U.S. FOOD & DRUG ADMINISTRATION

Evolving SUPAC for Today's Complex Products

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Office of Product Quality Assessment II | Office of Pharmaceutical Quality

CDER | US FDA

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Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

Outline

- **Key Post-Approval Regulations/Guidance** - Overview
- **SUPAC Limitations and Challenges** - SUPAC guidance (1990s) does not address today's complex products like autoinjectors
- **Regulatory Evolution and New Frameworks** - ICH Q12 (2021) and Comparability Protocols offer alternatives to prescriptive SUPAC approaches
- **ICH Q12 Core Concepts** - EC, CP (PACMP), PQS, and PLCM document
- **Risk-Based Change Management** - ICH Q12 enabling regulatory flexibility through robust product and process understanding

Post-Approval Changes: Key Regulation and Guidance

- **21 CFR 314.70**
- **21 CFR 314.97**

- SUPAC IR/MR/SS: mid to late 1990s
- PAC-ATLS: Postapproval Changes —Analytical Testing Laboratory Sites (1998)
- Changes to an Approved NDA or ANDA (2004)
- CMC Postapproval Manufacturing Changes to be Documented in Annual Reports (2014)
- Postapproval Changes to Drug Substances (2018, draft)
- ICH Q12 (2021)
- Comparability Protocols for Postapproval Changes to the CMC Information in an NDA, ANDA, or BLA (2022, final)

Post-Approval Change Regulation

- 21 CFR 314.70: Supplements and other changes to an approved application.
- 314.70(a)(1)(i): …the applicant must notify FDA about each change in **each condition established** in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully.
- 314.70(a)(2): The holder of an approved application…must **assess the effects of the change** before distributing a drug product made with a manufacturing change.

Risk-Based Reporting Categories

Major Changes

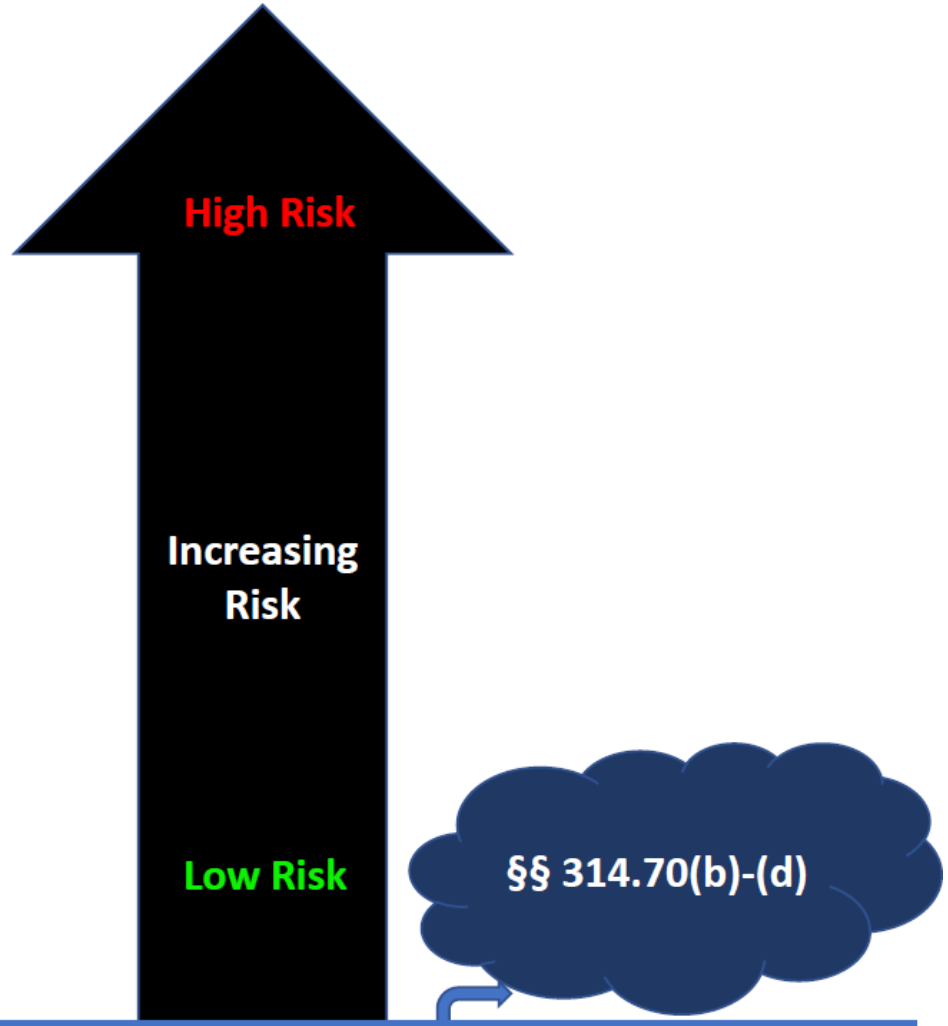
- PAS: Implement change after FDA approval

