# ICH Q12: What Industry Needs to Know

SBIA PQS symposium

**CDR Mahesh Ramanadham, Pharm.D., MBA**
Deputy Director
FDA/CDER/OPQ/OPPQ

Everyone deserves confidence in their *next* dose of medicine.

**Pharmaceutical quality** assures the availability, safety, and efficacy of *every* dose.

# ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

- ICH Q12 provides a framework to facilitate the management of postapproval CMC changes in a more predictable and efficient manner

- Applicants can reduce the number of CMC changes that require a postapproval submission by using ICH Q12 tools

- This benefit increases with stronger scientific development, risk management, and quality systems throughout the product lifecycle
  - Weaker: likely more established conditions
  - Stronger: opportunity for fewer established conditions

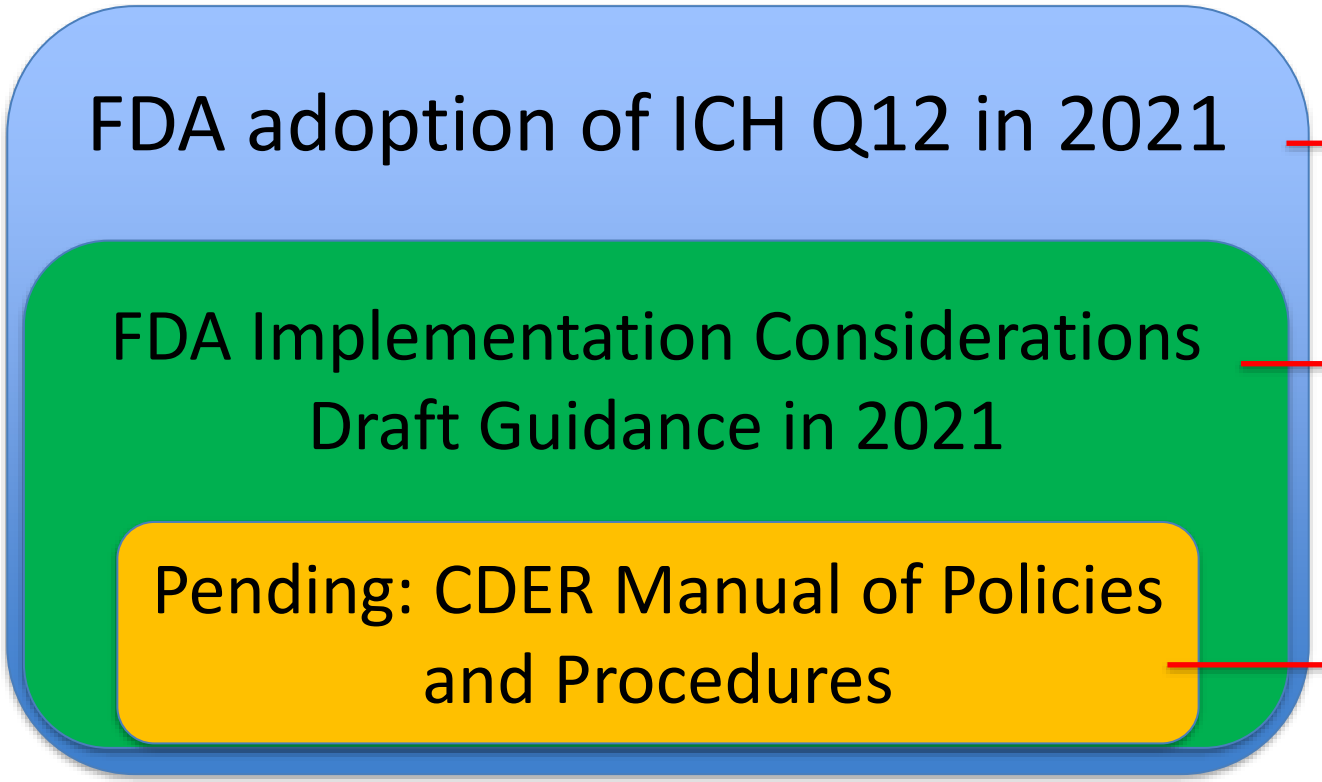
# ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

