ICH Q12: how it impacts the management of your CMC post-approval changes

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ABSTRACT

The new ICH Q12 guideline "Technical and regulatory considerations for pharmaceutical product lifecycle management" was adopted late last year (20 November 2019). The purpose of this guideline is to facilitate the management of post-approval chemistry, manufacturing and controls (CMC) changes in a more predictable and efficient manner both for pharmaceutical companies and competent authorities. In this article we discuss the benefits and challenges associated with this enhanced framework and illustrate these considerations based on real-life examples.

Introduction

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was founded in 1990 with the mission "to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. Now an organisation of 16 members and 32 observers, one of the outputs of the ICH's work in 2019 was the adoption of ICH Q12, Technical and Regulatory considerations for Pharmaceutical Product Lifecycle management, a topic first adopted by the ICH Steering Committee in June 2014.

The ICH Q12 guideline seeks to harmonise technical and regulatory considerations for lifecycle management of pharmaceutical products (drug substances [chemical and biological entities], drug products, and drug-device combinations meeting the definition of a pharmaceutical or biological product), provide the framework from within which post-approval CMC changes are managed in a risk-based and flexible manner and fulfilling opportunities for greater "operational flexibility" post authorisation, thus encouraging innovation. This principle was not considered to have been fully addressed by the current ICH Q8, Q9, Q10 and Q11 guidelines.

The guideline is thus structured according to the tools and enablers found within a product lifecycle, discussing the guiding principles of each one individually.

Established conditions

What are established conditions?

Established conditions (ECs) are a key concept of the guideline, intended to facilitate the management of post-approval CMC changes in a more predictable and efficient manner across the product lifecycle. The guideline defines ECs as "a clear understanding between the marketing authorisation holder (MAH) and regulatory authorities regarding the elements to assure product quality and that involve a regulatory communication, if changed." In other words, they are legally binding information considered necessary to assure product quality.

With ICH Q12, we move from a subjective consensual understanding to more clear definitions. A registration dossier can now be a mixture of those ECs and supportive data, the two of which should be clearly distinguished. As ECs are legally binding, the manufacturer commits on those elements by submitting the registration dossier and when regulatory authorities grant an approval, it is on the basis of the ECs defined in the dossier through a risk-based approach to development. Hence, any changes to the ECs should be communicated to the competent authorities for re-evaluation. On the other hand, supportive data are information provided to help regulatory authorities in understanding the product they are evaluating. Most of the time, they correspond to one-time studies that were performed in order to identify, validate or justify parameters, which will become legally binding. They also are the studies performed to demonstrate that the manufacture and control of the product are well mastered.

A list of the common technical document (CTD) sections that contain ECs is included in Appendix 1 of the guideline to help MAHs understand likely regulatory expectations. As a general rule, all process validation and analytical validation data will be considered as supportive (3.2.S.2.5, 3.2.S.4.3, 3.2.P.3.5, 3.2.P.4.3, 3.2.P.5.3), as will the stability data themselves. However, the conclusion drawn from those data (shelf-life, storage conditions) are ECs. Similarly, 3.2.P.2 is considered supportive to the EC (qualitative and quantitative composition of drug product) specified in 3.2.P.1. Also, ECs should not be confused with the CMC regulatory commitments. With the example of finished product stability section (3.2.P.8), there is a regulatory commitment provided in section 3.2.P.8.2 to complete the stability studies initiated. This section is classified as supportive data, and not EC.

Established conditions and changes reporting categories

For each defined EC, a level of potential risk associated with a proposed change must also be defined, and a reporting category to authorities anticipated. This is in line with the increasingly risk-based trend observed in the regulatory field and is intended to promote innovation by facilitating in advance the evaluation of post-approval changes.

Practical examples provided in the guideline

In line with its objective to provide practical support to both MAHs and competent authorities, the ICH guideline provides specific guidance for ECs related to manufacturing process and analytical procedures, and associated reporting categories, summarised hereafter.

Identification of ECs for the manufacturing process applies to drug

products developed using enhanced or traditional approaches, and should be defined taking into account inputs (eg, process parameters, material attributes) and outputs (that may include in-process controls) that are necessary to assure product quality. An assessment of the criticality of the parameters is performed during pharmaceutical development. All process parameters for which an impact on the product quality is known, likely or cannot be reasonably excluded should be identified as ECs. The guideline provides a decision tree (see Figure 1 below), which clearly defines the link between a parameter and its anticipated reporting category. It can be noted that this guideline should not be used as a means to provide a less detailed manufacturing description. It is expected that a certain level of detail is provided in order to facilitate understanding and evaluation of this section of the CTD Module 3.

