ICH Q12 Implementation and Submission Assessment for Biotechnology Products – FDA Experience

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What is Pharmaceutical Quality?

- A quality product of any kind consistently meets the expectations of the user
  - Drugs are no different
- Patients expect safe and effective medicine with every dose they take
- 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




Disclaimer

The experience shared in this presentation are those of the presenter and should not be used in place of regulations, published FDA guidance or discussion with the Agency.

Outline

- Overview of ICH Q12 implementation at FDA
- Current experience with ICH Q12 submission assessment for biotechnology products
- Lessons learned and challenges

Established Conditions (ECs) are Defined in the US Regulations

The term was coined in CFR referring to legally binding information considered necessary to assure product quality. Any change to ECs must be reported.

- **NDA:** *21CFR314.70(a)(1)(i) "the applicant must notify FDA about each change in **each condition established** in an approved NDA beyond variations already provided for in the NDA".*
- **ANDA:** *21CFR314.97(a) "The applicant must comply with the requirements of 314.70 and 314.71 regarding the submission of supplemental ANDAs and other changes to an approved ANDA".*
- **BLA:** *21CFR601.12 a) General. (1) As provided by this section, an applicant must inform the Food and Drug Administration (FDA) (see mailing addresses in § 600.2 of this chapter) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling **established** in the approved license application(s).*

ICH Q12: Purpose and Goals

- ICH Q12 foundation is built on strong scientific development (ICH Q8, Q11), good risk management (ICH Q9) and effective quality systems (ICH Q10) throughout product lifecycle
- ICH Q12 provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner
- Facilitate risk-based regulatory oversight
- Improve transparency and efficiency for industry and regulators with respect to post-approval CMC change management

ICH Q12 – FDA Implementation

- FDA adoption of ICH Q12: **May 2021**
  - Replace 2015 draft guidance - Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products
- FDA Draft Guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* published in **May 2021**
  - Clarify how to implement Q12 within FDA's regulatory system
  - Instruct applicants to identify in the cover letter and in Module 3.2R when ECs are specified.
- CDER MAPP on implementation of ICH Q12 is in progress
- Training executed (2018-present)
  - Successful Q12 implementation hinges on regulator and industry readiness
  - Developed and initiated a multi-phase strategy to build awareness and capability within FDA staff

Common Elements in Product Lifecycle Management (PLCM) document		Report post-approval changes to these elements	
Established Conditions (ECs)		Per regulation/guidance and/or Alternative approach per agreement with Health Authority	➢ Reporting categories for Post-approval changes to ECs, if proposed, are evaluated based on an understanding of the risk for "one change at a time" and at the time of submission. ➢ Post-approval changes to PLCM are reported commensurate with the risk for changes made to each element of the PLCM document. *PQS: Pharmaceutical Quality System * MAH: Market Authorization Holder
Supportive Information	Supportive information/data	Managed by MAH's PQS (no reporting necessary; changes assessed during inspection)	
	Commitments/ Agreements	Per regulation/guidance	
Post-Approval Change Management Protocols (PACMPs)		Per regulation/guidance	

What ICH Q12 Does not Do

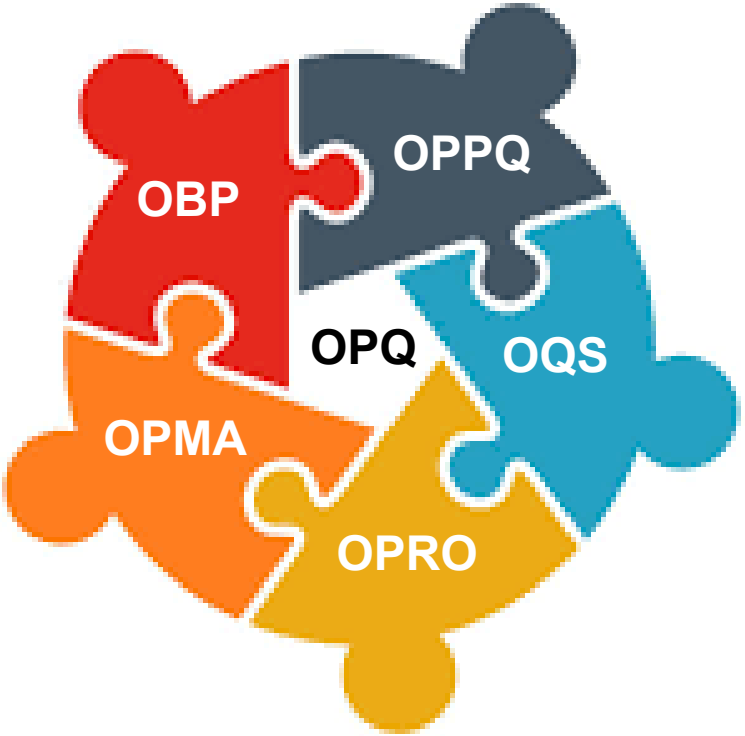
- Q12 implementation will NOT reduce the amount of CMC information that is expected to be provided in the submission

