

ICH Q12

Overview and Application to Generic Drugs

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Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



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Drugs are no different.

A close-up photograph of a person's hand holding an orange plastic pill bottle, pouring three white, oval-shaped pills into their palm. The background is blurred, showing the person's arm and clothing.

**Patients expect safe and effective
medicine with every dose they take.**

A close-up photograph of a person's hands. The left hand is holding an orange plastic pill bottle, tilted to pour three white, oval-shaped pills into the palm of the right hand. The background is blurred, focusing attention on the action of dispensing the medication.

Pharmaceutical quality is
assuring *every* dose is safe and
effective, free of contamination
and defects.



It is what gives patients confidence
in their *next* dose of medicine.

Learning Objectives

- Understand post-approval change management and the role of the ICH Q12 guideline
- Identify the key tools and enablers described in Q12
- Understand the concept of “established conditions”

Regulatory Background

- CDER regulations at 21 CFR 314.70 state:
 - “an applicant must notify FDA about each change in **each condition established** in an approved application beyond the variations already provided for in an application” (i.e., an NDA or ANDA)
 - Similar language exists in 21 CFR 601.12 for BLAs
- Historically, confusion about what is “each condition established,” has led to:
 - Unreported changes or supplements at the wrong categorization level
 - Confusion over which changes are to be reported vs. to be managed under Pharmaceutical Quality System (PQS) only

Addressing a Barrier to Continuous Improvement and Innovation

Global environment where each change requires approval from 100+ regulators



Uncertainty in timelines and data expectations



Management of multiple lines of inventory, increased costs, fewer changes to improve processes

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

ICH Q12 Objectives

- Objectives* include:
 - ...**Harmonize change management**...in a more transparent and efficient manner...across ICH regions
 - ...Facilitate **risk-based regulatory oversight**...
 - Emphasize...**control strategy** as a key component of the...dossier
 - Support **continual improvement** and facilitate introduction of **innovation**
 - Enhance use of regulatory tools for **prospective change management**...enabling **strategic management of post-approval changes**...

*From the ICH Q12 concept paper

Key Principles

- Provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner
- Presents a number of harmonised regulatory tools and enablers with associated guiding principles
- Demonstrates how increased product and process knowledge can contribute to a more precise and accurate understanding of which post-approval changes require regulatory submission
- Emphasizes the importance of an effective pharmaceutical quality systems in the management of changes during the product lifecycle

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

Change Management Tools in Q12

- Established Conditions
- Post-approval Change Management Protocols
- Product Lifecycle Management Document
- Structured Approaches for Frequent CMC Post-Approval Changes



Established Conditions (ECs)

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

Established Conditions - 2

- The extent (number and how narrowly defined) of ECs will vary based on a number of factors, including:
 - product and process understanding
 - characterization
 - the firm's development approach, and
 - potential risk to product quality
- Product and process understanding can come from development studies, platform knowledge, and/or commercial experience



Established Conditions - 3

- After identifying ECs, applicant may propose a reporting category for post-approval changes to the EC with justification
 - Follow existing regulations and guidance (e.g., SUPAC guidances; Changes to an Approved NDA or ANDA) or
 - Propose alternate reporting category (e.g., CBE-30 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 - 4

- ECs offer an opportunity to gain clarity regarding:
 - Which elements of the control strategy must be reported if changed
 - How much flexibility exists within an identified EC (e.g., if the EC is blend speed of 10-20 rpm, only changes to include speeds <10 rpm or >20 rpm need be reported)
 - How to report changes to ECs
- Could also be applied to device constituent parts of a drug-device or biologic-device combination products



Post-Approval Change Management Protocols (PACMP)*

- Provide predictability and transparency in terms of the requirements and studies needed to implement a 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 submission (PAS)

*Referred to as a “Comparability Protocol” in the US

Post-Approval Change Management Protocols - 2

Step 1

- Submission of a written protocol
 - proposed change(s) with rationale(s)
 - risk management activities
 - proposed studies and acceptance criteria to assess the impact of the change(s)
 - other conditions to be met
 - the proposed reporting category
 - any other supportive information
- Approved by regulator in advance of execution