Identification of ECs for analytical procedures should result in a comprehensive knowledge on how method parameters impact the method performance, thus allowing a wider operating window, and definition of parameter ranges, rather than set points. As for the manufacturing process description, the use of this guideline should not lead to a less detailed description of analytical procedures in the marketing authorisation application (MAA).

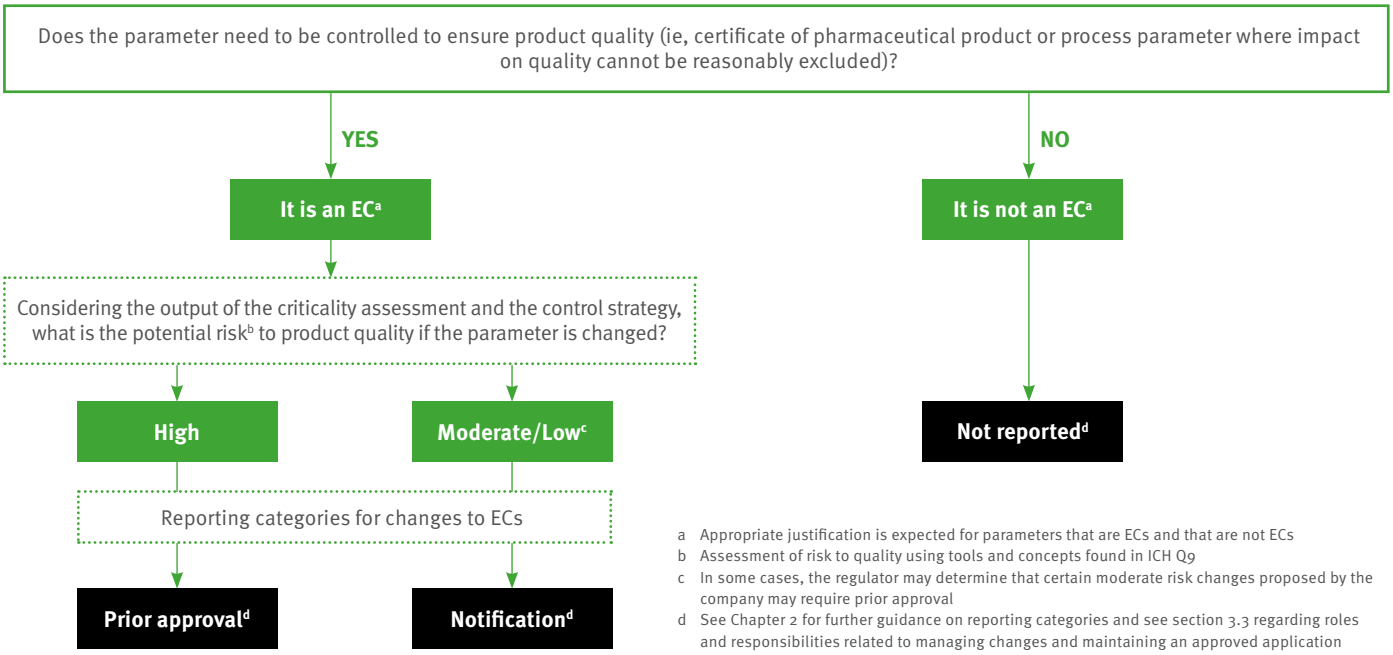
When there is a change in ECs, which might be triggered by experience gained from the manufacturing process, such revisions can be submitted by a "classic" variation. Alternatively, a post-approval change management protocol (PACMP) could be considered.

Post-approval change management protocol

The use of PACMPs is not a new concept as it has already existed in the US since 2003, in the EU since 2010 and a pilot PACMP scheme started in Japan in 2018. However, the revision of the guideline provides more clarity and practical examples of PACMPs. It is a regulatory tool that enables the applicant to submit the protocol of a planned CMC variation to competent authorities for review proactively. Following approval of the protocol, the studies are conducted, and the CMC change can be implemented if the conditions and acceptance criteria outlined in the protocol are met.

