# OPQ Policy Update: ICH Q12

**Ashley B. Boam, MSBE**
Director
Office of Policy for Pharmaceutical Quality
CDER/OPQ

# Learning Objectives

- Identify the tools described in ICH Q12
- Understand how to identify Established Conditions and reporting categories
- Understand the role of the pharmaceutical quality system in the use of Established Conditions
- Know where to go for more information

# ICH Q12

## *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*

- Provides a framework to facilitate the management of postapproval CMC changes in a more predictable and efficient manner
- Applicants can reduce the number of changes that require a postapproval submission by using Q12 tools
  - Incentivize changes and innovations in manufacturing that can minimize quality-related supply disruptions
- Benefit increases with stronger scientific development, risk management, and quality systems through product lifecycle
- Scope includes innovators, generics, biosimilars, CDER- and CBER-led combination products
- Can be used for new products and already marketed products

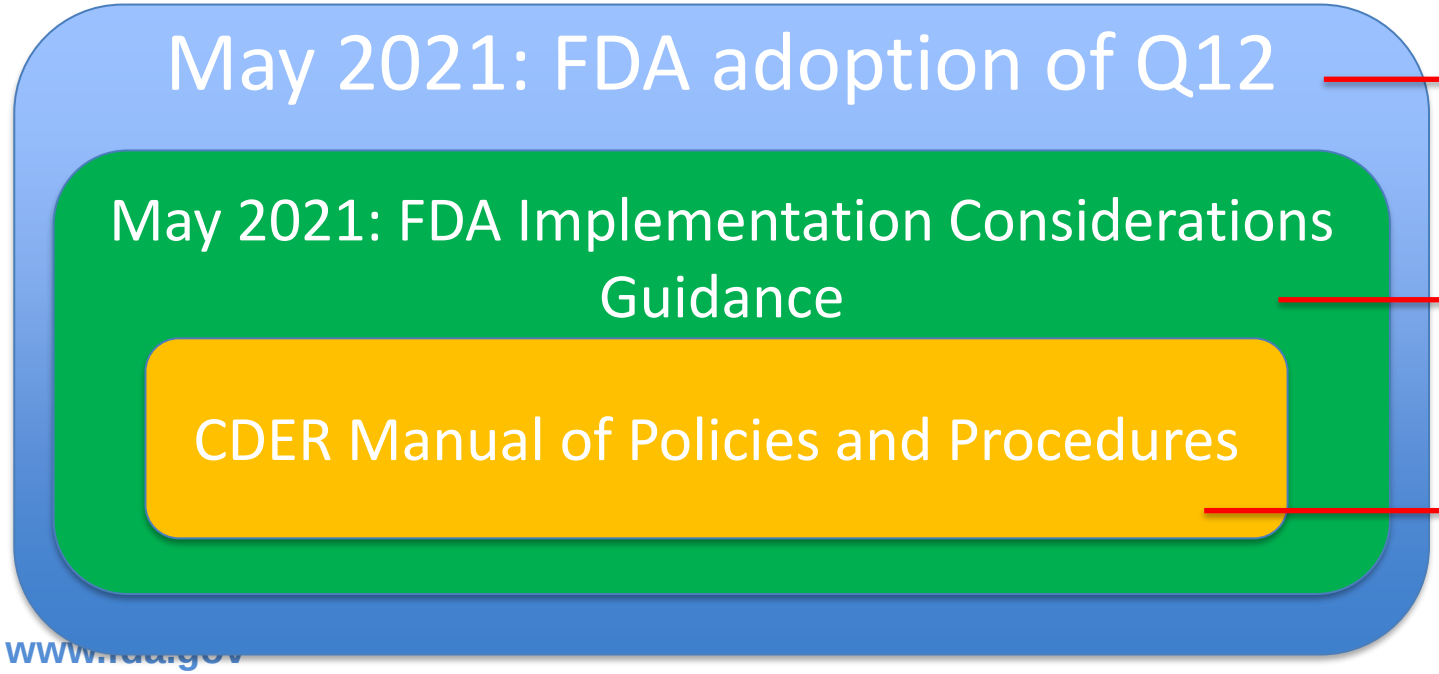
# Benefits of ICH Q12

- Implementation of ICH Q12 tools and supporting ICH Q guidance (Q8, Q9, Q10, Q11) leads to:
  - Greater assurance of high-quality drugs on the market
  - Reducing perceived barriers to innovation
  - Greater change agility to mitigate disruptions and shortages
  - Greater CMC flexibility for accelerated development programs
  - Reduction in unnecessary CMC supplements