Moderate Changes

- CBE-0: Implement change immediately after supplement receipt at FDA
- CBE-30: Implement change 30 days following supplement receipt at FDA

Minor Changes

- Annual Report (AR): Notification after implementation



Substantial (PAS), **moderate (CBE-0/30)**, or **minimal (AR)** **potential to have an adverse effect** on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product

Common Post-Approval Changes

- Manufacturing Sites
- Manufacturing Process & Equipment
- Specifications (Tests, Acceptance Criteria)
- Container Closure System
- Components and Composition (Formulation)
- Miscellaneous
  - Change to an approved stability protocol
  - Change in expiration dating period

Multiple changes may be proposed in the same supplement

Most restrictive reporting category will apply

SUPAC: Scale-Up and Post-Approval Changes

1. SUPAC-IR: Immediate Release Solid Oral Dosage Forms (1995)
2. SUPAC-IR Q&A (1997)
3. SUPAC-SS: Nonsterile Semisolid Dosage Forms (1997)
4. SUPAC-MR: Modified Release Solid Oral Dosage Forms (1997)
5. SUPAC: Manufacturing Equipment Addendum (2014)

- SUPAC guidance defines
  - levels of change & reporting category
  - recommended supporting documentation for each level of change
    - chemistry, manufacturing, and controls (CMC) tests
    - in vitro release or dissolution tests and/or in vivo bioequivalence tests

SUPAC: Focus

- Applies to solid and semi-solid dosage forms (IR/MR tablets/capsules and creams/ointments/gels/lotions)

- Focus on:
  - Components & Composition (excipients, levels)
  - Manufacturing Site & Process (equipment, process parameters)
  - Batch Size

SUPAC: Limitations

- Applicable to conventional dosage forms only
- Limited relevance for today's complex products such as:
  - Complex injectables (extended-release injectables - suspensions, emulsions, liposomes)
  - Peptides
  - Transdermal Delivery Systems (TDS)
  - Inhalation (MDI, DPI)
  - Drug-device combination products (e.g., prefilled autoinjector)

Regulatory Landscape

- FDA's SUPAC guidances not updated since mid-1990s
- Newer frameworks:
  - Comparability Protocols (CMC Post-Approval Change Management Protocol (PACMP))
  - ICH Q12: Lifecycle Management (globally harmonized)
  - Shift towards: risk-based, science-driven change control
- Risk-based Lifecycle Management

ICH Q12

- **Framework Purpose**: It establishes a predictable and efficient framework for managing postapproval CMC changes to benefit patients, industry, and regulatory authorities.
- **Enhanced Knowledge Application**: Increased product and process knowledge enables more precise understanding of which postapproval changes require regulatory submission and appropriate risk categorization.
- **Reduced Regulatory Burden**: Effective implementation allows firms to manage certain CMC changes within their Pharmaceutical Quality System (PQS) with less regulatory oversight, potentially reducing submission requirements.

☞ **Flexibility Requirements**: The operational and regulatory flexibility depends on the existing regulatory framework, **extent of product/process understanding**, quality risk management principles, and an effective PQS implementation.