FIGURE 1

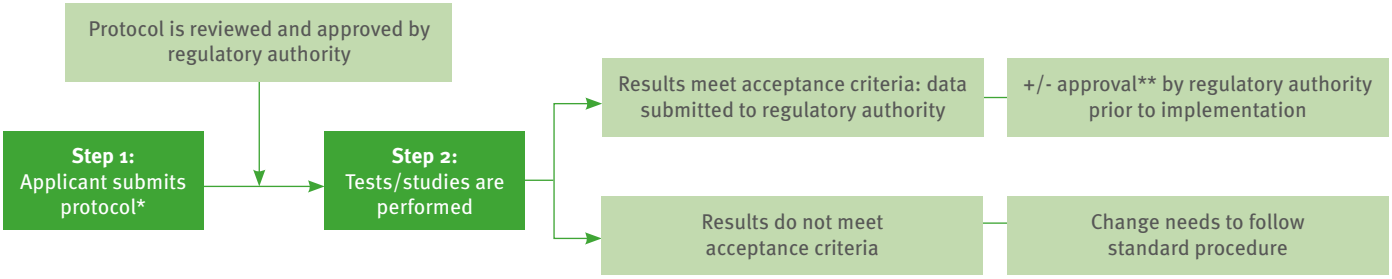
Decision tree for identification of ECs and associated reporting categories for manufacturing process parameters



a Appropriate justification is expected for parameters that are ECs and that are not ECs
b Assessment of risk to quality using tools and concepts found in ICH Q9
c In some cases, the regulator may determine that certain moderate risk changes proposed by the company may require prior approval
d See Chapter 2 for further guidance on reporting categories and see section 3.3 regarding roles and responsibilities related to managing changes and maintaining an approved application

FIGURE 2

PACMP application process



* with the initial MAA or as a standalone submission during the commercial phase of the product
** depending on classification/reporting category, approval by regulatory authority may or may not be required prior to implementation of the change

A PACMP can be submitted either with the MAA or for marketed products as a standalone submission. The regulatory procedure for a PACMP is summarised in Figure 2.

The procedural aspects of PACMPs are the same in the EU, US and Japan (ie, agreeing on the strategy of the change with the regulatory authority first and before conducting the studies, submitting the results and eventually implementing the change).

The PACMP includes:

- A description of the planned CMC change(s), including a rationale
- Risk management activities based on scientific knowledge and understanding of aspects impacted by the proposed change
- Proposed studies
- Acceptance criteria and other conditions to be met
- Proposed classification/reporting category for the change
- Any other supportive information
- Confirmation that the control strategy continues to ensure that the product will be produced consistently following implementation of the change(s).

The main advantages of this regulatory tool are:

- The early assessment by regulatory authorities of the strategy supporting the CMC change(s)
- The possibility to qualify for a lower reporting category following approval of the PACMP
- A shortened review period compared to similar procedure without an approved PACMP.

Two examples of PACMPs are provided in the guideline annexures. The first example is the addition of a manufacturing site for a small chemical entity. The quality risk management (QRM) activities and acceptance criteria for this change are outlined in the annex. A tabular summary of the PACMP contents for step 1 and step 2 is also provided. Although it is useful for applicants to have supportive information regarding key considerations to decide whether a change is eligible for a PACMP submission, clarity and transparency for practical aspects are still missing and need to be addressed on a national basis. Within the US and EU, for example, the reporting category could be determined as usual, using the variations guidelines. Also, the potential benefit to apply for a lower reporting category in step 2 is not demonstrated.

The second example provided in the Annexures concerns manufacturing site transfers of biotechnological drug substances. It is intended to show a protocol for multiple changes (multiple manufacturing site changes) that could be implemented for multiple products. As mentioned previously, QRM activities and acceptance criteria are defined, but details about the submission package expectations are not included.

Product lifecycle management

The PLCM document functions to facilitate regulatory inspection and assessment, by summarising the key elements of the product lifecycle strategy (ECs and reporting categories, PACMP, post-approval changes and reporting categories) and should be maintained throughout the product lifecycle, and updates to it, submitted with the post-approval submissions made.

The ICH Q12 guideline has been published with a separate appendix document that provides a clear and well-structured example of the PLCM document that could be considered representative of the general approach, which could be adopted for any product or dosage form. The guideline notes that "other formats or approaches can be used as appropriate", however the tabular summary would be easy to develop and maintain and could even be used internally as an effective tool for management and planning of regulatory submissions and workload. The US FDA has recently published tabular summaries of risk assessments for newly approved products.[2] These are not PLCM documents but could be used as supportive examples when creating one.

The PLCM document is submitted either with the MAA (new products), or with a variation defining ECs (currently approved products) and is generally placed in CTD Module 3.2.R.

Although carefully documented planning of PLCM could be perceived as an increase in administrative workload and reduction in agility, the document presents opportunity to manage in a timely and transparent manner, post-approval commitments, currently a challenge for both MAHs and regulators.

