

# Impacts of International Council for Harmonization Q12 (ICH Q12) in Lifecycle Management of the Post-Approval Changes

Pavithra G.M., Nagalakshmi S.\*

*Department of Pharmaceutics, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research (DU), Chennai, Tamil Nadu, India*

*Received: 26th February, 2022; Revised: 20th March, 2022; Accepted: 21st April, 2022; Available Online: 25th June, 2022*

---

## ABSTRACT

The complexity of the current pharma market needs the most effective drug product development and production. Product lifecycle management (PLM) can produce pharmaceutical manufacturing more efficiently and with less risk. The life cycle approach became adopted in numerous stages within the pharmaceutical company, considering its inception. This International Council for Harmonisation (ICH) Q12 guideline intends to enhance the supervision of the post-approval chemistry, manufacturing, and control changes most reliably and effectively both for pharmaceutical industries and regulatory authorities. In this review article, we discuss the benefits and challenges related to this enhanced framework. The new ICH Q12 guideline “Technical and regulatory considerations for pharmaceutical product lifecycle management” assist the management of post-approval chemistry, manufacturing, and controls (CMC) changes in an effective way with regard to the pharmaceutical companies.

**Keywords:** CMC, Established Conditions, ICH Q12, Lifecycle Management, Post approval changes.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.2.80

**How to cite this article:** Pavithra GM, Nagalakshmi S. Impacts of International Council for Harmonization Q12 (ICH Q12) in Lifecycle Management of the Post-Approval Changes. International Journal of Drug Delivery Technology. 2022;12(2):924-928.

**Source of support:** Nil.

**Conflict of interest:** None

---

## INTRODUCTION

International Council for Harmonisation was established in 1990, is an independent organization this brings the pharmaceutical industries, and the regulatory authorities of the United States, Europe, and Japan concurrently<sup>1</sup> for the registration of pharmaceutical products and to ensure the quality, safety, and efficacy of pharmaceuticals.<sup>2</sup> The ICH guidelines are split into four divisions namely quality guidelines, safety guidelines, efficacy guidelines, and multidisciplinary guidelines. Quality guidelines consist of crucial milestones like the performance of stability studies, describing applicable threshold value for impurities analysis, and a greater malleable approach to pharmaceutical product quality based on good manufacturing practice (GMP) risk management.<sup>3</sup>

The ICH Q12 was initiated to enhance the pharmaceutical industry's performance.<sup>4</sup> ICH Q12 intends to encourage innovation and continuous advancement within the pharmaceutical segment and improve quality assurance and dependable supply of the pharmaceutical product.<sup>5</sup> The ICH Q12 presents a context to assist the Control of post-approval Chemistry, Manufacturing, and Controls (CMC) modifications proficiently throughout the product lifecycle.<sup>6</sup> The PLM is defined as the process of controlling the complete lifecycle

of a pharmaceutical product from its conception, design, realization, use, and disposal of products.<sup>7</sup>

## MAIN TEXT

### Categorization of Post-approval CMC Changes

A well-distinguished, risk-based class of regulatory conversation requisites is prominent to the effective usage of regulatory agencies.<sup>8</sup> CMC modifications may be divergent from lowest to highest possibility hazards regarding pharmaceutical product quality, safety, and efficacy.

### Different Categories of Changes

Prior approval: sufficient risk changes need regulatory authority review and approval before implementation.

Notification: prior approval is not required for moderate- to low-risk changes and typically demands much less evidence to assist the change. This kind of change is conveying to the regulatory authority like a proper notification that occurs within a decided time frame earlier than or after implementation, as specified by regional requisites.<sup>9</sup>

### Established Conditions (ECs)

Established conditions (ECs) are statutory information required to guarantee the quality of drug products. As a result, any modifications to the established conditions require

---

\*Author for Correspondence: nagalakshimipharm@gmail.com

a submission to the regulatory agency. ECs as the information about the product, process for manufacturing, equipment, premises, and facilities, and factors of the related control strategies as described in an application.<sup>10</sup>

**ECs during Submission are Either Implicit or Explicit**

Implicit ECs are factors that are not especially proposed with the aid of using the Marketing Authorisation Holder; however, these are adapted from the guidance document and regional rules or regulations associated with post-approval changes.

