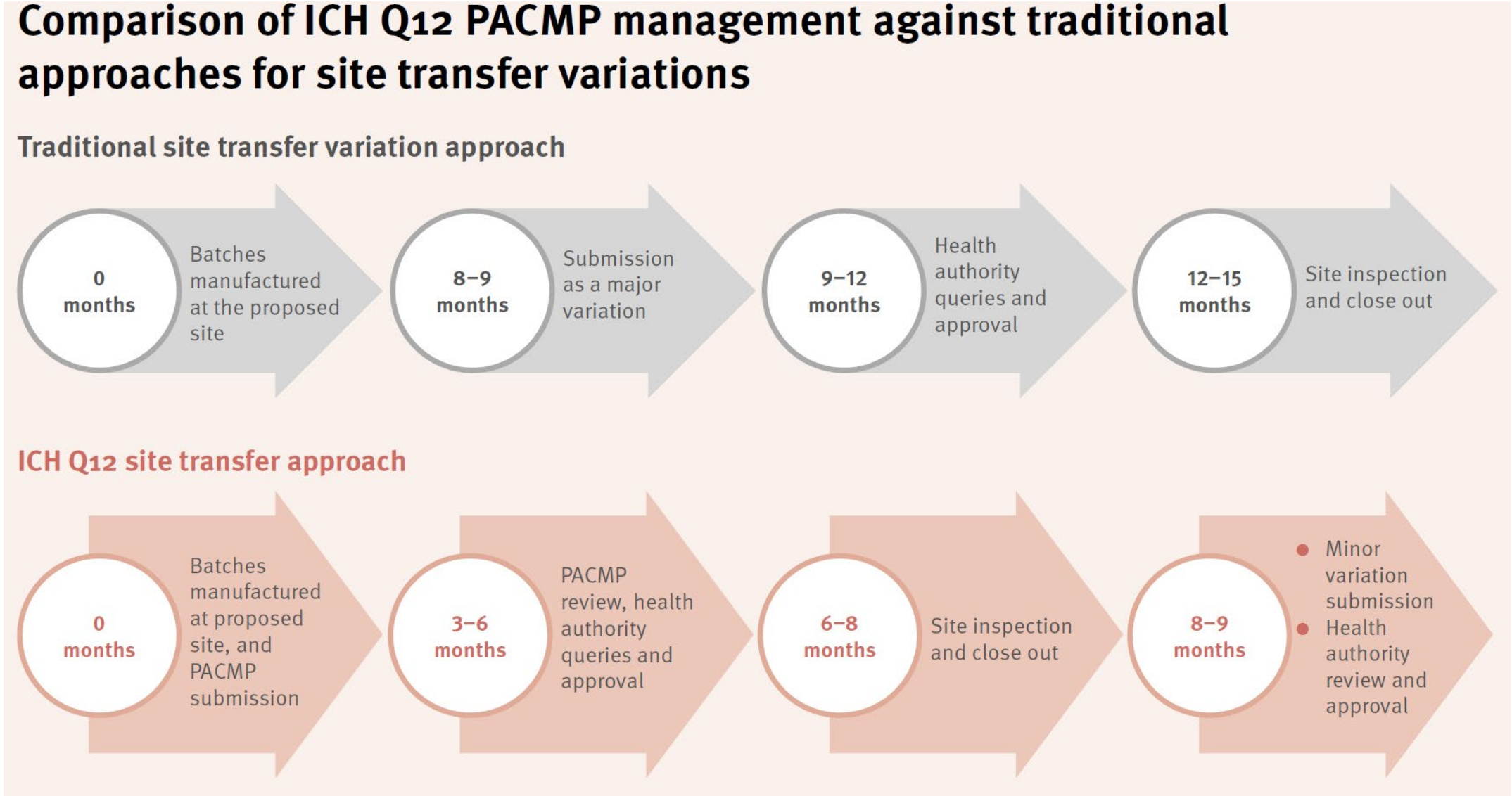



*Figure from Jagga et al, Regulatory Rapporteur, 2021*

# Benefits

## Patients

- Less risk of supply shortages
- Timely access to safe, well-tolerated, high-quality and compliant medicines

## Industry

- Harmonization of a global change management system and better operational flexibility
- Reduced cost of regulatory activities through fewer variations
- Innovation and continuous improvement
- Optimized supply chain

