EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

04 March 2020
EMA/CHMP/ICH/804273/2017
Committee for Medicinal Products for Human Use

ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management

Step 5

Transmission to CHMP	14 December 2017
Adoption by CHMP for release for consultation	14 December 2017
Start of consultation	14 December 2017
End of consultation (deadline for comments)	14 December 2018
Final adoption by CHMP	30 January 2020
Date for coming into effect*	See below*

*refer to the Note on EU implementation of ICH Q12 (EMA/CHMP/ICH/78332/2020) for further details.

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Q12 Document History

Code	History	Date
Q12	Adopted by the Regulatory Members of the ICH Assembly under Step 4 (document dated 19 November 2019).	20 November 2019
Q12	Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation (document dated 31 October 2017).	16 November 2017

ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management

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1. Introduction

1.1. Objectives

This guideline provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner. A harmonised approach regarding technical and regulatory considerations for lifecycle management will benefit patients, industry, and regulatory authorities by promoting innovation and continual improvement in the pharmaceutical sector, strengthening quality assurance and improving supply of medicinal products.

The concepts outlined in prior ICH Quality Guidelines (ICH Q8(R2), Q9, Q10 and Q11) provide opportunities for science- and risk-based approaches for use in drug development and regulatory decisions. These guidelines are valuable in the assessment of Chemistry, Manufacturing and Controls (CMC) changes across the product lifecycle. ICH Q8(R2) and Q11 guidelines focus mostly on early stage aspects of the product lifecycle (i.e., product development, registration and launch). This guideline addresses the commercial phase of the product lifecycle (as described in ICH Q10); and it both complements and adds to the flexible regulatory approaches to post-approval CMC changes described in ICH Q8(R2) and Q10 Annex 1.

This guideline is also intended to demonstrate how increased product and process knowledge can contribute to a more precise and accurate understanding of which post-approval changes require a regulatory submission as well as the definition of the level of reporting categories for such changes (i.e., a better understanding of risk to product quality). Increased knowledge and effective implementation of the tools and enablers described in this guideline should enhance industry's ability to manage many CMC changes effectively under the company's Pharmaceutical Quality System (PQS) with less need for extensive regulatory oversight prior to implementation. This approach can incentivize continual improvement by providing an opportunity for greater flexibility in making post-approval changes. It could also result in fewer associated post-approval submissions to the Marketing Authorisation Application (MAA), and less associated regulatory burden. The extent of this operational and regulatory flexibility and its adequate implementation is subject to the regulatory framework in place, as well as product and process understanding (ICH Q8(R2) and Q11), application of quality risk management principles (ICH Q9), and an effective pharmaceutical quality system (ICH Q10).

Regulatory Members of ICH are encouraged to provide publicly available information, preferably on their website, about the implementation of ICH Q12 in their region, especially with regard to regulatory considerations.

1.2. Scope

This guideline applies to pharmaceutical drug substances[1] and products (both chemical and biological) that require a marketing authorization; and to drug-device combination products that meet the definition of a pharmaceutical or biological product. Changes needed to comply with new or revised pharmacopoeial monographs are not within the scope of this guideline.

[1] For drug substance information incorporated by reference (e.g., a Master File) in an MAA, the holder of the referenced information may use Q12 tools where applicable. Use of Q12 tools is not intended to change the responsibilities for the holder of the referenced information, the MAH or the regulatory authority. For example, the holder of the referenced information has a responsibility to report relevant drug substance changes to the MAH referencing their submission, so that the MAH can assess the impact of the change and report any related changes to the approved MAA, as necessary and per regional requirements.

1.3. ICH Q12 regulatory tools and enablers

Use of the following harmonised regulatory tools and enablers with associated guiding principles, as described in this guideline, will enhance the management of post-approval changes, and transparency between industry and regulatory authorities, supporting innovation and continual improvement.

- Categorisation of Post-Approval CMC Changes (Categorisation of post-approval CMC changes)

  Categorisation of Post-Approval CMC Changes describes a framework that encompasses a risk-based categorisation for the type of communication expected of the Marketing Authorisation Holder (MAH) with the regulatory authority regarding CMC changes.

- Established Conditions (ECs) (Established Conditions (ECs))

  The concept of ECs provides a clear understanding between the MAH and regulatory authorities regarding the elements to assure product quality and that involve a regulatory communication, if changed. This guideline describes how ECs are identified as well as what information can be designated as supportive information that would not involve a regulatory communication, if changed. In addition, guidance is included for managing revisions of the ECs.

- Post-Approval Change Management Protocol (PACMP) (4.)

  The PACMP is a regulatory tool that provides predictability regarding the information required to support a CMC change and the type of regulatory submission based on prior agreement between the MAH and regulatory authority. Such a mechanism enables planning and implementation of future changes to ECs in an efficient and predictable manner.

- Product Lifecycle Management (PLCM) Document (5.)

  The PLCM document serves as a central repository for the ECs and the associated reporting category for changes made to ECs. The document also captures how a product will be managed during the commercial phase of the lifecycle including relevant post-approval CMC commitments and PACMPs.

- Pharmaceutical Quality System (PQS) and Change Management (6.)

  An effective PQS as described in ICH Q10 and compliance with regional GMPs are necessary to gain full benefit from this guideline. In particular, management of manufacturing changes across the supply chain is an essential part of an effective change management system. This guideline provides recommendations for robust change management across single or multiple entities involved in the manufacture of a pharmaceutical product.

- Relationship Between Regulatory Assessment and Inspection (7.)

  This guideline outlines the complementary roles of regulatory assessment and inspection in the oversight of post-approval changes; and how communication between assessors and inspectors facilitates the use of the tools included herein.

- Structured Approaches for Frequent CMC Post-Approval Changes (8.)

  In addition to the other tools described above, this guideline describes a strategy for a structured approach applicable to frequent CMC changes, and a discussion of data expectations, to enable the use of immediate or other post-implementation notification.

- Stability Data Approaches to Support the Evaluation of CMC Changes (9.)

This guideline provides additional science- and risk-based approaches that are relevant to strategies for confirmatory stability studies to enable more timely implementation of CMC changes.