Real-life example: Post-approval change management protocol (PACMP)

The following real-life example highlights the procedural aspects of a PACMP. The scope was the addition of an alternative manufacturing site for a biotechnology derived product in the EU. Step 1 consisted in the submission of a package comprised of all the elements listed above. More specifically, the following documents explaining how the change is prepared and verified were included: a validation protocol for the alternative production site, the design of a comparability study to demonstrate that the product issued by the alternative site is comparable with the one produced in the initial manufacturing site, and proposed conditions for the stability assessment conducted on the batches manufactured to validate the alternative manufacturing site.

Step 1 was submitted as part of an initial EU MAA with the following reporting category "B.II.g.2 Introduction of a post approval change management protocol related to the finished product", followed by data generation, implementation, and then submission of an immediate notification, submitted as a Type IAIN, "B.II.g.5 a Implementation of changes foreseen in an approved change management protocol which requires no further supportive data".

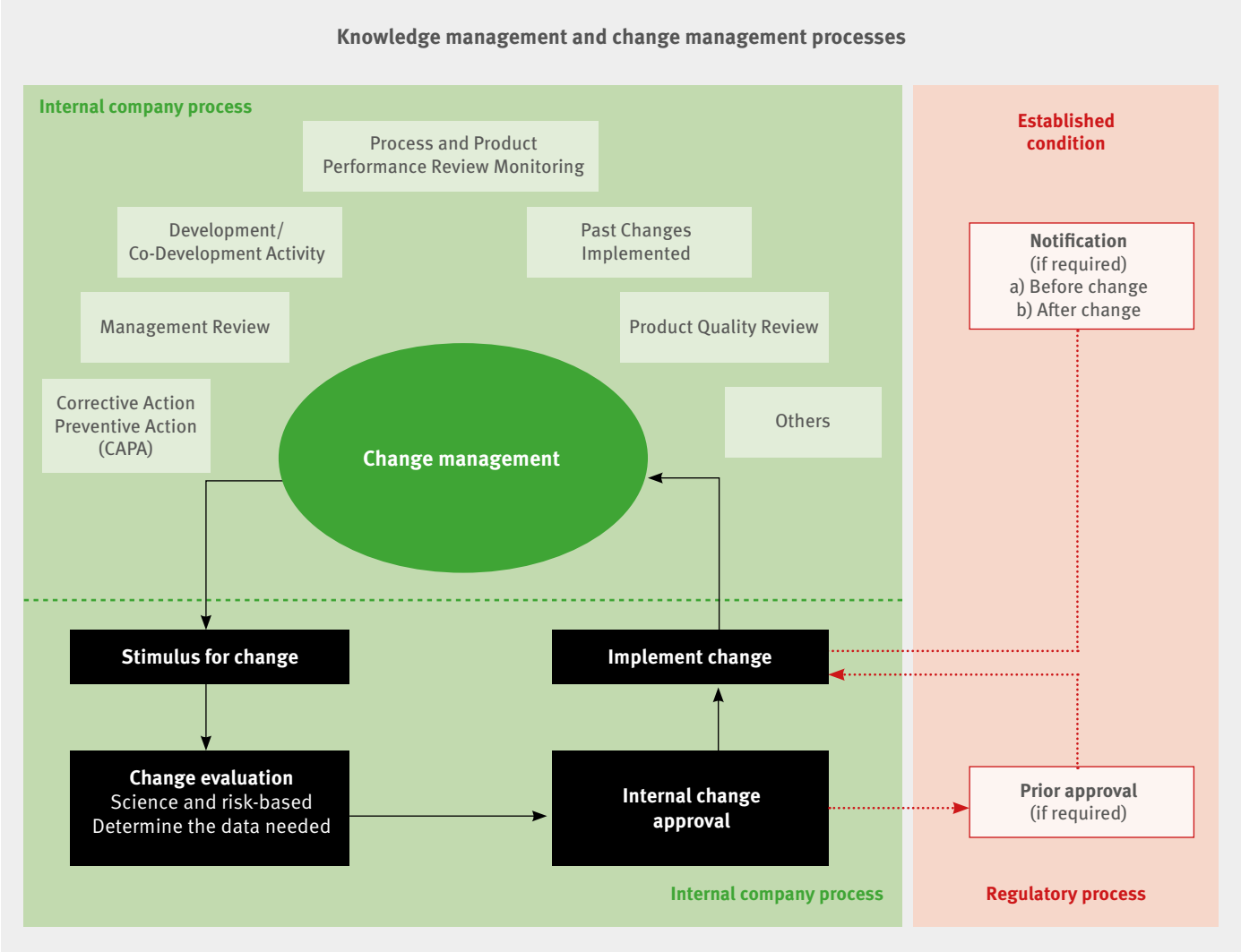
In some situations, the PACMP is not a suitable approach and the proposed change should follow a standard procedure if:

- the results do not meet the conditions initially outlined in the protocol
- the initial risk assessment indicates an increased level of risk associated with implementation of the change
- occurrence of significant changes to elements of the protocol that were not anticipated
- CMC change that requires nonclinical or clinical supportive studies (eg, for certain formulation changes, assessment of new impurities or immunogenicity).

