ICH Q12: What Industry Needs to Know

SBIA PQS symposium

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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

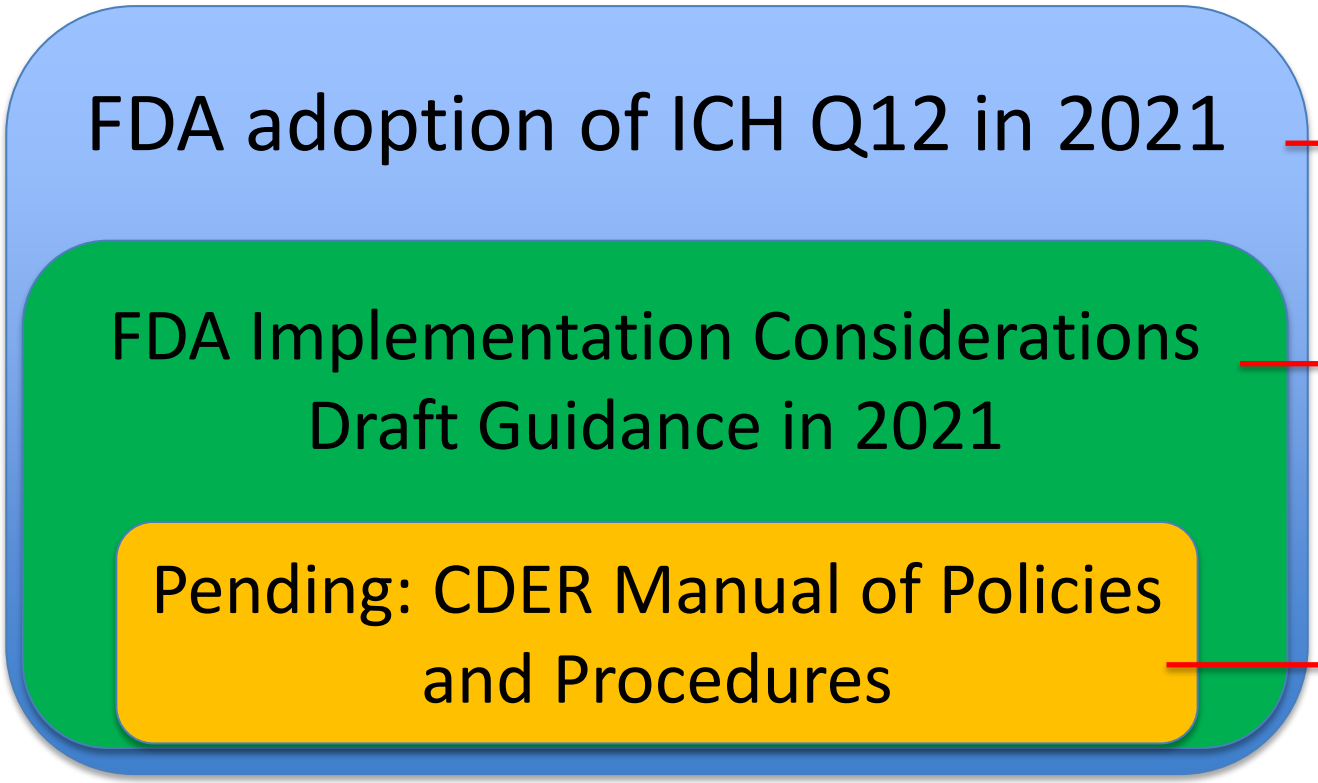
ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

- 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Replaced FDA 2015 draft guidance: Established Conditions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

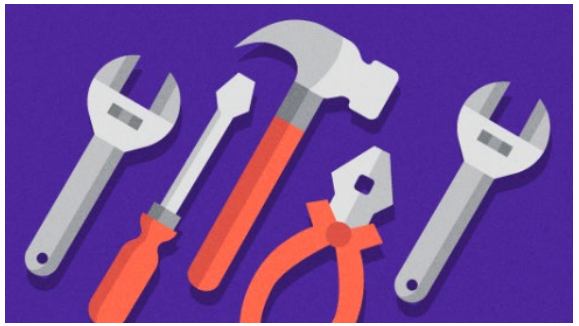
More specific procedures for assessors

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)