- Q12 implementation will NOT change PQS expectations for managing changes

- Q12 implementation does NOT change CGMP expectations

Current Experience with ICH Q12 Submission Assessment for Biotechnology Products

Multidisciplinary Assessment



Submission Receipt

Q12 component identification

Discipline notification
Assessor request

Team Assembly
Initiation of assessment

ICH Q12 Submissions – Biotechnology Products

- Pilot: 5 supplements
- Post Pilot and guidance implementation:
  - original BLAs
  - BLA supplements
  - meeting requests
- Some approvals, some withdrawn for variety of reasons

Current Experience

- ECs are proposed in stand-alone submissions or with other CMC changes.

- Applicants take different approaches for EC identification in their submissions
  - Designation of “EC sections”
  - Parameter-by-parameter assessment of ECs
  - ICH Q12 principles may be proposed for some (e.g., only specified for a single unit operation or method) or all M3 sections
  - Applicant’s proposals are often more complex than examples in Q12 annexes

Current Experience

- After identifying ECs, Applicants take different approaches for proposing reporting categories to manage post-approval changes to ECs
  - Propose ECs without specifying reporting categories by stating that changes will be reported following existing regulation and guidance
  - Explicitly specify reporting categories (PAS, CBE, etc.) that follow existing regulation and guidance: for transparency purpose
  - Propose alternate reporting categories with additional justifications/conditions
- Criticality assessments are more consequential when applicants propose to directly link them to reporting categories
- More effort upfront from industry and regulators to specify reporting categories and ensure shared risk understanding

Lessons Learned and Future Considerations

Lessons Learned

- As for all applications, the quality of submissions matters greatly for an assessment: clear, accurate, consistent, reader-friendly
  - Inclusion of a clear statement to identify Q12 submissions (including post-approval changes made to the ECs/PLCM) in the Cover Letter is crucial to ensure proper assessor teams are notified for timely review (described in FDA implementation guidance).
  - When making post-approval changes to approved ECs/PLCM, it would be helpful to provide clear indications of what is changed (e.g., by using highlighting features) for an efficient assessment.
  - The description of ECs needs to be sufficiently detailed and clear to enable a good understanding.
  - Justifications should be provided for “non-ECs” that are typically included as ECs, as well as for ECs.
  - Cross-reference/hyper-link to avoid duplicating identical content is highly recommended.

Lessons Learned

- Extent of regulatory relief from the applying ICH Q12 principles depends on extent of understanding of the product, the process, and the risk (and how effectively that understanding is communicated*).*
  - Product and process knowledge
  - Product and process characterization
  - The firm's development approach
  - Comprehensive understanding of the impact and potential risk to product quality

- A shared understanding of applicant's intent, scope, and nomenclature is essential for an evaluation, as applicants use diverse approaches for criticality assessment, EC identification, and structure for Q12 submissions.

Challenges and Future Considerations

- ECs may not have been an explicit consideration at the time of process development and regulatory approval.
- Identifying and evaluating EC proposals for products developed pre-ICH Q8 (i.e., without formal criticality assessments for process parameters).
- Capturing and communicating the vast of manufacturing experience/knowledge and evaluating what is the risk beyond data in support of EC and reporting category proposals.
- Regional expectations/requirements may impact how Q12 applications are structured.
- The long-term impact of utilization of ICH Q12 principles in regulatory submissions is yet to be evaluated as more experiences gained.

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