ICH Q12 Foundational Concepts & ICH Q-Series Integration

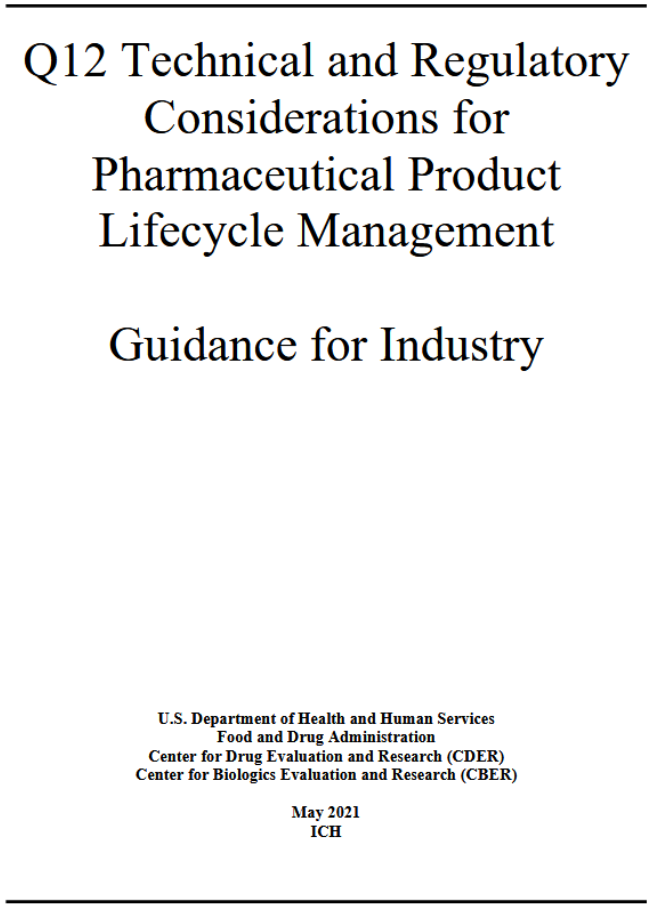
- ICH Q12 is not a standalone guideline. It relies on the principles established in previous ICH guidelines:
  - **ICH Q8 (Pharmaceutical Development):** Defines Quality by Design (QbD) and Design Space.
  - **ICH Q9 (Quality Risk Management):** Establishes a systematic approach to risk assessment.
  - **ICH Q10 (Pharmaceutical Quality System):** Describes the management system for achieving product quality.
  - **ICH Q11 (Development and Manufacture of Drug Substances):** Focuses on process and product knowledge.

The Role of Q12

- Provides the regulatory tools to enable a **science- and risk-based approach to post-approval changes**

- ICH Q12 provides a framework to determine the appropriate reporting category based on the potential risk to product quality
  - Leverages enhanced product and process understanding

3 ICH Q12 Guidance Documents

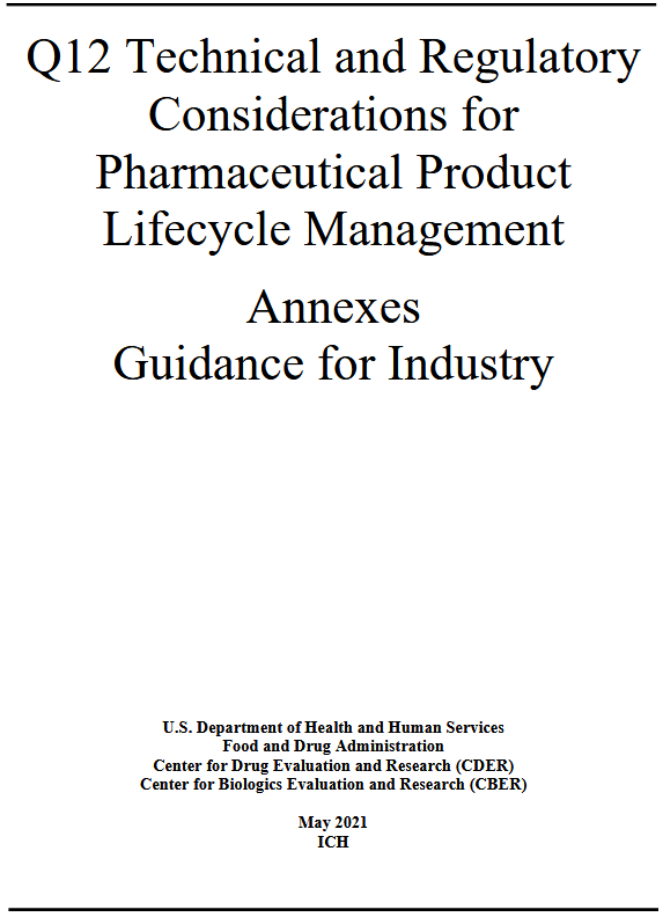


Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2021
ICH



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Annexes
Guidance for Industry