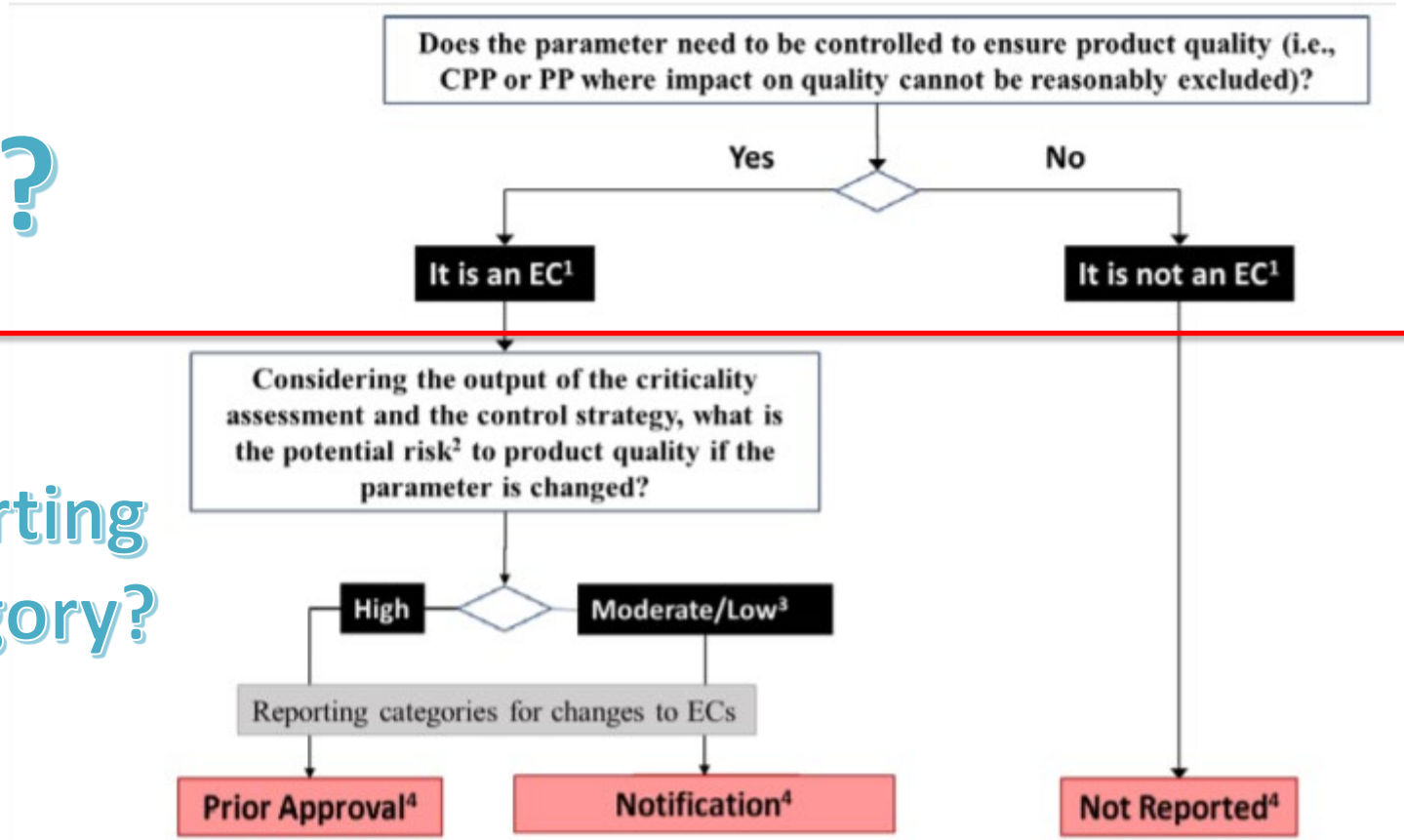
- Reporting category is dependent on the potential risk to quality
  - Risk assessment activities should follow approaches described in ICH Q9
  - Consider the overall control strategy and any possible concurrent changes

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 Increase >10x (NM)	200 kg Increase >10x (NL)	200-600 kg Increase >10x (NL)
	Blend Speed	20 rpm CPP (NM)	Design Space consisting of Blend speed: 10-20 rpm Blend time 15-25 minutes CPP (NM)	15 rpm CPP (NR)
	Blend Time	20 minutes CPP (NM)		20 minutes CPP (NR)

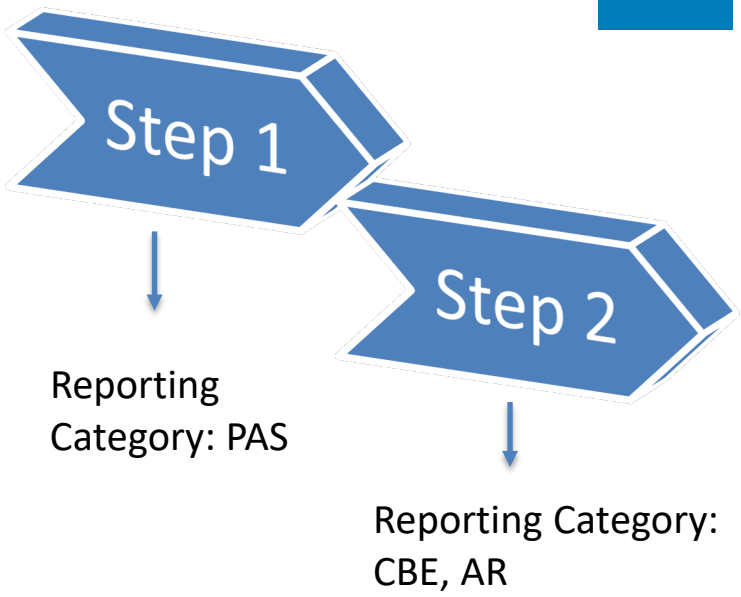
Post-Approval Change Management Protocols (PACMP)