- Applicant's use of ICH Q12 is voluntary

- Implementation is flexible:
  - Established Conditions can be proposed at any point in the lifecycle (e.g., original application, post approval supplement)

  - Established Conditions can be proposed for as little as a unit operation or method, or as large as the CMC section for the application

# ICH Q12: FDA Implementation




Replaced FDA 2015 draft guidance: Established Conditions

Clarifies how ICH Q12 tools can be implemented for CDER and CBER regulated products, using specific FDA terminology and tools

More specific procedures for assessors

# Scope

- Pharmaceutical drug substances and products (both chemical and biological) that require a marketing authorization
  - includes innovators, generics, biosimilars
- Drug-device combination products that meet the definition of a pharmaceutical or biological product
  - In the US, this includes CDER- and CBER-led drug-device and biologic-device combination products
- Does not include changes needed to comply with Pharmacopeial monographs

Fully Implemented

# Tools in ICH Q12

- Established Conditions (EC)
  - Elements (e.g. parameters, attributes, controls, specifications, etc…) necessary to assure product quality that require a submission if changed
- Post-approval Change Management Protocols
  - Aligned with US FDA's comparability protocol
  - Predictability regarding planning for future changes to ECs
- Product Lifecycle Management Document
  - Central repository in the application for ECs and their reporting categories
- Pharmaceutical Quality Systems (PQS)
  - Effective PQS is necessary to support the use of Q12 tools
- Relationship between Regulatory Assessment and Inspection:
  - Effective communication between assessors and inspectors to facilitate regulatory oversight of ICH Q12 implementation
- Structured Approaches for Frequent CMC Post-Approval Changes
  - Simplified approach to accomplish certain CMC changes for products where ECs were not identified

Fully Implemented

# Established Conditions (ECs)

- ECs are legally binding information [within an application] considered necessary to assure product quality

- EC examples:
  - API or drug product formulation
  - Processes and controls
  - Specifications
  - Facilities

- All regulatory submissions contain a combination of ECs and supportive information

- Any change to an EC necessitates a submission to the regulator

- **All changes require management under the pharmaceutical quality system (PQS)**

# Established Conditions

- The extent (number and how narrowly defined) of ECs will vary based on multiple factors, including:
  - product and process understanding
  - characterization
  - the firm's development approach, and
  - potential risk to product quality

- After identifying ECs, applicant may propose a reporting category for post-approval changes to the EC with justification
  - Follow existing regulations and guidance, or
  - Propose alternate reporting category (e.g., CBE instead of a PAS)