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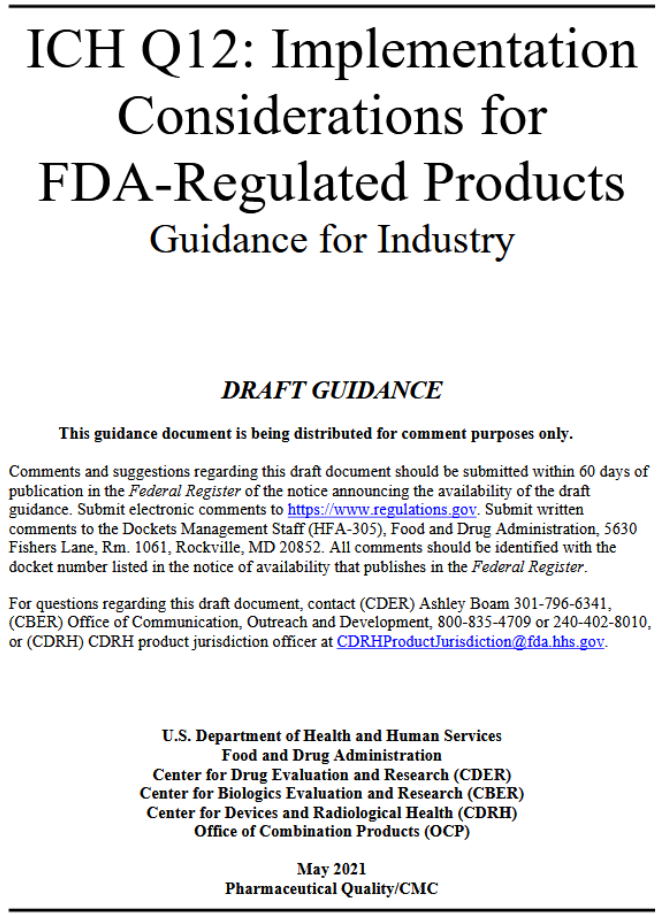


ICH Q12: Implementation Considerations for FDA-Regulated Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ashley Boam 301-796-6341, (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010, or (CDRH) CDRH product jurisdiction officer at CDRHProductJurisdiction@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Combination Products (OCP)

May 2021
Pharmaceutical Quality/CMC

The three ICH Q12 guidance documents collectively establish a comprehensive framework for pharmaceutical product lifecycle management that enables science- and risk-based post-approval changes for assuring product quality throughout the commercial lifecycle.

Key Concepts of ICH Q12

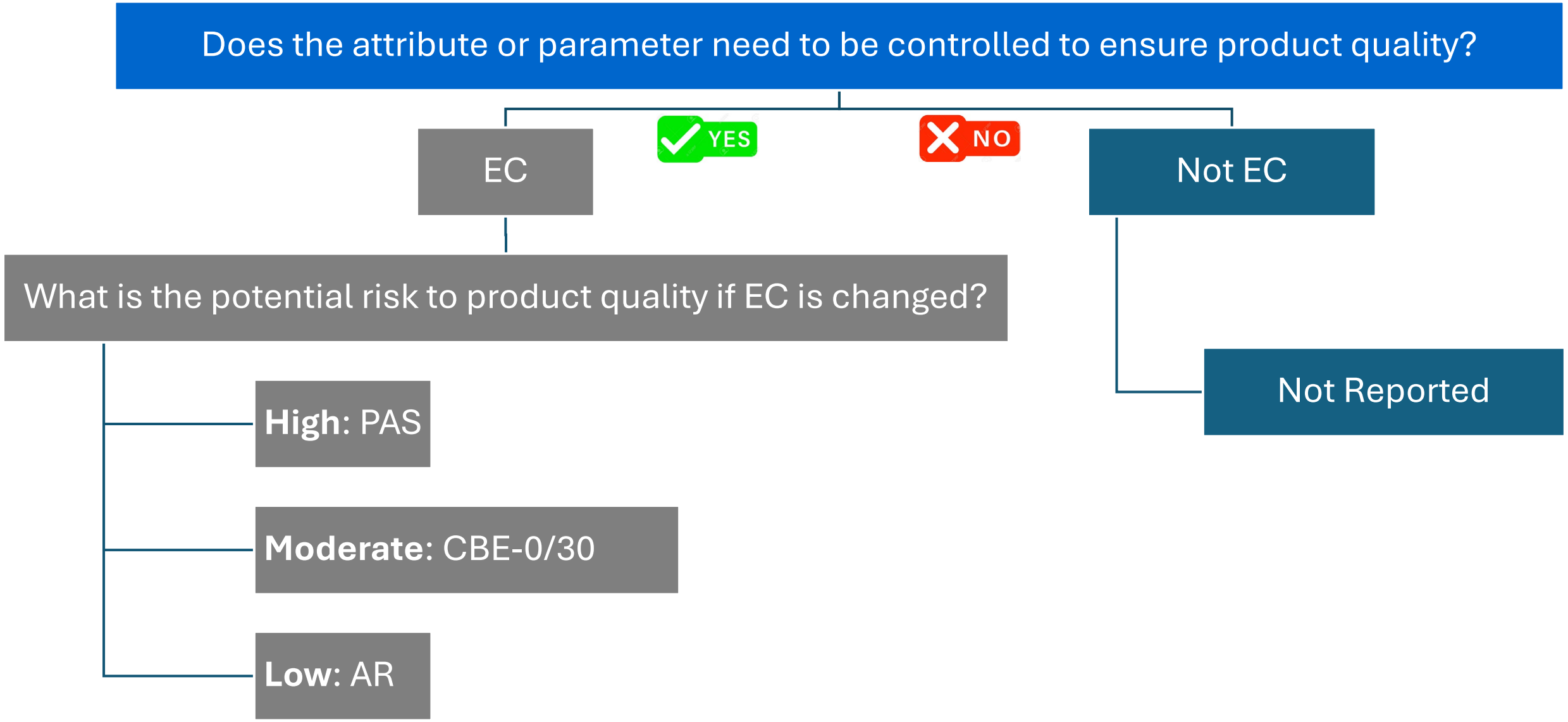
- Established Conditions (ECs)
- Post-Approval Change Management Protocol (PACMP)
- Pharmaceutical Quality System (PQS)
- Product Lifecycle Management (PLCM) Document