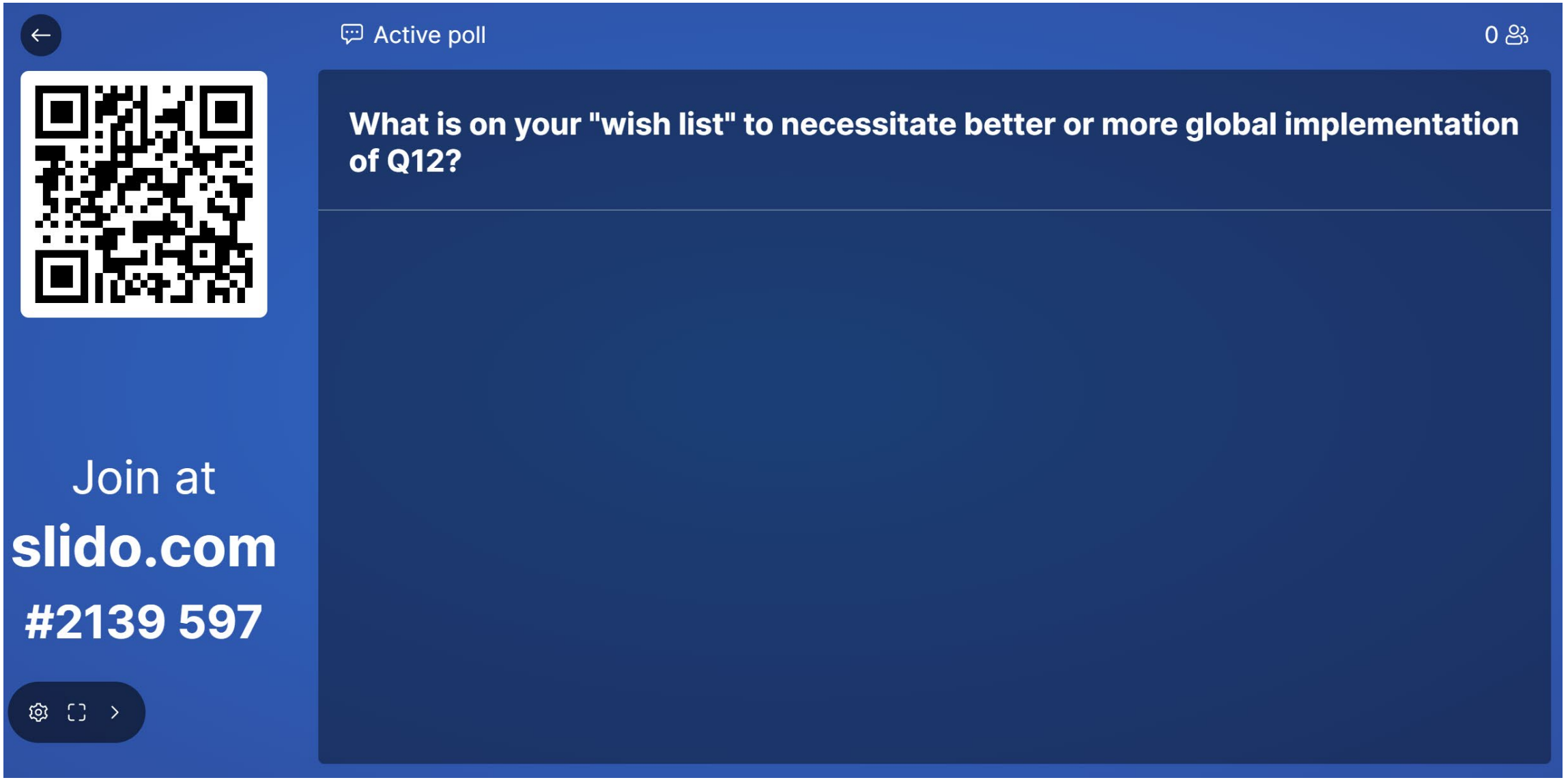
## Regulators

- Risk-based regulatory oversight with fewer number of major variations and optimization of resources for review and inspection
- Enhanced transparency between industry and regulators

# Global Challenges for Q12 implementation

- Established Conditions
  - Existing regulatory guidance with specified reporting categories for changes
    - Eg Canadian NoC guidance and EU variation guidance
  - Divergent supplemental documents required regionally eg, application form in Japan, Manufacturing Testing Protocol in China, CPID in Canada and Normative document in Russia
  - Potential for divergence during global review of sponsor-proposed established conditions

- Post Approval Protocol
  - Potential for divergence during global review of conditions sponsor-proposed PAP
  - Lack of globally aligned expectations/requirements for PAPs

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# Discussion Points

1. What are the barriers to global implementation of Q12?
2. What challenges have you encountered with PACMPs?
    a. Have you had success using a PACMP multiple times and/or for multiple products? What are the limitations you've experienced?
    b. What challenges have you encountered with global acceptance of your PACMP?
    c. Is there an opportunity to leverage PACMP in accelerated submissions?
    d. Submission to countries without PACMP framework?
3. How have you implemented established conditions?
    a. Dossier organization
    b. Managing low-risk changes with PQS
    c. Assignment of reporting category based on potential risk to product quality
    d. Products that were commercial before ICH Q12
    e. Are some parameters "always" critical?

# Open Questions from 2020 CASSS Workshop

- Are some parameters understood to “always” be critical?
- Can the reporting category for all non-CPP ECs be assumed to be low-level notification (e.g., annual reporting)?
- Will it be acceptable to propose different reporting categories, or even different EC/non-EC categories for a single process parameter, for different magnitudes or directions of change?
- Which in-process control tests need to be included as ECs?
- Are process parameters that affect non-CQAs or performance parameters and key performance indicators (KPIs) (always) ECs?