Explicit ECs are specially identified and suggested using the Marketing Authorisation Holder and their intended reporting class in the context of regulatory submission.<sup>11</sup>

**Identification of ECs**

Various approaches are used to describe the established conditions and must be justifiable by the Marketing Authorisation Holder (MAH) and authorized by the regulatory authorities. The range of ECs can differ in accordance with the Pharmaceutical company’s development approach, process and product understanding, and the possible risk to the drug product quality. Insufficient grounds must be submitted concerning the identity of ECs, the intended reporting classification for established conditions.<sup>12</sup>

*Identification of Established Conditions for the Manufacturing Process*

Various approaches are often used individually or jointly to identify the ECs for production processes; those encompass, however, are not appropriate for the following:

- *Parameter-based approaches:* A minimal approach, in the presence of insufficient knowledge on the connection among the inputs and consequent quality characteristics, will encompass a huge range of inputs (e.g., operation variables and material characteristics) together with outputs (e.g., In-process tests).

An enhanced approach, in the presence of a greater understanding of the interaction among inputs and drug product quality attributes as well as a consistent control strategy, may result in the identification of the ECs. These are a major focus on the essential input parameters together with outputs, as applicable.

- *Performance-based approach:* Established conditions might be mainly concerned with the control of process outputs (e.g., characteristics, responses, and measurements) instead of the process inputs (e.g., operation variables and material characteristics). This is often confirmed by intelligence acquired from improved procedures and a more suitable control strategy (e.g., models, Process Analytical Technology).

*Examples of Variations for a Drug Substance*

- Changes in raw material quantity from 200 kg to 235kg.
- The low concentration of NaOH resulted in a higher quantity loaded into the reaction.
- A smaller quantity of class 2 solvent was used from 2200 kg to 2000 kg.

- Based on the process understanding stirring time is modified from 3 hours to not less than 1 hour.<sup>13</sup>

**Identification of ECs for Analytical Procedures**

ECs associated with analytical procedures must encompass factors that guarantee the process’s overall performance. The extent of established conditions and their reporting classes might differ on the basis of the comprehension of the connection among process variables, the method complication, overall performance, and controlling tactics. The reason to assist the identity of ECs and equivalent reporting classes for modifications to the ECs primarily based on the risk management must be submitted (Figure 1).

Various approaches are often used to become aware of established conditions for analytical methods, as an illustration, analytical technique, and development processes; such methods encompass, however, are unlimited to the following:

- When greater constrained development research were performed, this might lead to a restricted operating window to assure analytical process performance. In these circumstances, ECs can be broader with tight and fixed conditions.
- Greater understanding may result in a broader operating window that guarantees an analytical method’s overall performance, in which ECs may be decreased and concerned with the method’s overall performance.

Based on the ICH Q12 Guideline, the Marketing Authorization Application (MAA) must provide a complete explanation of analytical methods in the submission (Figure 1).