Established Condition (EC)

- Legally binding information in the application that is considered necessary to assure product quality.
- Any change to an EC requires a regulatory submission.
- ECs are distinct from "supporting information," which does not require a submission if changed.
- The goal is to proactively define a justified set of ECs (science- and risk-based, increased product/process knowledge) – allows for increased flexibility

Proposing ECs is Optional: If an applicant **does not** propose ECs, ECs are those FDA would **typically** consider ECs under existing regs/guidances (e.g., 21 CFR 314.70, SUPAC, Changes guidance).

Identification of ECs and Associated Reporting Categories



ICH Q12: Risk-Based Change Management

- **Regulatory Flexibility** - The extent of ECs and the associated reporting category will depend on the firm's design & development approach, the depth of product and process knowledge including development & experience accumulated throughout the product lifecycle, and understanding the potential risk to product quality

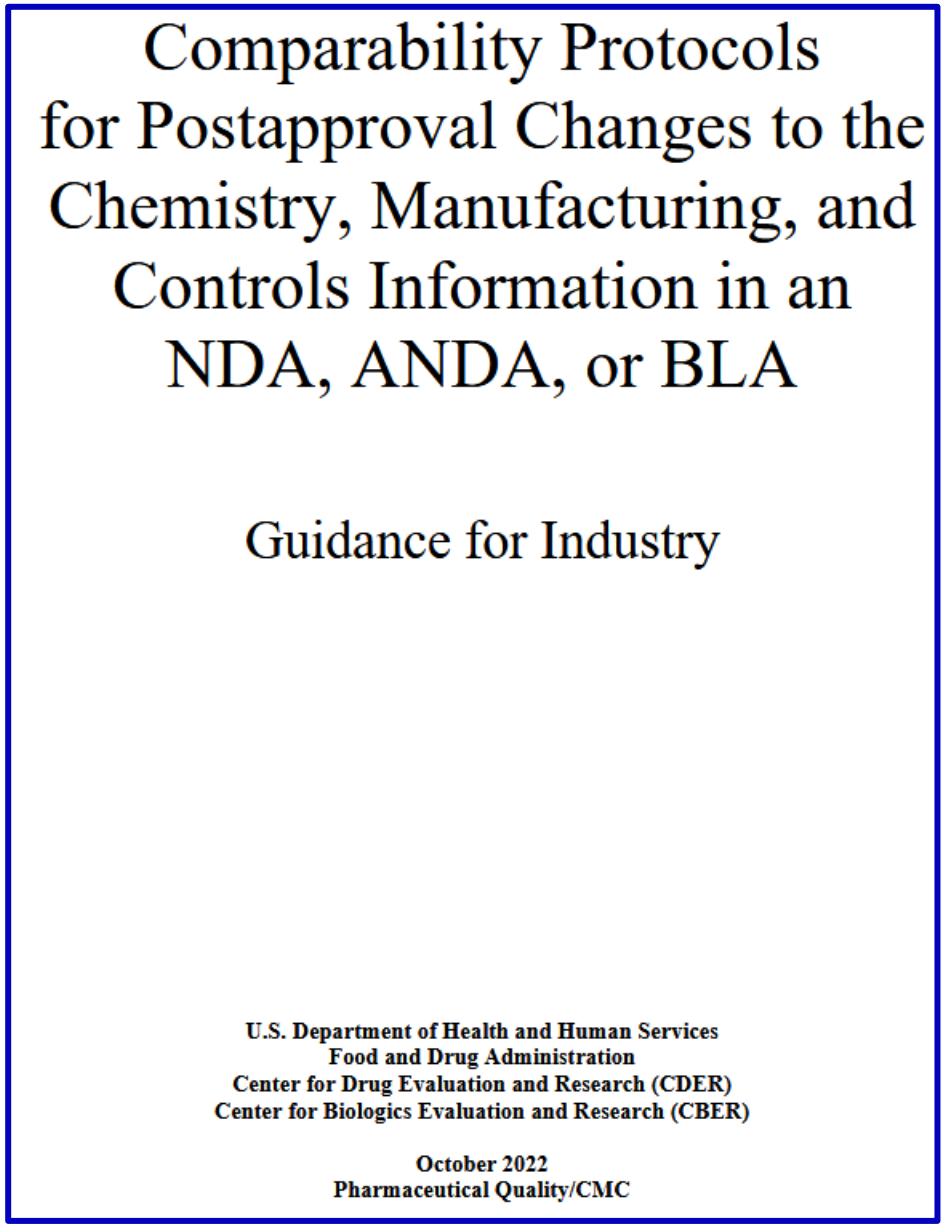
- **Supporting Justification** - Appropriate and sufficient justification should be provided in support of the identification of ECs, the proposed reporting categories for ECs, and those aspects that are not ECs.

Post-Approval Change Management Protocol (PACMP)

- Comparability Protocol (CP) – submitted as a PAS in eCTD section 3.2.R.
- Written plan/protocol that describes tests, studies, and acceptance criteria to demonstrate the absence of an adverse effect from specified changes.
- CP may propose a reduced reporting category (e.g., CBE-0/30 or AR) to report the implementation of the proposed change(s).
- CP requires FDA approval before the change is executed by the applicant.

An approved CP provides an **agreed-upon plan** to implement the specific change + supporting data, and therefore provides **predictability** for applicants