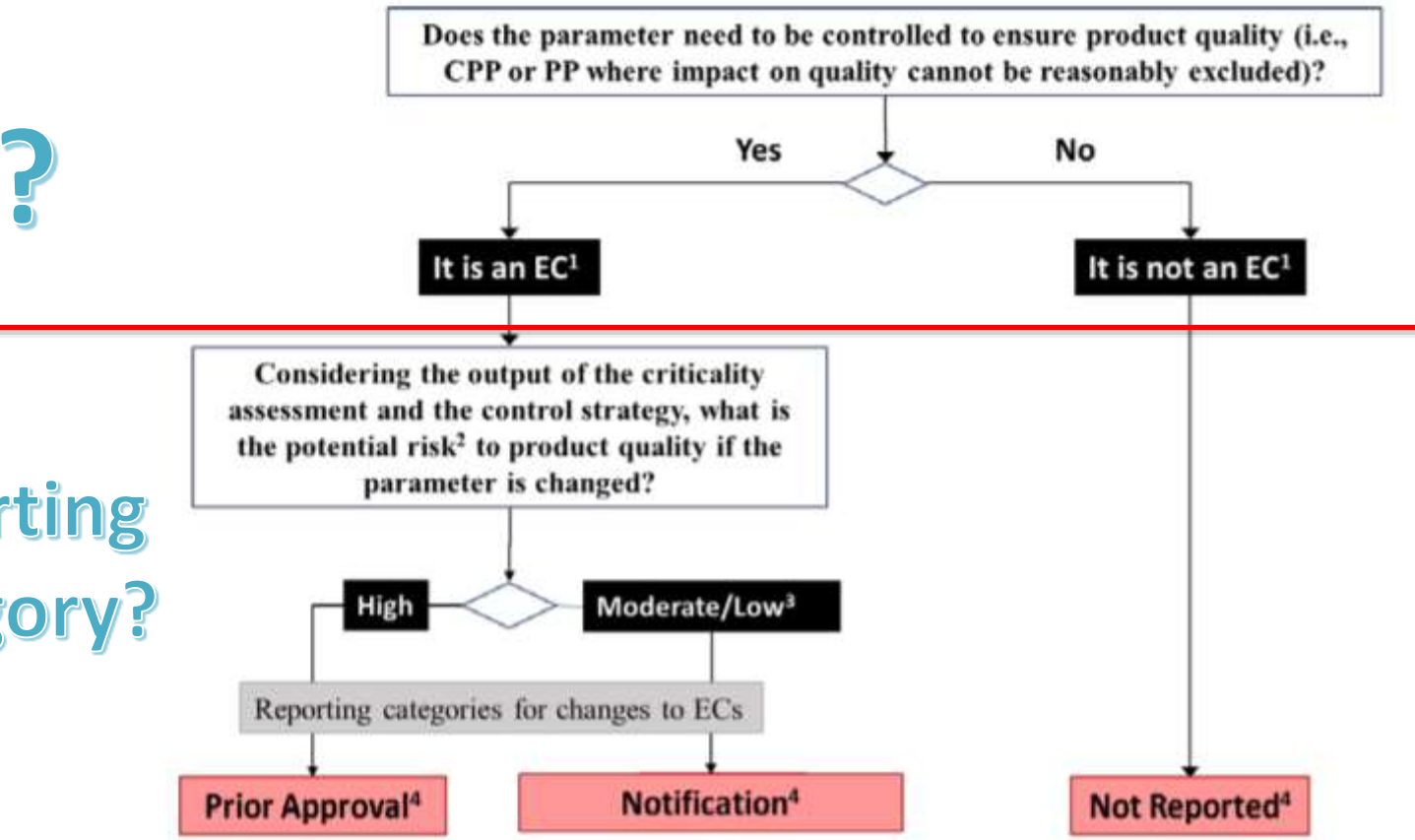
- Reporting category is dependent on the potential risk to quality
  - Risk assessment activities should follow approaches described in ICH Q9
  - Consider the overall control strategy and any possible concurrent changes

# Established Conditions

EC?

Reporting Category?

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




1 Appropriate justification is expected for parameters that are ECs and that are not ECs
2 Assessment of risk to quality using tools and concepts found in ICH Q9
3 In some cases, the regulator may determine that certain moderate risk changes proposed by the company may require prior approval
4 See Chapter 2 for further guidance on reporting categories and see section 3.3. regarding roles and responsibilities related to managing changes and maintaining an approved application

# Established Conditions

- Example from ICH Q12 training materials which depicts example ECs, and juxtaposes how different levels of product and process understanding could impact ECs and their reporting categories

| | Parameter | Acceptable ranges and reporting categories (White boxes are ECs and grey boxes are not ECs.) | | |
|---|---|---|---|---|
| | | **Minimal Parameter-Based Approach** | **Enhanced Parameter-Based Approach** | **Performance-Based Approach** |
| Equipment and Parameters | Operating Principle | Diffusion Mixing (PA) | Diffusion Mixing (PA) | Diffusion Mixing (PA) |
| | Equipment type | V-blender (NM) | V-blender (NL) | (NR) |
| | Scale | 200 kg<br>Increase >10x (NM) | 200 kg<br>Increase >10x (NL) | 200-600 kg<br>Increase >10x (NL) |
| | Blend Speed | 20 rpm<br>CPP (NM) | Design Space consisting of<br>Blend speed: 10-20 rpm<br>Blend time 15-25 minutes<br>CPP (NM) | 15 rpm<br>CPP (NR) |
| | Blend Time | 20 minutes<br>CPP (NM) | | 20 minutes<br>CPP (NR) |