Tools and enablers described above are complementary and are intended to link different phases of the product lifecycle. Pharmaceutical development activities result in an appropriate control strategy, elements of which are considered to be **Established Conditions**. All CMC changes to an approved product are managed through a company's **Pharmaceutical Quality System**; changes to ECs must also be reported to the regulatory authority. Where the regulatory system provides for **Categorisation of Post-approval CMC Changes** for reporting according to risk, the MAH may propose reporting categories for changes to ECs based on risk and knowledge gained through enhanced pharmaceutical development. A system with risk-based reporting categories also facilitates the use of **Post-Approval Change Management Protocols**, which provide predictability regarding planning for future changes to ECs. The **Product Lifecycle Management Document** is a summary that transparently conveys to the regulatory authority how the MAH plans to manage post-approval CMC changes. The tools and enablers in this guideline do not change the **Relationship Between Regulatory Assessment and Inspection**; however, collaboration and communication between assessors and inspectors are necessary for the implementation of this guideline by regulators. This guideline provides **Structured Approaches for Frequent CMC Post-Approval Changes** to enable the implementation of certain CMC changes for authorised products without the need for prior regulatory review and approval. Finally, this guideline provides **Stability Data Approaches to Support the Evaluation of CMC Changes**; i.e., where the stability study is undertaken to confirm previously approved storage conditions and shelf-life.

2. Categorisation of post-approval CMC changes

Regulatory mechanisms that allow the timely and efficient introduction of CMC changes are important for drug quality, safety, and availability. There is a range of potential CMC changes for which communication between a company and the regulatory authority is required. CMC changes vary from low to high potential risk with respect to product quality, safety, and efficacy. A well-characterised, risk-based categorisation of regulatory communication requirements is important to the efficient use of industry and regulatory resources.

In such a regulatory system, the types of CMC changes that occur during the commercial phase of the pharmaceutical product lifecycle that invoke communication with regulatory authorities are classified with regard to the potential to have an adverse effect on product quality of the drug product. The regulatory communication category, supporting information/documentation requirements, and associated time frame for evaluation are commensurate with that potential risk. Based on potential risk, an inspection may be needed.

Regulatory authorities are encouraged to utilise a system that incorporates risk-based regulatory processes for (a) requesting prior approval from the regulatory authority, (b) notifying the regulatory authority, or (c) simply recording CMC changes, with associated information requirements and, where applicable, timeframes for decision. Such a system would include the following categories for regulatory communications with one or more levels in each case:

- **Prior approval**: Certain changes are considered to have sufficient risk to require regulatory authority review and approval prior to implementation and are requested by the MAH in a suitably detailed regulatory submission.
- **Notification**: Certain moderate- to low-risk changes are judged to not require prior approval and generally require less information to support the change. These changes are communicated to the regulatory authority as a formal notification that takes place within a defined period of time before

or after implementation, according to regional requirements. A mechanism for immediate notification is useful when prior approval is not required, but timely awareness of the change by the regulator is considered necessary.

In addition, the changes that are not required to be reported to regulators are only managed and documented within the PQS, but may be verified during routine or other inspection.

Harmonisation or convergence toward a system of risk-based categorisation of post-approval changes is encouraged as an important step toward achieving the objectives of this guideline. Such a system provides inherent, valuable flexibility in regulatory approach and a framework that can support additional regulatory opportunities such as:

- Facilitating the use of tools and enablers described in this guideline by providing a range of request and notification categories available as a target for a lowering of regulatory submission requirements.
- The use of a lower category for request/notification if certain criteria/conditions are met and the relevant supporting documentation is provided as described in regional regulatory guidance; the need for regulatory inspection associated with the change may preclude the ability to use a lower category.
- Providing options for converging to the same or similar reporting category as that in other jurisdictions.

A risk-based categorisation system may be accomplished by having the principles captured in regulations with further details in guidance, which can provide additional flexibility to modify expectations as science and technology evolve. For examples of risk-based categorisation systems, refer to existing regulations and guidance of ICH members, and WHO guidelines and guidance on changes to authorised products.

3. Established Conditions (ECs)

3.1. Introduction

This guideline establishes a harmonised approach to defining which elements in an application are considered necessary to assure product quality and therefore would require a regulatory submission if changed post-approval. These elements are being defined in this guideline as "Established Conditions for Manufacturing and Control" (referred to as ECs throughout this guideline).

3.2. ECs in the regulatory submission

3.2.1. ECs definition

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.

3.2.2. ECs in a regulatory dossier

This chapter describes scientific risk-based approaches which can be used when defining ECs and their reporting categories. Regional legal frameworks, supplemented through regulation and guidance, may define ECs with their reporting categories and/or may allow the scientific risk-based approaches described in this chapter to be considered.

All regulatory dossiers 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. Knowledge gained throughout the product lifecycle (including pharmaceutical development and characterisation of chemical and biological drug substance and drug product) is the basis for identifying the elements of CMC that are ECs and those elements which are supportive information.

An MAH should clearly identify the elements of CMC which they consider to be an EC and those which they consider to be supportive information. The rationales for the ECs are provided in the appropriate CTD modules.

Similarly, the rationales for the associated reporting categories for changes to the ECs should be provided in the appropriate CTD modules. The regulator assesses the ECs with respect to established scientific guidelines. Where appropriate, regulators approve the EC and associated reporting category in line with the principles outlined in 2. .

See 20 for more information regarding sections of the dossier that contain ECs and supportive information. Unless otherwise specified by regulatory requirement identifying ECs for a given product is not mandatory.

ECs should not be confused with CMC regulatory commitments (e.g., stability, post-approval CMC commitment and other commitments) made by a MAH to provide data or information to the regulatory agency in a MAA. Such information, in the context of this guideline, is considered supportive information. Changes to CMC regulatory commitments are managed according to existing regional regulations and guidance.

3.2.3. Identification of ECs

This chapter outlines approaches to define ECs for manufacturing processes and analytical procedures. A similar approach can be used to define other types of ECs (e.g., performance of the container closure system, device elements of drug-device combination products) and should be justified by the applicant and approved by the regulatory agency.

The extent of ECs may vary based on the company's development approach, product and process understanding, and the potential risk to product quality. Appropriate justification should be provided in support of the identification of ECs, the proposed reporting categories for ECs, and those aspects that are not ECs.

3.2.3.1. Identification of ECs for the manufacturing processes

A control strategy is designed to ensure that a product of required quality will be produced consistently (ICH Q8(R2)). It is a planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (ICH Q10).