# ICH Q12 – Implementation

- ICH:
  - Step 4 adoption November 2019
  - Global regulators in varying stages of implementation

- FDA:




Replaces FDA 2015 draft guidance: Established Conditions

Guidance on how to use Q12 tools in the FDA system

Specific internal procedures for OPQ and OC (in development)

# Tools in Q12

- Established Conditions (EC)
  - Elements (e.g., parameters, attributes, controls, specifications) necessary to assure product quality and that require a submission if changed
- Post-approval Change Management Protocols (same as 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
- Structured Approaches for Frequent CMC Post-Approval Changes
  - Simplified approach to accomplish certain CMC changes for products where ECs were not identified
- Pharmaceutical Quality System (PQS)
  - Effective PQS is necessary to support the use of Q12 tools

# Established Conditions (ECs)

- Established Conditions:
  - Are legally binding information considered necessary to assure product quality
  - A change to an Established Condition requires a submission to the regulatory authority that is consistent with regional regulations or guidance; or as agreed upon during review and approval of the marketing application
  - Are contained in a regulatory submission, submitted and justified by the applicant, and approved, by the regulatory authority
  - Are based on existing regulation and guidance, and can be further targeted based on science and risk-based approaches described in Q12
- ECs and reporting category impacted by knowledge and risk management
- Should be revised based on knowledge gained over the lifecycle
- All changes require management under the PQS

# Established Conditions (ECs), cont.

- ECs offer an opportunity to:
  - Modify the total number of changes that require a supplement
  - Modify the reporting category (RC) associated with the change
- Enabled by utilizing product and process knowledge, enhanced development, and quality risk management principles (ICH Q8, ICH Q9, ICH Q11)
- Enabled by implementing an effective PQS (ICH Q10)

# Established Conditions (ECs), cont.

- All regulatory submissions contain a combination of ECs and supportive information, i.e., not all information in an application is an EC
  - Supportive information is not considered to be ECs, but is provided to share with FDA the development and manufacturing information at an appropriate level of detail, and to justify the initial selection of ECs and their reporting category

# Step 1 - Identifying ECs

- Explain how you identified the parameters or attributes that are proposed to be ECs vs. others that might typically be considered to be ECs (e.g., based on existing guidance) but are not included
  - For example, a unit operation has 5 parameters. If only 3 are proposed to be ECs, explain how you reached that conclusion
- A scientific justification should include:
  - risk assessment process used to identify particular parameters or attributes as ECs
  - criticality assessment conducted to determine the level of impact of each parameter on product quality, and
  - supporting information for each (e.g., fundamental knowledge, empirical investigation, prior knowledge from experience with other products, commercial experience)

# Step 2 - Proposing Reporting Categories

- For each EC, propose a reporting category (PAS, CBE-30, CBE-0, annual report)
- If the category is different from what is recommended in existing guidance, provide a justification
  - Can be part of or complementary to the justification provided to support how you identified ECs
  - Should be the result of comprehensive risk assessment (impact on quality of changing the element)
- Otherwise, include a statement that the reporting categories will follow existing guidance