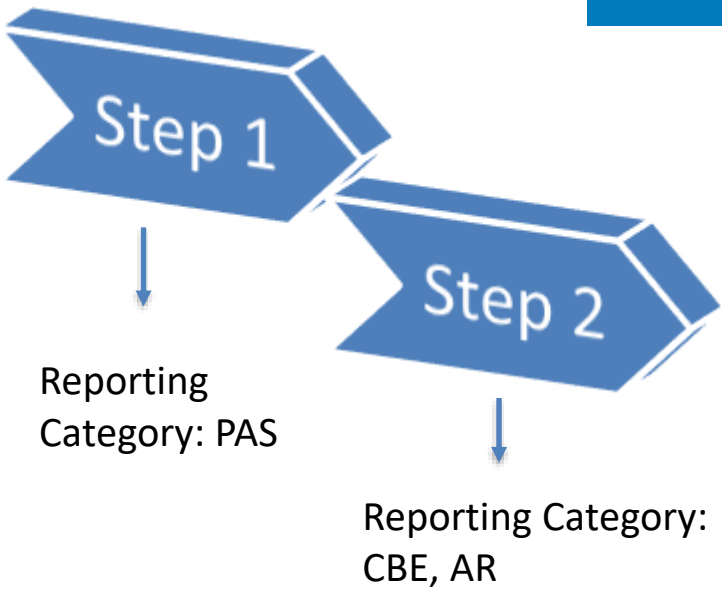
# Post-Approval Change Management Protocols (PACMP)

- In FDA system, PACMP is the same as a Comparability Protocol (CP)

- PACMP:
  - Provides predictability and transparency in terms of the requirements and studies needed to implement a change
  - Provides opportunity for lower reporting category when implementing change
  - Can address one or more changes for a single product, or may address one or more changes to be applied to multiple products

- PACMP may be submitted with the original application or subsequently as a stand-alone supplement

# PACMP




## Step 1

- Submission of a written protocol
- Approved by regulator in advance of execution

## Step 2

- Carry out tests and studies outlined in the protocol
- If results/data generated meet the protocol acceptance criteria and any other conditions are met, submit this information to the regulator according to the category in the approved protocol
- Depending on the reporting category, approval by the regulator may or may not be required prior to implementation of the change.

# What's the Difference?

| | Established Conditions (ECs) | PACMP |
|---|---|---|
| Facilitates agreement with regulator regarding changes to be reported | X | X |
| May allow for reduced reporting category compared to existing regulations and guidance | X | X |
| Requires justification to support approach | X | X |
| Studies and acceptance criteria for making changes to ECs are defined in advance | | X |

# Product Lifecycle Management (PLCM) Document

- Serves as a central repository of key elements to provide transparency and facilitate:
  - Strategic approaches to lifecycle management
  - Lifecycle regulatory assessment and inspection
- Maintenance
  - Updated list should be submitted in post-approval submissions for CMC changes
  - ECs should be updated based on knowledge gained during the lifecycle

| CTD Section | Established Conditions<br><br>*(Note that identification and justification of EC is presented in the relevant section of CTD)* | Reporting Category when making a change to the Established Condition |
|---|---|---|
| **3.2.S.4.1** | Input Material - API PSD (5-200 um) | **Tighten (NL)** |
| **3.2.P.3.3** | The manufacturing process consists of the following sequence of unit operations;<br>1. Powder blending<br>2. Roller compaction<br>3. Tablet compression<br>4. Film-coating | |
| | Operating principle: Diffusion mixing | PA |
| | Equipment Type: V-blender | NL |