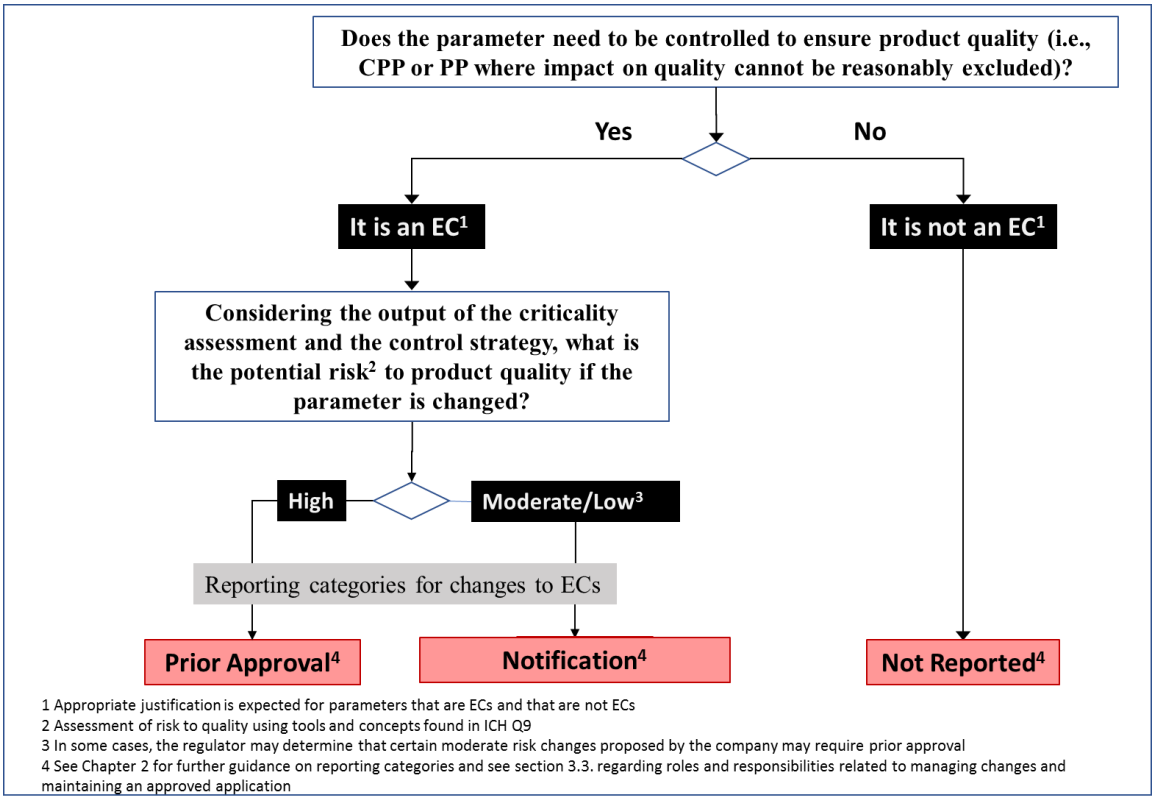
The ECs for a manufacturing process should be defined, based on product and process understanding, taking into account all the relevant elements of the control strategy. In addition to the unit operation and the sequence of steps, and in considering the overall control strategy, ECs proposed and justified in a manufacturing process description should be those inputs (e.g., process parameters, material attributes) and outputs (that may include in-process controls) that are necessary to assure product quality.

Process parameters that need to be controlled to ensure that a product of required quality will be produced should be considered ECs. These ECs are identified through an initial risk assessment and application of knowledge gained from executed studies, prior knowledge, and a criticality assessment that determines the level of impact that a process parameter could have on product quality. The criticality assessment should account for severity of harm and whether the ranges studied sufficiently account for the expected variability in the EC. CPPs and other process parameters where an impact on product quality cannot be reasonably excluded should be identified as ECs.

Once ECs are identified, an updated assessment of the potential risk to product quality associated with changing the EC, taking into account the overall control strategy informs the reporting category for the EC. The assessment of potential risk is derived from risk management activities as described in ICH Q9. The output of the risk assessment can include changes to manufacturing process ECs that range from high to low risk to product quality. The reporting category should be defined based on level of risk. A justification of the potential risk for changing ECs and corresponding reporting categories should be provided.

A decision tree which illustrates the above step-wise approach to identifying ECs and reporting categories for process parameters is shown in Figure 1. The principles in the decision tree can be applied to identify ECs for other parts of the manufacturing process and control strategy (e.g., relevant elements of input material attributes, equipment, and in-process controls) and associated reporting categories.

Figure 1: Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters



1 Appropriate justification is expected for parameters that are ECs and that are not ECs
2 Assessment of risk to quality using tools and concepts found in ICH Q9
3 In some cases, the regulator may determine that certain moderate risk changes proposed by the company may require prior approval
4 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

The details of ECs and the associated reporting category will depend on the extent to which the company can apply knowledge from product and process understanding (i.e., development and experience accumulated throughout the product lifecycle) to manage the risks to product quality.

Different approaches can be used alone, or in combination, to identify ECs for manufacturing processes; these include, but are not limited to the following:

- **Parameter-based approaches**, including:
  - A **minimal**[2] **approach,** with a limited understanding of the relationship between inputs and resulting quality attributes, will include a large number of inputs (e.g., process parameters and material attributes) along with outputs (including in-process tests).
  - An **enhanced approach** with increased understanding of interaction between inputs and product quality attributes together with a corresponding control strategy can lead to identification of ECs that are focused on the most important input parameters along with outputs, as appropriate.
- In a **performance-based approach**, ECs could be primarily focused on control of process outputs (e.g., attributes, measurements, responses) rather than process inputs (e.g., process parameters and material attributes). This is enabled by knowledge gained from an enhanced approach, a data-rich environment, and an enhanced control strategy (e.g., models, Process Analytical Technology (PAT)). For example, a performance-based approach could be considered for manufacturing process steps with in-line monitoring of relevant attributes or with feedback controls or optimisation algorithms to achieve the relevant targets for that process step. When considering this approach, it is important to ensure that all relevant parameters and material attributes that have a potential to impact product quality are monitored and equipment used remains qualified in order to assure a stable process It should be noted that not all elements of the decision tree in Figure 1 apply because the enhanced control strategy used may remove the need for certain process parameters to be ECs.

Use of this guideline should not lead to providing a less detailed manufacturing process description in the MAA. A suitably detailed description of the manufacturing process in Module 3 is expected to provide a clear understanding regardless of the approach used to identify ECs for manufacturing process parameters. Manufacturing process descriptions include supportive information as well as identified ECs. Information regarding product-specific post-approval change activities, such as post-change monitoring, may be provided as supporting information to aid in the determination of ECs and associated reporting categories. Criticality and risk should be periodically reviewed (as expected by ICH Q10) during the lifecycle of the product and the ECs and reporting categories should be updated based on acquired knowledge.

When implementing the change, and consistent with 30, an MAH should consider the impact of the planned change, whether concurrent changes are planned, and if the originally proposed reporting category should be revised.

This guidance does not impose additional regulatory filing expectations for process ECs due to non-conformance during routine operations. Non-conformance to process-related ECs should be handled in accordance with GMP regulations (i.e., deviation/non-conformance handling process).