**Identification of Established Condition**

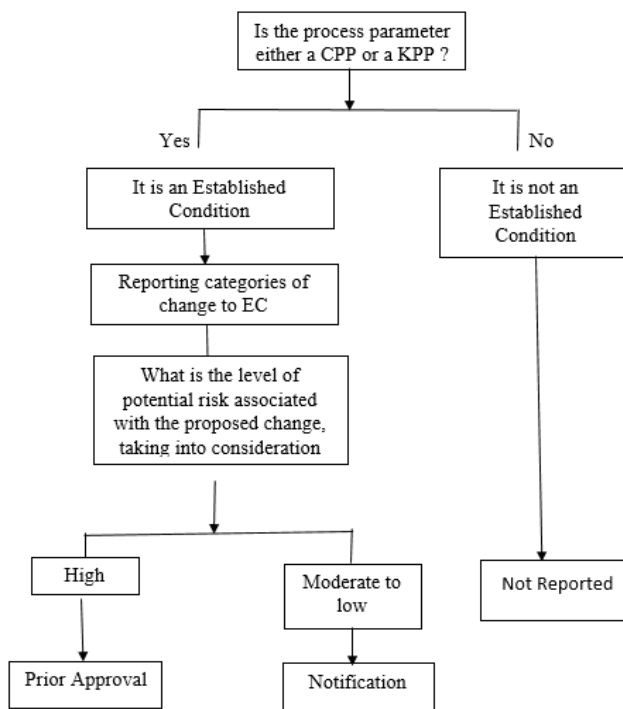


Figure 1: Identification of established condition <sup>14</sup>

A comprehensive overview of the analytical methods in Module 3 is predicted to offer a thorough insight irrespective of the method used to become aware of ECs for analytical and strategy procedures.<sup>15</sup>

**Benefits of ECs**

- Increased openness among a company and with regulatory agencies.
- More attention to the alleviation of serious risk factors.
- Possibilities to utilize the most efficient and effective post-approval change management strategies.
- Greater opportunities to offer supporting details.
- Significant incentive to make investments within the development of their products and their pharmaceutical quality system.
- Facilitating persistent development and looking for possibilities for technological advancements.<sup>16</sup>

**Post-Approval Change Management Protocol (PACMP)**

A PACMP is a regulatory tool that gives transparency and predictability regarding the necessities and research required to execute a modification as an already authorized protocol offers an agreement between the Marketing Authorization Holder and the regulatory agency. The protocol outlines the CMC change an applicant purports to implement throughout the marketing phase of the drug product, in what way the alteration might be developed and examined, consisting of an evaluation of the effect of the suggested change, and the proposed reporting class according to the regulations.

The PACMP can be submitted either as part of the initial MAA or as a stand-alone submission. The PACMP needs approval from the regulatory agency, and the requirements and conditions are described in the protocol that needs to be fulfilled to implement the changes.<sup>17</sup>

**PACMPs Elements**

- Explanation and the intent for the particular change.
- Additional information about the changes.
- Specific assessment, research, acceptance criteria, and analytical methods.
- Conversation with regard to the suitability of the approved controlling strategy.
- Any different requirements to be fulfilled.
- Suggested reporting category for step 2 of the application process.
- Confirm that the in-progress verification could be conducted within the PQS.<sup>18</sup>

**Types of PACMPs**

There are distinct types of PACMPs

- One or more changes related to a one-product – A PACMP can be prepared be utilized frequently to carry out a specific kind of CMC changes throughout the lifecycle of the particular drug product. If the protocol outlines numerous changes for a specific product, a rationale must be introduced to demonstrate how the changes are connected (Figure 2).

- *Broader protocols:* The hazards of the intended changes must be identical to the entire product; other factors need to be taken into consideration based on the approach, for example:

- \* One or several changes to be executed throughout the different products (e.g., changes in the stopper within different drug products that employ a similar container closure system)
- \* One or more changes to be executed throughout the different products and at several sites (e.g., changes in the analytical procedure across several sites, change in the production site across the different products).<sup>20</sup>

**Product Lifecycle Management (PLCM)**

The PLCM document is used to assist the regulatory inspection and evaluation utilizing summarizing the important factors of the product lifecycle strategy and will be retained complete product lifecycle, and any updates in PLCM, the changes are submitted within the post-approval submissions.

The ICH Q12 guideline appendix document offers an obvious and well-established instance of the PLCM document that might be considered for the product.

The US FDA has issued the tabular outlines of risk assessments for recently approved drug products. The product lifecycle management document is presented within the marketing authorization application or with a change defining established conditions and is usually included in CTD Module 3.2.R. Even though cautiously documented plans of PLCM might be perceived as a rise in the administrative workload