# FDA Draft Guidance: ICH Q12 Implementation Considerations for FDA-Regulated Products

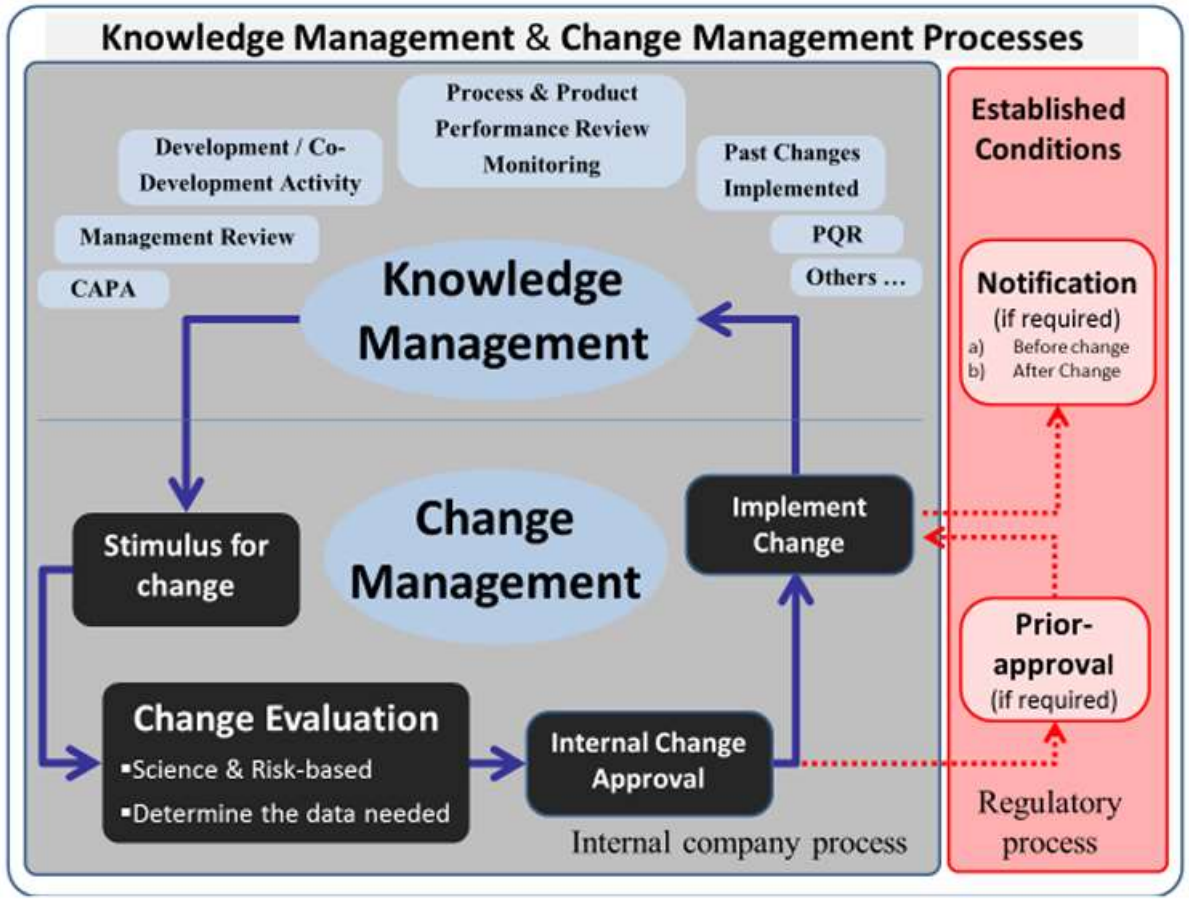
- Clarifies how ICH Q12 tools can be implemented for CDER and CBER regulated products, using specific FDA terminology and tools
- Accounts for additional FDA specific frameworks (e.g. Drug Master Files, drug-device combination products)
- Recommendations for applicants on how to capture ECs in the submission, e.g.:
  - Clarity in the cover letter regarding proposed ECs
  - Clear and specific identification of EC, reporting category, and justifications
  - Clearly indicate the facilities implementing specific ECs on the PLCM

# Role of the PQS in ICH Q12

- Effective PQS provides confidence in EC proposals:
  - Feasible and robust control strategy
  - Competent quality oversight
  - Consideration of all relevant data
  - Effective change management
- Effective change management across the supply chain and product lifecycle is essential
- Knowledge gained during commercial phase should drive a periodic reassessment of criticality and risk to ensure approved ECs are congruent with current knowledge and controls

# After Application Approval

- Effective PQS and change management needed
  - ECs should be updated based on knowledge gained during the lifecycle
  - PQS controls all changes
  - Correctly identifies when supplement / variation is needed
    - (up to date EC list should be submitted with each supplement or variation)