3.2.3.2. Identification of ECs for analytical procedures

Similar to the principles described for manufacturing process, ECs related to analytical procedures should include elements which assure performance of the procedure. The extent of ECs and their reporting categories could vary based on the degree of the understanding of the relationship between method parameters and method performance, the method complexity, and control strategy. A

[2] Also referred to as "traditional" in ICH Q11.

justification to support the identification of ECs and corresponding reporting categories for changes to ECs based on risk management should be provided.

Different approaches can be used to identify ECs for analytical procedures, for example as analytical technology and development approaches advance; these approaches include, but are not limited to the following:

- When more limited development studies have been conducted this may result in a narrow operating window to ensure method performance. In such cases ECs may be more extensive with fixed and/or tight conditions.
- Enhanced understanding can lead to a wider operating window that ensures method performance, where ECs can be reduced and focused on method performance (e.g., method parameters acceptable ranges rather than set points, performance criteria).

Use of this guideline should not lead to providing a less detailed description of analytical procedures in the MAA. A suitably detailed description of the analytical procedures in Module 3 is expected to provide a clear understanding regardless of the approach used to identify ECs for analytical procedures. Description of analytical procedures includes supportive information as well as identified ECs.

3.2.4. Revision of ECs

It may be necessary to change approved ECs as a result of knowledge gained during the product lifecycle (e.g., manufacturing experience, introduction of new technologies or changes in the control strategy).

Options available for the MAH to change approved ECs, and to revise the associated reporting category for approved ECs include:

- Submission of an appropriate post-approval regulatory submission describing and justifying the proposed revision to the approved ECs. Justification may include information such as validation data and batch analyses.
- Submission of a PACMP, in the original MAA or as part of a post-approval submission, describing a revision to ECs or reporting categories, and how the change will be justified and reported.
- Use of an approved post-approval regulatory commitment, as appropriate.

3.3. Roles and responsibilities

The management of all changes to, and maintenance of, the approved marketing authorisation is the responsibility of the MAH. There is a joint responsibility to share and utilise information between the MAH and any manufacturing organisations to assure the marketing authorisation is maintained, reflects current operations, and that changes are implemented appropriately across relevant sites. Maintenance of the marketing authorisation should follow regional expectations. See Chapter 6 for information related to interactions between an MAH and any manufacturing organisations.

For any referenced submission (e.g., Type II Drug Master File, Active Substance Master File) in an MAA, the holder of the referenced submission has a responsibility to communicate changes to their ECs to the MAH referencing their submission, so that the MAH can assess the impact of the change and report any related change to the ECs found in the approved MAA, as necessary and per regional requirements.

The approval of ECs and subsequent changes to ECs is the responsibility of the regulatory authorities.

4. Post-approval Change Management Protocol (PACMP)

4.1. Definition of a PACMP

A PACMP is a regulatory tool that provides predictability and transparency in terms of the requirements and studies needed to implement a change as the approved protocol provides an agreement between the MAH and the regulatory authority. A protocol describes the CMC change an MAH intends to implement during the commercial phase of a product lifecycle, how the change would be prepared and verified, including assessment of the impact of the proposed change, and the suggested reporting category in line with regional regulations and guidance, i.e., a lower reporting category and/or shortened review period as compared to similar change procedure without an approved PACMP. The PACMP also identifies specific conditions and acceptance criteria to be met. A PACMP can address one or more changes for a single product, or may address one or more changes to be applied to multiple products (see section 4.5). The PACMP may be submitted with the original MAA or subsequently as a standalone submission and can be proposed independent of any prior identification of ECs. The PACMP requires approval by the regulatory authority, and the conditions and acceptance criteria outlined in the protocol must be met and results communicated to the regulatory authority in the manner previously agreed, in order to implement the change(s).

A PACMP should describe changes with a level of detail commensurate with the complexity of the change. Once approved, there is an expectation that the validity of the proposed approach and control strategy is confirmed prior to implementation of the change(s). For example, if new information becomes available following approval of the protocol, the risk assessment provided in the initial PACMP submission should be reviewed by the MAH before implementing the change(s), to ensure that the outcomes of that risk assessment as they pertain to the planned change(s) are still valid. If the review of the initial risk assessment indicates an increased level of risk associated with execution of the change, the previously approved reporting category should no longer be considered appropriate; instead, existing regional regulation or guidance should be followed or the relevant regulatory authority consulted.

The MAH is responsible for ensuring that whenever a CMC change is to be introduced under a PACMP, the facility meets the regulatory requirements of the regulatory jurisdiction where the PACMP was approved with respect to GMP compliance, and inspection or licensing status.

4.2. Application of a PACMP

The application of a PACMP process typically involves the following two steps:

Step 1: Submission of a written protocol that describes the proposed change(s), its rationale(s), risk management activities, proposed studies and acceptance criteria to assess the impact of the change(s), other conditions to be met (e.g., confirmation that there is no change to the approved specification), the proposed reporting category for the change(s), and any other supportive information (see also below). The PACMP document can be located in CTD Module 3.2.R.[3] This protocol is reviewed and approved by the regulatory authority in advance of execution of the protocol.

Step 2: The tests and studies outlined in the protocol are performed. If the results/data generated meet the acceptance criteria in the protocol and any other conditions are met, the MAH submits this information to the regulatory authority according to the categorisation (classification) in the approved protocol for review by the regulatory authority as appropriate. Depending on the reporting category, approval by the regulatory authority may or may not be required prior to implementation of the

[3] In some regions, the PACMP may be included in other modules.

change. If the acceptance criteria and/or other conditions in the protocol (see step 1) are not met, the change cannot be implemented using this approach and should instead follow existing regulation or guidance and associated reporting category.

Significant changes to the manufacturing process or controls that were not anticipated in the PACMP step 1 (e.g., change of order of unit operations) cannot be implemented as part of step 2 and should be the subject of a regulatory submission as governed by regional regulation or guidance. However, minor unanticipated modifications of the process or controls related to the intended change and not affecting the technical principles of the protocol are normally considered within scope, if appropriately justified.

No change outlined in a PACMP should introduce any additional risks to patient safety, product quality or efficacy. A CMC change that would require supportive efficacy, safety (clinical or non-clinical), or human PK/PD data to evaluate the effect of the change (e.g., certain formulation changes, clinical or non-clinical studies to evaluate new impurities, assessment of immunogenicity/antigenicity) is not suitable for inclusion in a PACMP.