**PACMP Process**

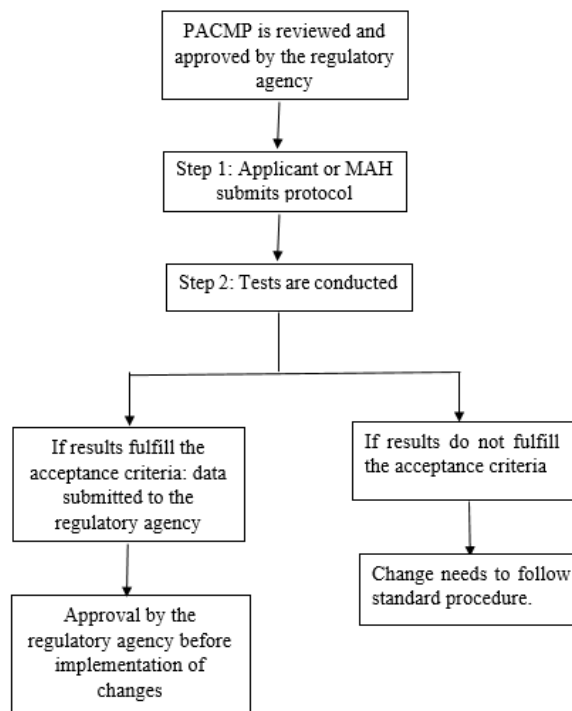


Figure 2: Application process for PACMP<sup>19</sup>

and decline in agility. The document introduces the possibility to control in a well-timed and obvious manner post-approval commitments, which nowadays is a challenge for both Marketing Authorization Holders and regulators.<sup>21</sup>

### Pharmaceutical Quality System (PQS) and Change Management

An efficient pharmaceutical quality system, as introduced in the ICH Q10 guideline and conformity with provincial cGMPs, is the company's main function. Q12 fails to need a specified review to assess the condition of the PQS earlier than the concepts might be utilized. In these circumstances, the PQS finds-fails to comply, it can lead to constraints on the possibility of using the flexibility in that ICH Q12 guideline. According to the fundamental needs of ICH Q10, an effectual change management system is required to implement this ICH Q12 guideline. As explained in the ICH Q10 guideline, it does not at all add to the regulatory needs for a proper knowledge management system.<sup>22</sup>

### Post-Approval Changes for Marketed Products

#### Principles

In order to use this approach, the following must be met:

- The higher-level explanation of the novel and modified approaches must be identical to spectroscopic and chromatographic detection.
- Validation outcomes must reveal that the modified approach is equal to or upwards of the novel approach.
- Test results acquired under the novel and modified approaches must be equal to each other. This needs to be evaluated by two methods: First, the modified approach should provide an identical result. Second, the validation

plan should include explicit conditions that compare with the new and modified approach outcomes.

- System suitability necessities have to be introduced for the modified approach. System suitability guarantees the everyday overall performance of the approach throughout routine use.
- Specification modifications can't be delivered using this mechanism until current regulations permit.
- This method might not be utilized in case toxicological or clinical information is needed as a consequence of the procedure changes (Figure 3).<sup>23</sup>

### CONCLUSION

The ICH Q12 guideline is organized in accordance with the four tools and enablers. This may be applied within the product lifecycle. This guidance promotes the lifecycle management of post-approval Chemistry, Manufacturing, and Control changes most predictably and effectively. PACMP Application will decrease the forthcoming submission efforts and related costs. There is an overall benefit in expenditures and time burdens for pharmaceutical companies and regulators while ensuring that patients gain access to the drug products.<sup>25</sup> ICH Q12 tools and enablers will enhance post-approval change management throughout the lifecycle by offering a risk-based approach to describe the extent of regulatory Control and anticipating forthcoming modifications and their reporting classes.<sup>26</sup> ICH Q12 is meant to expand the utilization of QbD to established drug products and hence supplements the existent QbD guidance that is issued for drug substances and drug products throughout product development, registration, and launch.<sup>27</sup>