- 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 *(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; 1. Powder blending 2. Roller compaction 3. Tablet compression 4. Film-coating	
	Operating principle: Diffusion mixing	PA
	Equipment Type: V-blender	NL

FDA Draft Guidance: ICH Q12 Implementation Considerations for FDA-Regulated Products

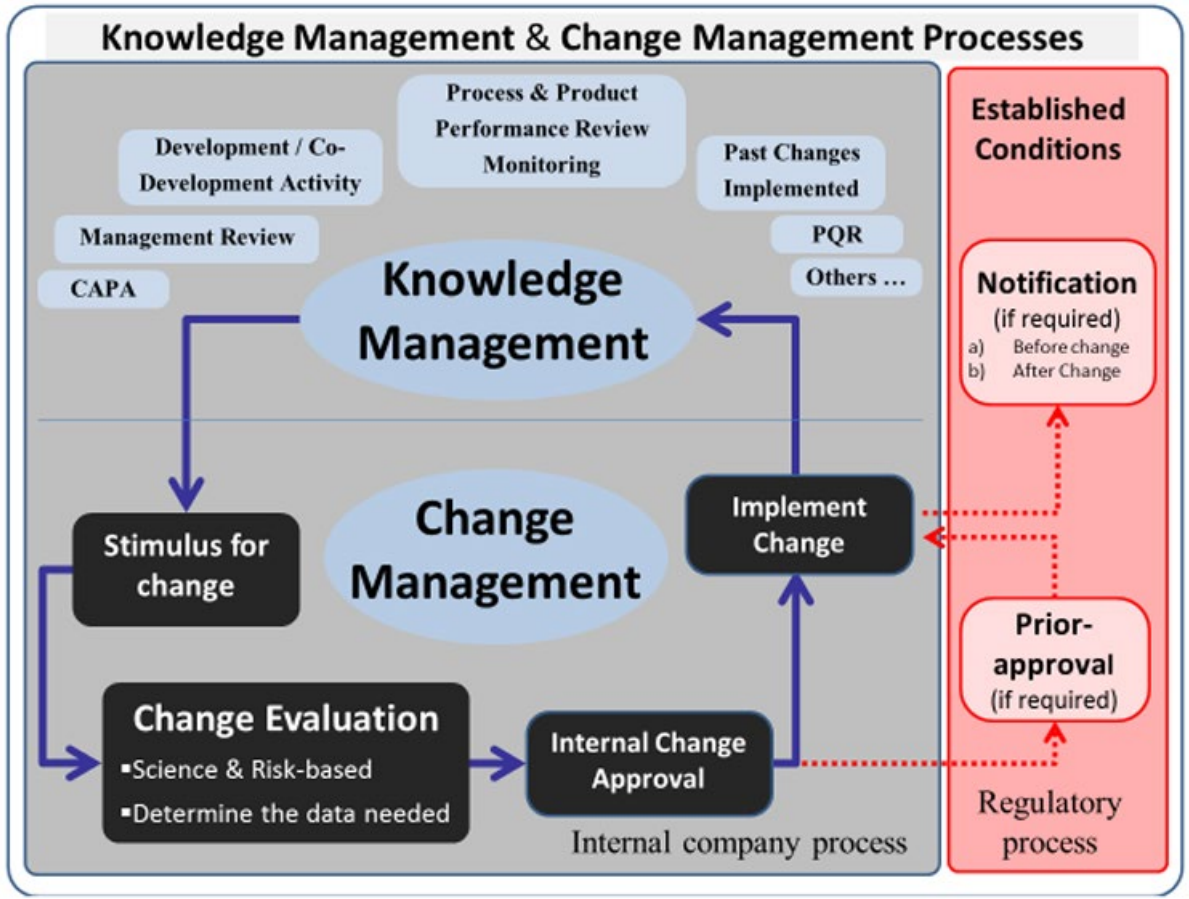
- Clarifies how ICH Q12 tools can be implemented for CDER and CBER regulated products, using specific FDA terminology and tools
- Accounts for additional FDA specific frameworks (e.g. Drug Master Files, drug-device combination products)
- Recommendations for applicants on how to capture ECs in the submission, 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

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