The principles discussed thus far are the tools that form the product lifecycle management (PLCM) document, which communicates the MAH's approach to the regulatory authorities.

FIGURE 3

Connection between knowledge management and change management processes



Pharmaceutical quality system and change management

The principles of change management are listed in Appendix 2 of the Guideline and are consistent with the principles of ICH Q10. They are summarised as follows:

- Captures change stimuli
- Ensures full understanding of the change and implications, and requires a science and risk-based approach, leveraging existing knowledge
- Encourages development of protocols in line with the data needed, which underpins decisions regarding the necessity for a regulatory submission (or not)
- A defined change control process is then used to approve or reject the change, ensuring the change implementation remains aligned with existing documentation (study protocols, PLCM, PACMP)
- Verification of change effectiveness, and management of deviations through the MAH deviation and Corrective Action Preventive Action (CAPA) system
- Ensures risk-mitigating steps are developed and captures new knowledge.

The relationship between knowledge and change management principles and processes is summarised in Figure 3.

ICH Q12 indicates that an effective pharmaceutical quality system (PQS) should be established in line with ICH Q10 and that should the PQS be found non-compliant, then restrictions on flexibility, which ICH Q12 seeks to grant, may result. While this seems logical, the term "effective PQS" may be applied to PQSs of a wide range of maturity and/or complexity. For companies that retain all manufacturing activities in house for a single product, the system may be simple and straightforward to maintain, with an accompanying high degree of change predictability and timely reporting. Conversely, for large companies with many globally authorised products, who adopt an outsourcing/contract manufacturing model, the complexities may be high and predictability of changes may be challenging due to an extended "manufacturing chain" and lack of harmonisation of PQS and ways of working. Furthermore, any process optimisation activities requested by the MAH would likely be subject to financial and contractual negotiations/agreements.

The PQS considerations could be viewed as a challenge within the ICH Q12 structure, or, if all parties are aligned to the ICH Q12 principles, some aspects (eg, PACMPs) could be viewed as supportive, particularly in relationships where products are intended for registration through

procedures where time to market is compressed or where competent authorities agreement of study design prior to investment could de-risk a project. Embracing such an opportunity for closer collaboration between MAH and contract manufacturing organisations (CMOs) could surely be beneficial for both, but more importantly, for patients who would ultimately be the beneficiaries of more timely reporting of changes and thus reduced stock outs, shortages etc.

ICH Q12 advises that a failure in the PQS at any point in the supply chain will impact the ability to use the tools described. In a landscape in which approximately 60% MAHs in North America, EU and Asia outsource manufacturing activities[3] to an industry forecasted to grow to approximately $238.3bn by 2023,[4] it will be interesting to learn how this responsibility will be shared throughout the supply chain as industry adopt this approach.

Conclusion

The ICH Q12 guideline is structured according to the four tools and enablers that can be used during a product lifecycle, discussing the guiding principles of each one individually and providing clear examples both within the guideline itself, and also within a separate annex. The enablers and tools described are ECs, PACMPs, PLCMs and the PQS and seem a logical follow-on from the ICH Q8–Q11 guidelines. Following adoption of the guideline by the ICH and the Committee for Medicinal Products for Human Use, it is now the national competent authorities which will translate the guideline into regulatory requirements. This process has already been initiated by the EMA, which has published a note[5] indicating their initial views, and highlighting where some divergence in the EU legal framework and the recommendations of the guideline may be anticipated.

On first glance, the implementation of additional tools, and the associated regulatory review processes, could be viewed as an additional administrative burden for the MAH, However it is equally possible that this short term investment in time and process understanding could reap the rewards of clear and more strategic planning long term as we move from close regulatory oversight to a more risk-based but still highly transparent relationship based on improved scientific understanding. Will the guideline encourage closer collaboration between MAH and CMOs, facilitating incentivisation of enhanced process understanding and increased process optimisation? Finally, and perhaps of most pertinence, could this approach ultimately offer substantial benefits to patients through more timely reporting of changes and thus reduced stock outs, shortages, etc? ■

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