### REFERENCES

1. ICH Official web site: ICH [Internet]. Ich.org. [cited 4 November 2020]. Available from: <https://www.ich.org/home.html>
2. Bitragunta S, Suresh P, RamaRao N. Concepts and philosophy of ICH | PharmaTutor [Internet]. Pharmatutor.org. 2020 [cited 4 November 2020]. Available from: <https://www.pharmatutor.org/articles/ich-guidelines-concepts-philosophy>
3. Somvanshi Y, Satbhai P. ICH Guidelines And Main Focus On Stability Guidelines For New Formulation And Dosage Forms. World Journal of Pharmaceutical Research. 2020; 4(10).
4. Witcher M. What Should Pharma Expect When ICH Q12 is Implemented? [Internet]. ISPE | International Society for Pharmaceutical Engineering. 2019 [cited 4 November 2020]. Available from: <https://ispe.org/pharmaceutical-engineering/ispeak/what-should-pharma-expect-when-ich-q12-implemented>
5. Davuluri S. ICH Q12 is here. What Does it Mean for Pharma? [Internet]. Neuland Labs. 2020 [cited 4 November 2020]. Available from: <https://www.neulandlabs.com/blog/2020/02/24/ich-q12-is-here-what-does-it-mean-for-pharma/>
6. ICH Q12 Annexes. [Internet]. Database.ich.org. 2019 [cited 4 November 2020]. Available from: [https://database.ich.org/sites/default/files/Q12\\_Annexes\\_Step4\\_2019\\_1119.pdf](https://database.ich.org/sites/default/files/Q12_Annexes_Step4_2019_1119.pdf)
7. Sethy S, Sameena T, Patil P, Shailaja K. Product Life Cycle Management In Pharmaceuticals: A Review | PharmaTutor [Internet]. Pharmatutor.org. [cited 4 November 2020]. Available