Step 2

- Carry out tests and studies outlined in the protocol
- If results/data generated meet the acceptance criteria in the protocol 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 Document (PLCM)

- Serves as a central repository for ECs, reporting categories for changes to approved ECs, PACMPs (where submitted), and post-approval CMC commitments
- Facilitates and encourages a more strategic approach to lifecycle management
- Enables transparency and facilitates continuous improvement
- Submit with original application or as supplement/variation (marketed products)
 - In the US, submit in section 3.2R
- Submit updated PLCM document in post-approval submissions for CMC changes

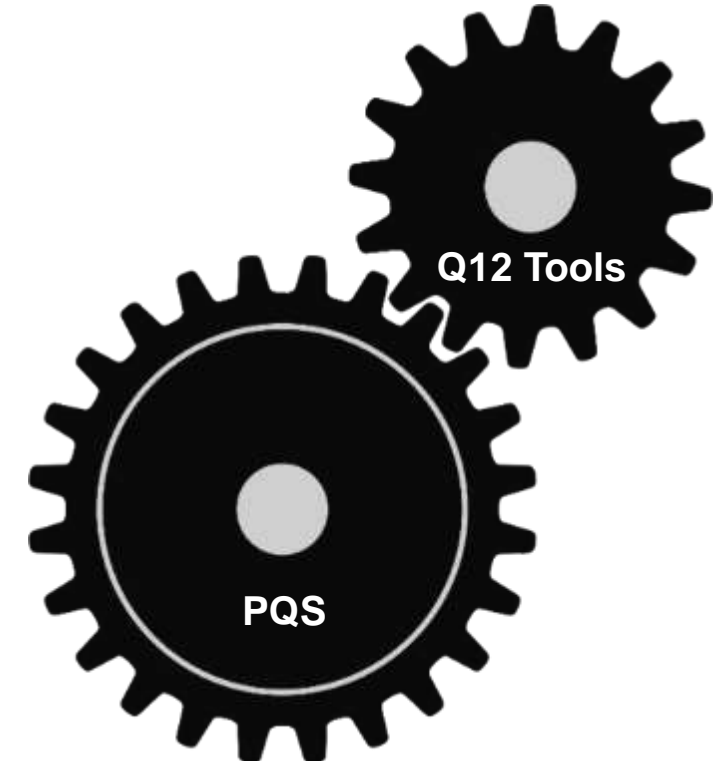
Structured Approaches to Frequent CMC Post-Approval Changes

- For products whose application did not involve identification of ECs and reporting categories
- A simplified approach to accomplish certain CMC changes through the use of immediate or other post-implementation notification
- In one example of this approach, specific criteria are defined for changes to analytical procedures used to test marketed products
- If this approach is followed and all criteria are met, the analytical procedure change can be made with immediate or other post-implementation notification, as appropriate, to the regulator
- Intent of this approach is to incentivize structured implementation of at least equivalent analytical procedures that are fit for purpose



Change Management is Key to an Effective PQS

- Effective PQS includes change management, enabled by knowledge management, and management review
- ICH Q10 describes principles for effective management of CMC changes under the PQS
- ICH Q12 elaborates on the principles of change management and management review



How Can I Use ICH Q12 Tools?

- ICH Q12 will be published as a final FDA guidance for implementation
- PACMPs (comparability protocols) can be submitted at any time (see existing [draft guidance](#), April 2016)
- FDA intends to publish a draft implementation guidance with more details on using ICH Q12 in the US
- ICH Q12 training materials now in development for worldwide use

Conclusions

- ICH Q12 offers multiple tools to gain clarity and regulatory flexibility regarding which CMC changes require reporting and the reporting mechanism for those that do
 - As product and process knowledge is gained, applicants can gain additional flexibility to make changes under the PQS without the need for a regulatory submission
- Maintaining an effective PQS, especially with respect to change management, is key to successful use of these tools

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Challenge Question

- Is this statement true or false?

“Under ICH Q12, Established Conditions (ECs) can be proposed by the applicant only as part of an original application.”



Challenge Question

- Which of the following is not a Q12 tool or enabler?
 - Product Lifecycle Management Document
 - Post-approval Change Management Protocol
 - Manufacturing Site Certification
 - Established Conditions





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