4.3. Elements of a PACMP

The development of the PACMP is informed by the application of process and product understanding gained from product development and/or manufacturing experience. A PACMP would typically include the following, e.g.:

- A detailed description of the proposed change(s), including a rationale. The differences before and after the proposed change(s) should be clearly highlighted (e.g., in a tabular format).
- Based on an initial risk assessment, a list of specific tests and studies to be performed to evaluate the potential impact of the proposed change(s), such as: characterisation, batch release, stability (as appropriate, see 9.), in-process controls. The PACMP should include an appropriate description of the analytical procedures and proposed acceptance criteria for each test or study.
- Discussion regarding the suitability of the approved control strategy or any changes needed to the control strategy associated with the planned change(s).
- Any other conditions to be met, such as confirmation that certain process qualification steps will be completed before implementation.
- Where applicable, supportive data from previous experience with the same or similar products related to: development, manufacturing, characterisation, batch release, and stability to allow for risk mitigation.
- Proposed reporting category for step 2 of the PACMP.
- Confirmation, as appropriate, that ongoing verification will be performed under the PQS to continue to evaluate and ensure that there is no adverse effect of the change(s) on product quality. In cases where monitoring of the impact on product quality following implementation of the change(s) is required, a summary of the quality risk management activities should be provided to support the proposed PACMP. If multiple changes are to be implemented, these activities should address the potential risk from the cumulative effect of multiple changes and how they are linked.

The MAH should demonstrate in the PACMP suitable scientific knowledge and understanding of aspects impacted by the proposed change in order to conduct an appropriate risk assessment of the proposed change(s). Typically, more complex changes would require enhanced product/process understanding.

4.4. Modification to an Approved PACMP

A modification to an already approved PACMP, such as replacement or revision of a test, study or acceptance criterion, should provide the same or greater capability to assess the effect of the proposed change on the product quality and would normally involve a notification type of communication with the regulatory authority. A modification that more significantly alters the content of the protocol may require either prior approval of a protocol amendment or submission of a new protocol, as agreed upon with the regulatory authority.

4.5. Types of PACMPs

There are different types of PACMPs:

- One or more change(s) associated with a single product – see above and Annexes ID and 1E, for content and implementation. A PACMP can also be designed to be used repeatedly to make a specified type of CMC change over the lifecycle of a product, applying the same principles.

  If the protocol describes several changes for a particular product, a justification should be added showing how the changes are related and that inclusion in a single protocol is appropriate.

- Broader protocols – the general principles outlined above apply. The risk of the proposed change(s) should be similar across products; additional considerations should be taken into account depending on the approach, for example:

  a) One or more changes to be implemented across multiple products (e.g., change in stopper across multiple products that use the same container closure system): the same risk mitigation strategy should be applicable across all impacted products;

  b) One or more changes to be implemented across multiple products and at multiple sites (e.g., change in analytical method across multiple sites, change in manufacturing site(s) across multiple products): the same risk mitigation strategy should be applicable across all impacted products and/or sites (see Annex IE).

5. Product Lifecycle Management (PLCM) document

The PLCM document outlines the specific plan for product lifecycle management that includes the ECs, reporting categories for changes to ECs, PACMPs (if used) and any post-approval CMC commitments. Its purpose is to encourage prospective lifecycle management planning by the MAH and to facilitate regulatory assessment and inspection. The PLCM document should be updated throughout the product lifecycle as needed.

5.1. PLCM Document: Scope

The PLCM document serves as a central repository in the MAA for ECs and reporting categories for making changes to ECs. It includes the key elements described below and references to the related information located elsewhere in the MAA (see Annex IF). Submission of the PLCM document is critical when the MAH proposes ECs in line with the risk-based approaches in Chapter 3.

The elements of the PLCM document are summarised below:

- **ECs** (refer to Chapter 3)**:** The ECs for the product should be listed in the PLCM document. The identification and justification of ECs are located in the relevant sections of the CTD.

- **Reporting category for making changes to approved ECs** (refer to Chapter 3)**:** The reporting categories when making a change to an EC should be listed in the PLCM document. The detailed justification of the reporting categories is located in the relevant sections of the CTD.
- **PACMPs** (refer to Chapter 4)**:** PACMPs that are submitted to prospectively manage and implement one or more post-approval changes should be listed.
- **Post-approval CMC commitments:** specified CMC development activities, agreed between the MAH and regulatory authority at the time of approval (e.g., specific process monitoring, additional testing) that will be performed during the commercial phase should be listed in the PLCM document.

5.2. Submitting the PLCM document

The PLCM document is submitted in the original MAA or in a supplement/variation for marketed products when defining ECs (Chapter 3).

5.3. Maintenance of the PLCM document

An updated PLCM document should be included in post-approval submissions for CMC changes. The updated PLCM document will capture the change in ECs and other associated elements (reporting category, commitments, PACMP). The MAH should follow regional expectations for maintaining a revision history for the PLCM document.

5.4. Format and location of PLCM document

A tabular format is recommended to capture certain elements of PLCM described in section 5.1, but other appropriate formats can be used. See Annex IF for an example PLCM table.

The PLCM document can be located in CTD Module 3.2.R.[4]

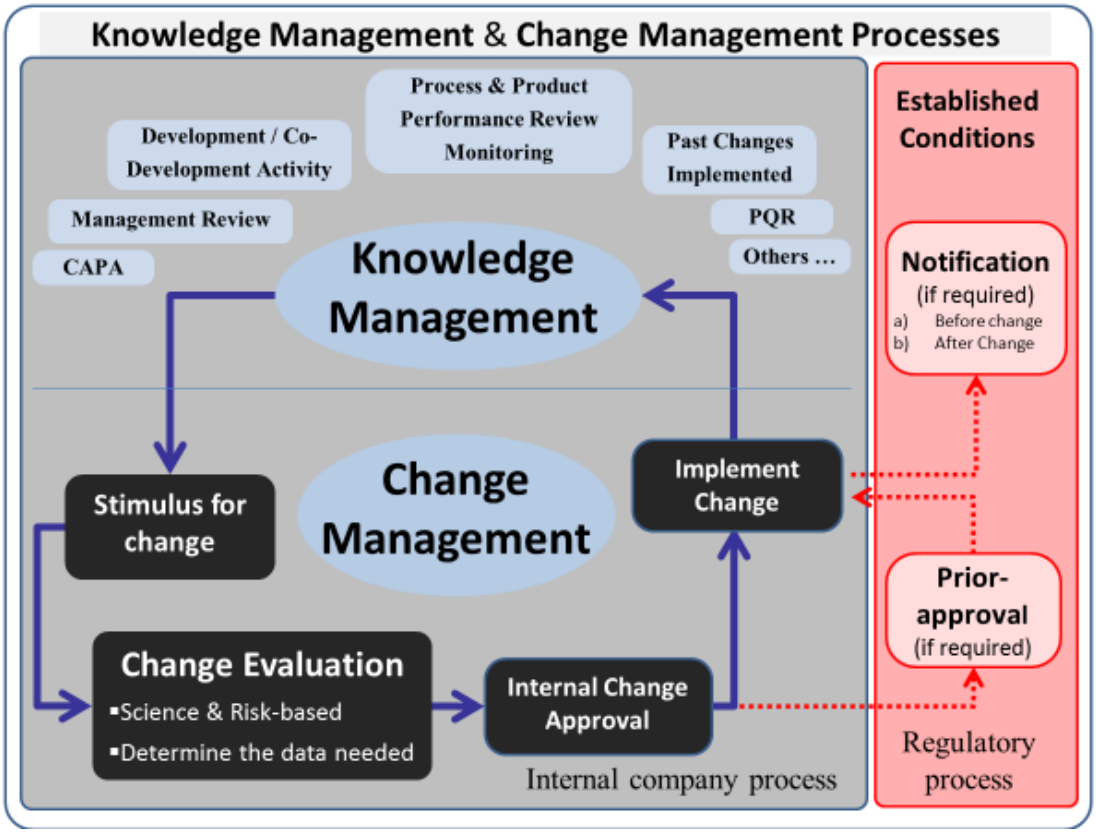
6. Pharmaceutical Quality System (PQS) and change management