# Impact to Inspections

- No expectation for investigators to review ECs on site
- Inspection activities gather critical information on the effectiveness and health of the PQS
- Inspections should assess change management effectiveness at the facility and product specific level
- ECs may be reviewed and modified as part of remediation efforts following a violative inspection
- Surveillance and PAI compliance programs updated in 2022, in part, to facilitate ICH Q12 implementation

# ICH Q12 FDA Implementation: Training, Oversight, and Support

- Multi-year technical and policy training for OPQ staff and investigators
  - Focusing on overall policy, examples, and feedback from assessors in FDA's Q12 pilot
  - Updated drug surveillance and pre-approval inspection compliance programs to include concepts from ICH Q9, Q10, and Q12 (e.g., PQS, change management system, established conditions)

- OPQ oversight:
  - Established Conditions Coordinating Committee (ECCC) – to provide *regulatory* support and oversight for the implementation of ICH Q12 principles related to ECs
  - Q12 Assessment Implementation Team (Q12AIT) – to provide *scientific* support and oversight to ensure consistency in assessment of risk and scientific decision-making
  - When an application is received, the OPQ assessment team includes traditional CMC team + PQS assessor, ECCC, and AIT members

# ICH Q12 FDA Implementation: Application Demographics to Date

| Application Type | Original | Supplement | Approved |
|---|---|---|---|
| Biologic License Application | 4 | 14 | 8 |
| New Drug Application | 2 | 5 | 6 |
| Abbreviated New Drug Application | 0 | 0 | 0 |
| Total | 6 | 19 | 14 |

- Table includes applications from FDA's established conditions pilot (2019) and post implementation (2021 – September 2023)
- Examples of approved ECs include:
  - Reduced volume of ECs, with reporting categories consistent with regulation & guidance
  - Reduced volume of ECs and reduced reporting categories
  - Both parameter-based and performance-based approaches for manufacturing process and analytical methods
  - Manufacturing facility specific ECs
  - ECs for device constituent part for a drug-device combination product (e.g., CCS, performance specification)

# Reflections from FDA's Initial Experience

- Application cover letter should clearly identify when the application:
  - Proposes ECs
  - Proposes revisions to approved ECs
  - Proposes changes made in accordance with previously approved ECs

# Reflections from FDA's Initial Experience

- Scientific justification for proposed ECs and reporting categories
  - Justifications for ECs should focus on *explaining* the approach to criticality assessment, etc. (not necessarily *changing* the approach)
  - Justifications and risk assessments should clearly describe scientific rationale for why an element is considered an EC (or not) accounting for the overall control strategy
  - Justification for reporting categories that differ from FDA regulation/guidance should be provided considering potential risk to quality when changing element

# Reflections from FDA's Initial Experience

- PLCM:
  - Should include all ECs for the relevant eCTD section
    - A few examples of discrepancies between module 3 and PLCM
  - Should clearly state the proposed reporting category (when different than regulation / guidance)
  - Manufacturing sites by FEI number where proposed established conditions (ECs) will be implemented

- FDA assessment of PQS driven by understanding:
  - Which facilities will implement ECs
  - Whether the proposed reporting categories differ from regulation & guidance

# Applicant Interactions

- Responsive to FDA information requests, e.g.:
  - Additional clarity in PLCM (e.g., specific reporting categories, facilities)
  - Additional information to justify ECs or reporting categories
  - Requested EC and reporting category revisions
- Some applicants did not provide requested clarifications, rather, withdrew proposals for ECs
- To date, FDA has not denied approval of an application due to Q12

# Broader Efforts to Encourage Use of ICH Q12

- Applied ICH Q12-like concepts during the pandemic to help expedite critical postapproval changes
- Addressing common misperceptions and questions
- Supporting global efforts to implement ICH Q12 tools (e.g., ECs, PACMP)
  - ICH Q12 Implementation Working Group
  - ICMRA pilots
  - Sharing experiences with other regulators
- Supporting related ICH guidance (e.g., M4Q(R2))

# Acknowledgements


- ICH Q12 expert / implementation working group
  - FDA ICH Q12 EWG/IWG team:
    - Ashley Boam
    - Bhagwant Rege
    - Rebecca McKnight
    - Chikako Torigoe
- FDA ECCC and Q12 AIT members