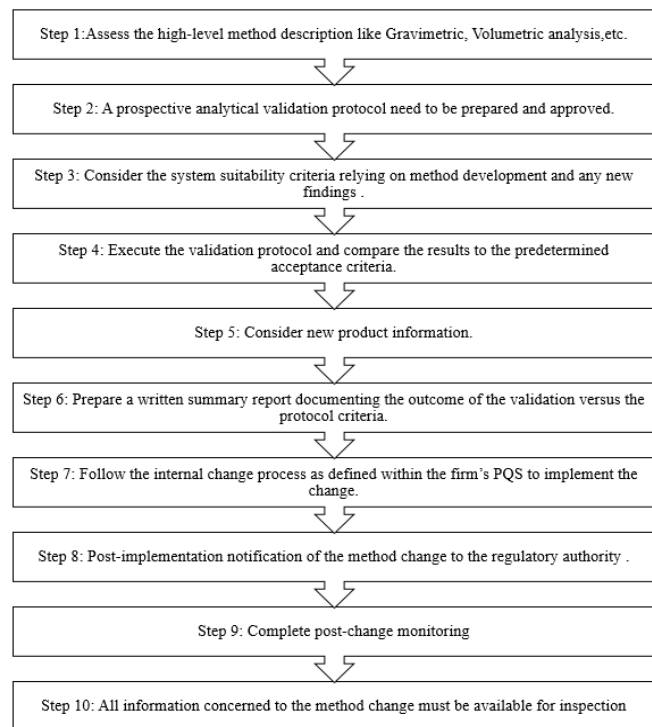


Figure: 3 Steps involved in Post-Approval Changes <sup>24</sup>

- from: <https://www.pharmatutor.org/articles/product-life-cycle-management-in-pharmaceuticals-review>
8. Pharmaceutical Product Lifecycle Management: A Regulatory Consideration [Internet]. Apcerls.com. [cited 4 November 2020]. Available from: <https://www.apcerls.com/wp-content/uploads/2019/03/LCM.pdf>
  9. ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. Presentation presented at; 2020; ICH.
  10. U.S. Department of Health and Human Services Food and Drug Administration. Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products. Hillandale: Food and Drug Administration Center for Drug Evaluation and Research; 2015.
  11. Boam A. ICH Q12 Overview and Applicability to Combination Products. Presentation presented at; 2018.
  12. FDA's Pilot Program for Established Conditions - ECA Academy [Internet]. Gmp-compliance.org. 2019 [cited 4 November 2020]. Available from: <https://www.gmp-compliance.org/gmp-news/fdas-pilot-program-for-established-conditions>
  13. Hirschlerova B. ICH Q12 Lifecycle Management Overview of draft guideline. Presentation presented at; 2018; Europe.
  14. Technical And Regulatory Considerations For Pharmaceutical Product Lifecycle Management Q12 Annexes [Internet]. Database.ich.org. 2019 [cited 4 November 2020]. Available from: [https://database.ich.org/sites/default/files/Q12\\_Annexes\\_Step4\\_2019\\_1119.pdf](https://database.ich.org/sites/default/files/Q12_Annexes_Step4_2019_1119.pdf)
  15. Sakurai K. Established Conditions for manufacturing process – PMDA perspective. Presentation presented at; 2016; Pharmaceuticals and Medical Devices Agency.
  16. Case studies on Established Conditions [Internet]. Ema.europa.eu. 2020 [cited 4 November 2020]. Available from: [https://www.ema.europa.eu/en/documents/presentation/presentation-case-studies-established-conditions\\_en.pdf](https://www.ema.europa.eu/en/documents/presentation/presentation-case-studies-established-conditions_en.pdf)
  17. Ahmed S. Technical And Regulatory Considerations For Pharmaceutical Product Lifecycle: ICH Q12 [Internet]. Contract Pharma. 2018 [cited 4 November 2020]. Available from: [https://www.contractpharma.com/issues/2018-04-01/view\\_fda-watch/technical-and-regulatory-considerations-for-pharmaceutical-product-lifecycle-ich-q12/](https://www.contractpharma.com/issues/2018-04-01/view_fda-watch/technical-and-regulatory-considerations-for-pharmaceutical-product-lifecycle-ich-q12/)
  18. Moorkoth S, Haldar T. Post-approval Change Submission: ICH Q12 Impact Analysis on India and Japan. Indian Journal of Pharmaceutical Sciences. 2020;82(1).
  19. Ramanadham M. ICH Q12: Post Approval Change Management Protocol (PACMP). Presentation presented at; 2019; FDA
  20. Technical And Regulatory Considerations For Pharmaceutical Product Lifecycle Management Q12 Final version [Internet]. Database.ich.org. 2019 [cited 4 November 2020]. Available from: [https://database.ich.org/sites/default/files/Q12\\_Guideline\\_Step4\\_2019\\_1119.pdf](https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf)
  21. Millichamp L, Nageotte S, Bohl G, Robin K. ICH Q12: how it impacts the management of your CMC post-approval changes. Regulatory Rapporteur. 2020;17(8).
  22. Does the International Council for Harmonization Offer a Solution via ICH Q12? [Internet]. 2019 [cited 4 November 2020]. Available from: <http://www.americanpharmaceuticalreview.com/Featured-Articles/358866-Does-the-International-Council-for-Harmonization-Offer-a-Solution-via-ICH-Q12/>
  23. ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management Step 5 [Internet]. Ema.europa.eu. 2020 [cited 4 November 2020]. Available from: [https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q12-technical-regulatory-considerations-pharmaceutical-product-lifecycle-management\\_en-0.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q12-technical-regulatory-considerations-pharmaceutical-product-lifecycle-management_en-0.pdf)
  24. Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management Core Guideline [Internet]. Fda.gov. 2017 [cited 4 November 2020]. Available from: <https://www.fda.gov/media/113483/download>
  25. Sayeed N, Pazhayattil A, Ingram M. ICH Q12: Bringing Regulatory Flexibility To Post-Approval Changes [Internet]. Pharmaceuticalonline.com. 2019 [cited 4 November 2020]. Available from: <https://www.pharmaceuticalonline.com/doc/ich-q-bringing-regulatory-flexibility-to-post-approval-changes-0001>
  26. ICH Q12 Implementation from an Industry Perspective [Internet]. A3P-Pharmaceutical & Biotechnology Industry. 2020 [cited 4 November 2020]. Available from: <https://www.a3p.org/en/ich-q12-implementation/>
  27. Elder D. ICH Q12: Technical and regulatory considerations for pharmaceutical product lifecycle management [Internet]. European Pharmaceutical Review. 2019 [cited 4 November 2020]. Available from: <https://www.europeanpharmaceuticalreview.com/article/103609/ich-q12-technical-and-regulatory-considerations-for-pharmaceutical-product-lifecycle-management/>