6.1. PQS general considerations

An effective PQS as described in ICH Q10 and in compliance with regional GMP requirements where the application is filed, is necessary across the entire supply chain and product lifecycle to support use of the tools described in this guideline. It includes appropriate change management, enabled by knowledge management, and management review. The principles are further elaborated in 30. The relationship between knowledge management, change management, and the regulatory process for ECs are illustrated in Figure 2.

[4] In some regions, the PLCM may be included in Module 1.

Figure 2: Connection Between Knowledge Management and Change Management Process



Maintaining an effective PQS is the responsibility of a company (manufacturing sites and MAH where relevant). It is not the intent of this guideline to require a specific inspection assessing the state of the PQS before the company can use the principles in this guideline. The conduct of inspections in connection with submitted MAAs and surveillance will nevertheless continue as foreseen by regional regulatory requirements.

It is understood that a manufacturing site can be considered to be in general GMP compliance while resolving deficiencies that do not require regulatory action. In the event that such deficiencies have an impact on the effectiveness of change management in the PQS, it may result in restrictions on the ability to utilise flexibility in this guideline.

6.2. Change management across the supply chain and product lifecycle

Supply chains involve multiple stakeholders (e.g., MAHs, R&D organisations, manufacturers, Contract Manufacturing Organisations, suppliers). It is important that these stakeholders interact to effectively utilise knowledge and manage changes during the product lifecycle.

A company has to manage communication of information and interactions of PQSs across multiple entities (internal and external). Therefore, the implementation of robust change management across multiple sites (outsourced or not) is necessary. In conjunction with change control principles in 30, the following change management activities should be considered to support the approaches defined in this guideline:

- Changes to ECs should be communicated in a timely fashion between the MAH and the regulators, and between the MAH and the manufacturing chain (and vice versa).

- The timeliness of communication is driven by the impact of any change related to ECs and should be targeted to those entities in the chain that need to be aware of or to implement the change over the lifecycle of the product.
- Process knowledge and continual improvement are drivers for change. For example, a CMO may be in a position to propose process improvements which significantly improve control and product consistency. These data can be utilised to revise the ECs and associated PLCM document. The organisation responsible for batch release should be aware of all relevant changes and where applicable, be involved in the decision making.
- The communication mechanisms regarding MAA changes and GMP issues should be defined in relevant documentation, including contracts with CMOs.
- A critical failure in a PQS anywhere in the supply chain may impact the ability to use the tools in this guideline; therefore, the company should communicate such failures to affected regulatory authorities.

7. Relationship between regulatory assessment and inspection

Regulatory assessment and inspection are complementary activities and their fundamental roles remain unchanged by this guideline. Nevertheless, effective communication between assessors and inspectors can facilitate regulatory oversight of product lifecycle management.

Appropriate mechanisms to share knowledge and information obtained through inspection or assessment activities can facilitate access to necessary information and mitigate increased submission burden on the MAH. For example, the conclusions from inspections should be available to assessors to support ongoing oversight of product lifecycle management and the most recent PLCM document, when applicable, should be available to inspectors so they are aware of the currently approved status of the PLCM elements.

Communication is encouraged between regulators across regions, in accordance with appropriate bilateral/multilateral arrangements; for example, to communicate about critical failures in aspects of a company's PQS that may impact the use of tools described in this guideline.

8. Structured approaches for frequent CMC post-approval changes

In addition to the other tools described in this guideline, a simplified approach to accomplish certain CMC changes is needed for products whose marketing authorization did not involve identification of ECs with associated reporting categories. This chapter describes a strategy for a structured approach for frequent CMC changes and includes a discussion of the data requirements for CMC changes (e.g., stability).

The strategy described for structured approaches to frequent CMC changes is exemplified with a description of an approach for analytical procedure changes in Annex II. Similar structured approaches could be developed and applied for other frequent CMC changes such as scale, packaging, etc. These approaches may be applied when the following conditions exist:

- The company's PQS change management process is effective and in compliance as described in Chapter 6 and incorporates an appropriate risk management system.

- A structured approach can be found in Annex II and describes the scope and the steps to be followed, including, where appropriate, data to be generated and criteria to be met. Compliance with the requirements of relevant internationally-agreed Standards and/or regulatory guidelines may be specified as part of the structured approach.

If the approach is followed and all criteria are met, the change can be made with immediate or other post-implementation notification, as appropriate, to the relevant regulatory authorities. The flexibility provided in Annex II may not be available in all regions and in all situations; some specific changes may require prior approval as defined in regional guidance.

9. Stability data approaches to support the evaluation of cmc changes

The data needed for submission to the regulatory authority in support of a post-approval change is established by regional regulations and guidance. This guideline provides additional science- and risk-based approaches that can be used to develop strategies for confirmatory stability studies supporting post-approval changes to enable more timely filing, approval, and implementation of the changes. Such approaches could be included in a PACMP (see Annexes ID and IE).