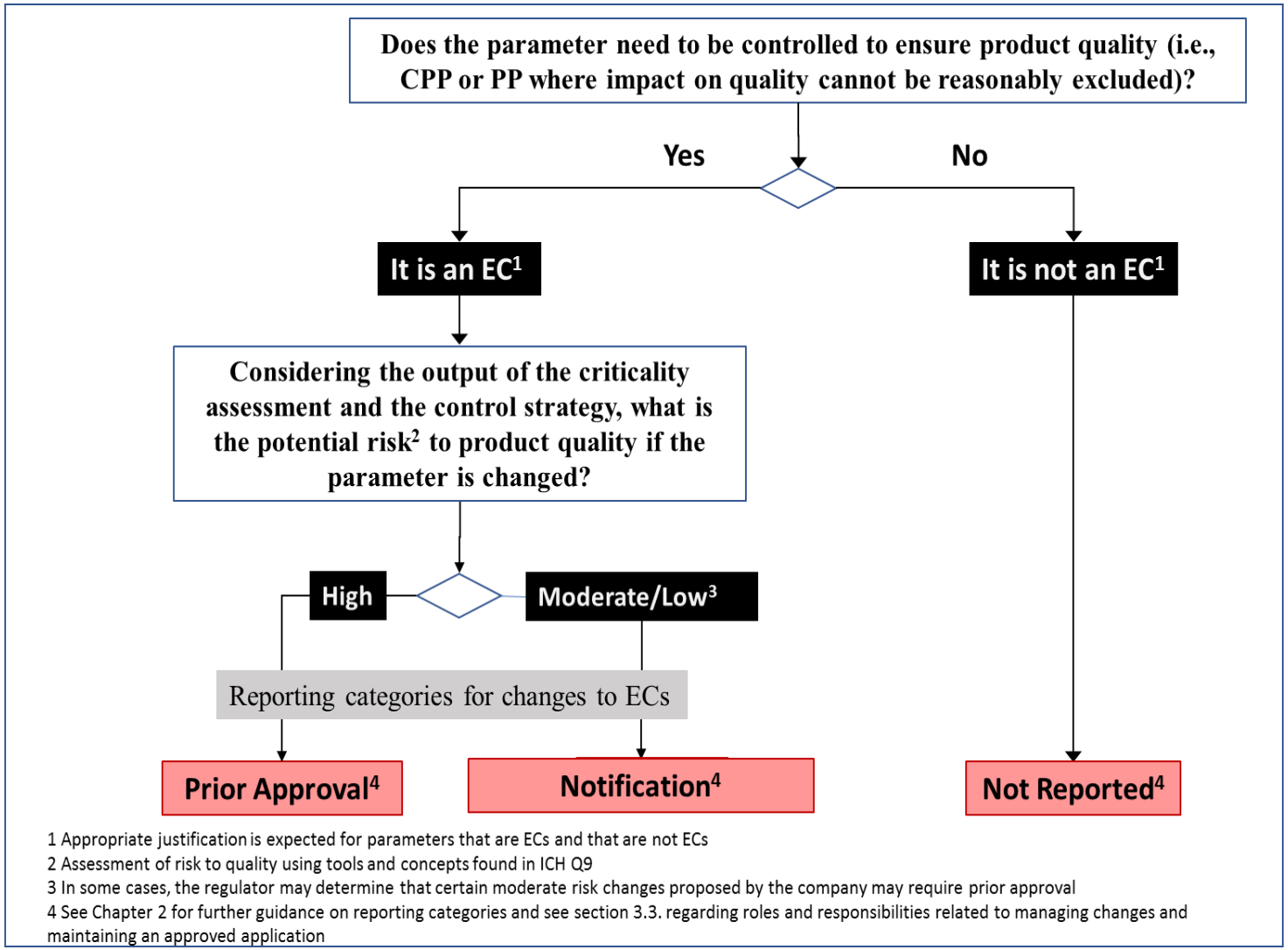
# Criticality and Risk Assessment

- Defining ECs (e.g., CPP/CMA) and reporting categories
  - Initial impact assessment of material and process inputs
  - Identification of potential critical process parameters
  - Evaluation of impact of process parameters on quality
  - Final risk assessment of impact to quality when changing critical process parameters and material attributes in context of control strategy



CPP = Critical Process Parameter; CMA = Critical Material Attribute

# ECs and Reporting Categories for Manufacturing Process Parameters (Fig 1 from ICH Q12)




Is the parameter an EC?

If an EC, what is the appropriate reporting category?

# Role of the PQS

- Confidence in EC proposals also supported by an effective PQS
  - Feasible and robust control strategy
  - Competent quality oversight
  - Consideration of all relevant data
  - Effective change management
- A periodic reassessment of criticality and risk is needed to ensure initial decisions are congruent with current knowledge and controls
- An inspection is not necessary to support proposed ECs/ reporting categories

# Common Misperceptions/Questions

*ANDA applicants shouldn't pursue ECs because they don't conduct pharmaceutical development studies like innovators*

- Generic drug manufacturers may have a wealth of product and process information that can support ECs, for example, from:
  - Commercial experience (for an already marketed product)
  - Platform experience (i.e., from similar products/processes)
  - Comparative assessments conducted against the reference listed drug (RLD)

  in addition to traditional pharmaceutical development studies

# Common Misperceptions/Questions

*I don't have time to develop a proposal for ECs; I'm fighting an exclusivity/patent clock*

- Use of Q12 tools such as ECs is voluntary
- Consider proposing ECs in a PAS if development timelines for the original ANDA aren't amenable
- ECs can be submitted for one or more sub-sections of the CMC portion of the application (e.g., 3.2.P.3.3, 3.2.P.3.4)