Comparability Protocol – FDA Guidance



Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA

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October 2022
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Pharmaceutical Quality System (PQS)

- A robust PQS is a mandatory enabler for ICH Q12 implementation.
- All changes, regardless of reporting category, must be managed and documented within the firm's PQS.
- A strong PQS allows for greater flexibility and "internal" management of certain changes with no regulatory reporting required.

Product Lifecycle Management (PLCM) Document

- It serves as a central repository for key lifecycle information, providing transparency for both the applicants and regulators.
- What it contains:
  - A list of all approved ECs and associated reporting categories for changes to ECs
  - Any approved Comparability Protocols (that is, PACMPs)
  - All post-approval CMC commitments and their status
- PLCM document maintained throughout the lifecycle in eCTD section 3.2.R, while scientific justification resides in Module 3
  - Justification - include rationale for EC selection and reporting categories (if applicable)

Required only if ECs are proposed

SUPAC vs ICH Q12

SUPAC (1990s)

- Dosage form specific
- Prescriptive reporting categories
- Recommended documentation
- Narrow scope with specific changes

ICH Q12 (2019+)

- Applies across modalities
- Risk-based categorization*
- CP (PACMP)
- Broader scope beyond SUPAC

* ECs are clearly defined; changes to non-ECs can be managed under PQS

Key Takeaways

SUPAC was revolutionary but limited to 90s-era dosage forms

Today's ever-evolving complex products call for alternate frameworks

Shift from "change = CBE or PAS" to risk-based and enhanced knowledge-based lifecycle management with ICH Q12 integration

Use **science-based and risk-based approach, plus guidance**, to assess product quality impact as a result of the proposed change(s)


Thank You!