Unlike the formal stability studies recommended in ICH Q1A(R2), whose objective is to establish a useful shelf-life and storage conditions for a new, yet-to-be-marketed drug substance/drug product, the purpose of stability studies, if needed, to support a post-approval CMC change is to confirm the previously approved shelf-life and storage conditions. The scope and design of such stability studies are informed by the knowledge and experience of the drug product and drug substance acquired since authorisation. Approaches to the design of such studies should be appropriately justified and may include:

- Identifying the stability-related quality attributes and shelf-life-limiting attributes relative to the intended CMC changes, based on risk assessments and previously generated data
- Use of appropriate tools to evaluate the impact of the intended change. These may include:
  - Drug substance and/or drug product accelerated and/or stress studies on representative material (which may be pilot or laboratory scale rather than full scale)
  - Pre-and post-change comparability studies on representative material
  - Statistical evaluation of relevant data including existing stability studies
  - Predictive degradation and other empirical or first-principles kinetic models
  - Utilisation of prior knowledge including relevant company knowledge and the scientific literature
- Use of confirmatory stability studies post-change instead of submission of data as part of a regulatory change submission

Where applicable, a commitment to initiate or complete ongoing, long-term stability testing on post-change batches can assure that the approved shelf life and storage conditions continue to be applicable after implementing the CMC change.

10. Glossary

Term	Definition
CAPA	Corrective Action and Preventive Action – System that focuses on investigating, understanding, and correcting discrepancies while attempting to prevent their occurrence
CMO	Contract Manufacturing Organisation
CPP	Critical Process Parameter – process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to assure the process produces the desired product quality. (Q8(R2))
CQA	Critical Quality Attribute – a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to assure the desired product quality. (Q8(R2))
CTD	Common Technical Document
Company	Manufacturing sites and MAH where relevant
EC	Established Condition
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
Notification	A change to an approved established condition that does not require approval prior to implementation.
PACMP	Post-Approval Change Management Protocol
PLCM	Product Lifecycle Management
Post-approval CMC commitment	Commitment by the MAH to undertake specific CMC activities to be implemented during the commercial phase.
Prior approval	Change to an approved established condition that requires regulatory review and approval prior to implementation
PQR	Product Quality Review – regular periodic review of API or drug products with the objective to verify process consistency, to highlight any trends and to identify product and process improvements
PQS	Pharmaceutical Quality System
QRM	Quality Risk Management

Term	Definition
Submission	Communication to a regulatory authority regarding a change to an established condition that could be prior approval or notification.

11. References

ICH *M4: The CTD -- Quality*

ICH *Q1A(R2) Stability Testing of New Drug Substances and Products*

ICH *Q2(R1) Validation of Analytical Procedures: Text and Methodology*

ICH *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*

ICH *Q8(R2) Pharmaceutical Development*

ICH *Q9 Quality Risk Management*

ICH *Q10 Pharmaceutical Quality System*

ICH *Q11 Development and Manufacture of Drug Substances*

ICH *Q8, Q9, and Q10 Questions and Answers*

ICH *Q8, Q9, & Q10 Questions and Answers -- Appendix: Q&As from Training Sessions (Q8, Q9, & Q10 Points to Consider)*

Appendix 1: CTD sections that contain ECs

Notes:

- This table does not contain a complete list of ECs for a product. The intention of the table is to provide general guidance about the elements of manufacture and control that constitute ECs and their location within the CTD structure.
- White rows indicate CTD sections where ECs are generally located. Grey rows indicate CTD sections where supportive information is generally located.
- CTD sections containing ECs may also contain elements of supportive information.
- For information related to the drug delivery system for a drug-device combination product, the location or the relevant content within the CTD structure may vary depending on the design of the particular product and region.

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.S	**DRUG SUBSTANCE**	
3.2.S.1	General Information	
3.2.S.1.1	Nomenclature	Drug Substance Name, Structure.
3.2.S.1.2	Structure	
3.2.S.1.3	General properties	Supportive information
3.2.S.2	Manufacture	
3.2.S.2.1	Manufacturer(s)	Drug Substance Manufacturing Site(s) (including testing)

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.S.2.2	Description of manufacturing process and process controls	Individual unit operations and their sequence in the manufacturing process For levels/details of ECs for inputs (process parameters and material attributes) and outputs of individual unit operations, reference is made to Chapter 3, section 3.2.3.1 – *Identification of ECs for the Manufacturing Processes*
3.2.S.2.3	Control of Materials	Starting material specifications (test, elements of analytical procedure and acceptance criteria) Raw material/reagent/solvent critical controls Source of materials (e.g., cell and seed source, raw materials) and control of critical materials of biological origin Generation and control of Master - Working Cell Bank / Master - Working Seed Lot, etc. (Applicable to biotechnological/biological products)
3.2.S.2.4	Control of critical steps and intermediates	Specifications (e.g., test, elements of analytical procedure and acceptance criteria) for critical steps and intermediates which may include storage conditions of critical intermediates
3.2.S.2.5	Process validation and/or evaluation	Supportive information
3.2.S.2.6	Manufacturing process development	Supportive information
3.2.S.3	Characterisation	Supportive information

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.S.3.1 3.2.S.3.2	Elucidation of structure and other characteristics Impurities	Supportive information
3.2.S.4	Control of Drug Substance	
3.2.S.4.1	Specification	Drug Substance Specification For each Quality Attribute on the specification • Test Method • Acceptance Criteria
3.2.S.4.2	Analytical Procedures	Reference is made to Chapter 3, section 3.2.3.2 *Identification of ECs for Analytical Procedures*
3.2.S.4.3	Validation of analytical procedure	Supportive information
3.2.S.4.4	Batch analyses	Supportive information
3.2.S.4.5	Justification of specification	Supportive information
3.2.S.5	Reference Material	Reference Material specification (e.g., test, elements of analytical procedure, where appropriate, and acceptance criteria)

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.S.6	Container Closure	Material of construction and specification
3.2.S.7	Stability	
3.2.S.7.1	Stability Summary and Conclusions	Drug Substance storage conditions and shelf-life (or Retest period for chemicals)
3.2.S.7.2	Post-approval stability protocol and stability commitments	Supportive information (also see Chapter 3, section 3.2.2)
3.2.S.7.3	Stability data	Supportive information
3.2.P	**DRUG PRODUCT**	
3.2.P.1	Description and Composition of Drug Product	Drug Product qualitative and quantitative composition
3.2.P.2	Pharmaceutical development	
3.2.P.2.1	Components of the drug product	
3.2.P.2.2	Drug product	
3.2.P.2.3	Manufacturing process development	