# Common Misperceptions/Questions, cont.

*Can ECs be proposed for a Drug Substance in a Type II DMF?*

- ECs can be proposed for a drug substance located in a DMF, *but* should only be proposed within the ANDA application
  - ECs are approved with the application. FDA approves applications; we do not approve DMFs
- DMF holders will need to share sufficient information with the ANDA applicant so that the proposed ECs and reporting categories can be specified and approved in the ANDA
- Justification for proposed ECs can be located in the DMF if the application includes a reference to the specific location for the justification
- ECs can be submitted for one or more sub-sections of the CMC portion of the application (e.g., drug product only; drug substance specification, but not manufacturing process)

# Common Misperceptions/Questions, cont.

*Do I have to compare my ECs to those for the RLD? I couldn't possibly know what the RLD ECs are.*

- No, ECs for a generic product are based on the product and process understanding held by the ANDA applicant
- A comparison to the RLD is not needed

*How could ECs be helpful to a generic manufacturer?*

- Approved ECs can provide more flexibility for daily manufacturing operations as well as for making postapproval changes to further optimize manufacturing processes (e.g. fewer submissions, lower reporting categories)
- Implementation of ICH Q8-Q12 should result in improved product quality and quality systems, which may facilitate streamlined regulatory oversight

# Internal Governance

- OPQ Quality Assessment Governance Council has established:
  - Established Conditions Coordinating Committee (ECCC) – to provide *regulatory* support and oversight for the implementation of 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
- For now, each application or supplement proposing ECs will be assigned a member of the ECCC and one or more members of the Q12AIT
  - Expect to phase out involvement of ECCC and then Q12AIT over time as assessment teams gain experience and comfort with these concepts

# Reflections from FDA's Initial Experience

- FDA has received both original applications and supplements proposing established conditions (ECs)
- FDA implementation guidance provides important advice:
  - Flag the submission as proposing ECs (cover letter and 3.2R)
  - Specify the facility(ies) where ECs will be implemented
  - Denote submission types for reporting changes using FDA terminology
    - NL could be either CBE-0 or annual report
- Take advantage of pre-ANDA meetings, where available, to request feedback on your planned approach

# Reflections from FDA's Initial Experience, cont.

- FDA's assessment of ECs will focus on:
  - Scientific justification for proposed ECs and reporting categories
    - Justifications for ECs should focus on *explaining* your approach to criticality assessment, etc. (not necessarily *changing* your approach)
    - Justifications should be current, accessible, and their location specified
  - Available information about the PQS at the facilities where ECs will be implemented
    - Inspection history, assessments using alternate tools (records requests, remote interactive evaluations), quality management maturity (once available)
    - Depth of PQS assessment commensurate with level of flexibility proposed

# Global Status of ICH Q12

- Q12 Implementation Working Group (IWG) developing training materials for assessors and inspectors in cooperation with PIC/S, for use in all regions – initial materials posted at www.ich.org
- Additional case studies to be posted, will include examples of:
  - ECs for APIs, vaccines, analytical methods
  - ECs for the device constituent part of a drug-device combination product
  - PLCM
  - How the PQS influences use of Q12 tools

# Challenge Question #1

**Which of the following best describes Established Conditions?**

A. Can reduce the number of CMC changes that require a postapproval submission

B. Should be identified for every part of eCTD Module 3

C. Should be the same for every product

D. If proposed, will mean an inspection is needed

# Challenge Question #2

**Which of the following statements is NOT true?**

A. Established Conditions can be proposed in either an original ANDA or in a PAS

B. Proposed Established Conditions should be supported by a scientific justification

C. The use of Established Conditions is required

D. The applicant should provide a justification for proposed reporting categories that differ from existing guidance

# Resources

- Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
- Q12 Annexes
- ICH Q12: Implementation Considerations for FDA-Regulated Products (draft)
- ICH training materials

# Summary

- ICH Q12 tools such as Established Conditions offer opportunities to generic applicants to reduce the number of supplements needed for postapproval CMC changes
- Established Conditions can be submitted in original ANDA applications or in a PAS
- An effective PQS is foundational for use of Q12 tools
- Please read the final ICH Q12 guidance and its Annexes as well as the FDA Implementation Guidance!

U.S. FOOD & DRUG ADMINISTRATION

# Questions?

**Ashley B. Boam**
Director
Office of Policy for Pharmaceutical Quality
OPQ | CDER