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.P.2.4	Container closure system	Supportive information
3.2.P.2.5	Microbiological attributes	
3.3.P.2.6	Compatibility	
3.2.P.3	Manufacture	
3.2.P.3.1	Manufacturer(s)	Drug Product Manufacturing sites (including those for testing, primary and secondary packaging, device assembly for drug product-device combination products
3.2.P.3.2	Batch Formula	Drug Product Batch Formula (Qualitative and Quantitative)
3.2.P.3.3	Description of manufacturing process and process controls	Individual unit operations and their sequence in the manufacturing process For levels/details of ECs for inputs (process parameters and material attributes) and outputs of individual unit operations, reference is made to Chapter 3, section 3.2.3.1
3.2.P.3.4	Controls of Critical Steps and Intermediates	Specifications (e.g., test, elements of analytical procedure and acceptance criteria) for critical steps and intermediates which may include storage conditions of critical intermediates.
3.2.P.3.5	Process validation and/or evaluation	Supportive information
3.2.P.4	Control of Excipients	
3.2.P.4.1	Specifications	Excipient Specification

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
		For each Quality Attribute on the specification • Test Method • Acceptance Criteria Or, if applicable, Reference to pharmacopoeial monograph
3.2.P.4.2	Analytical Procedures	Reference to pharmacopoeial monograph and if none exists, refer to Chapter 3, section 3.2.3.2
3.2.P.4.3	Validation of analytical procedures	Supportive information
3.2.P.4.4	Justification of specifications	Supportive information
3.2.P.4.5	Excipients of Human or Animal Origin	Excipient source and controls
3.2.P.4.6	Novel excipients	(If Novel Excipient Specification is not described in 3.2.P.4.1) Novel Excipient Specification For each Quality Attribute on the specification • Test Method

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
		• Acceptance Criteria
3.2.P.5	Control of Drug Product	
3.2.P.5.1	Specification(s)	Drug Product Specification For each Quality Attribute on the specification • Test Method • Acceptance Criteria
3.2.P.5.2	Analytical Procedures	Reference is made to Chapter 3, section 3.2.3.2
3.2.P.5.3	Validation of analytical procedures	Supportive information
3.3.P.5.4	Batch analyses	Supportive information
3.2.P.5.5	Characterisation of impurities	
3.2.P.5.6	Justification of specification(s)	

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.P.6	Reference Materials	Reference material specification (e.g., test, elements of analytical procedure, where appropriate, and acceptance criteria)
3.2.P.7	Container Closure System	Material of construction and specification Where applicable, supplier/manufacturer of primary container closure system
3.2.P.8	Stability	
3.2.P.8.1	Stability Summary and Conclusion	Drug product storage conditions and shelf-life Where applicable, in-use storage conditions and shelf-life
3.2.P.8.2	Post-approval stability protocol and stability commitment	Supportive information (also see Chapter 3, section 3.2.2)
3.3 P.8.3	Stability data	Supportive information
3.2.A	**APPENDICES**	
3.2.A.1	Facilities and equipment	Regional regulation and guidance apply
3.2.A.2	Adventitious agents safety evaluation	Supportive information (Applicable to biotechnological/biological products)

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.A.3	Excipients	Supportive information
3.2.R	**REGIONAL INFORMATION**	
	Not Applicable	Regional regulation and guidance apply.

Appendix 2: Principles of change management

Consistent with the basic requirements of ICH Q10, an effective change management system supports the principles of this guideline and is described below:

1. Captures stimuli for change, including those that can improve product performance or process robustness;
2. Ensures full understanding of the scope of the change and its implications for all aspects of the process and control strategy including the impact on ECs and aspects that are not ECs in affected marketing authorisations;
3. Leverages existing process performance and product quality knowledge;
4. Requires science-based risk management and risk categorisation of the intended change; considers the potential impact if the intended change is not implemented;
5. Determines data (existing and/or to be newly generated) needed to support the change and accordingly develops study protocols describing the methods, prospective acceptance criteria as well as additional post-implementation process performance and/or product quality monitoring as necessary;
6. Ensures that an appropriate regulatory submission is filed when required;
7. Uses a defined change control process to approve or reject the intended change and involve appropriate stakeholders, including but not restricted to Manufacturing, Quality, and Regulatory Affairs personnel;
8. Ensures implementation of the change is based on:
    a. Review that the change as implemented remains aligned with the relevant study protocols, PLCM document, or PACMP;
    b. Assessment of data generated to demonstrate that the change objective and acceptance criteria were met;
9. Ensures that risk-mitigating steps are developed in the case of deviations from acceptance criteria, or identification of unanticipated risks;
10. Verifies, post-implementation, that relevant changes have been effective in achieving the desired outcome with no unintended consequences for product quality;

    If deviations associated with post-approval changes are detected, ensures that the issue is managed via the company's deviation management process and appropriate corrective and/or preventive actions are identified and undertaken via the company's corrective and preventive action (CAPA) system;

11. Post-implementation:

a. Captures new product/process knowledge gained during implementation of the change;

b. Where applicable, ensures that regulatory filings are updated, and an assessment is made as to whether updates to the PLCM document are needed;

c. Where applicable, ensures that the change is included and assessed as part of the Product Quality Review (PQR);

12. The change management system should be available for review during audit/inspection.

Use of knowledge in change management

An effective change management system includes active knowledge management, in which information from multiple sources is integrated to identify stimuli for changes needed to improve product and/or process robustness. The connection between knowledge management and change management is illustrated in Figure 2. These sources can include, but are not limited to, developmental studies, process understanding documents, product or process trending, and product-specific CAPA outcomes. Provisions should be made for sharing knowledge (e.g., in quality agreements and/or contracts) that relates to product and process robustness or otherwise informs changes between the MAH and relevant manufacturing stakeholders (research and development organisations, manufacturers, CMOs, suppliers, etc.).

In addition to individual sources of information, there should be a mechanism to provide a holistic view of quality performance for a specific product or product family on a regular basis, as captured in the product quality review (PQR) and shown in Figure 2. This should include steps taken to identify and manage sources of variability, which allows for the identification of further need for change not apparent when the data are viewed in isolation. As described in ICH Quality Implementation Working Group on Q8, Q9, and Q10 Questions & Answers, there is no added regulatory requirement for a formal knowledge management system.

Management review

In addition to the guidance provided in ICH Q10 regarding an effective change management system, the following should be considered in the Management Review:

- Monitoring the timeliness of the change management system to assure that changes are implemented in a timely manner commensurate with the criticality/urgency identified for the change. When implementation is delayed, an assessment and mitigation of any risks associated with the delay should be made;
- Monitoring the performance of the change management system, such as assessing the frequency of intended changes that are not approved for implementation by the quality unit;
- Ensuring that post-implementation verification occurs and reviewing the results of that verification as a measure of change management effectiveness (e.g., to identify improvements to the change management system).