Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Core Guideline

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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
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Q12

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At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

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1. INTRODUCTION[1]

1.1. Objectives

The concepts outlined in prior ICH Quality Guidelines (ICH Q8, Q9, Q10 and Q11) provide opportunities for science and risk-based approaches for drug development and risk-based regulatory decisions. These guidelines are valuable in the assessment of Chemistry, Manufacturing and Controls (CMC) changes across the product lifecycle. ICH Q8 and Q11 guidelines focus mostly on early stage aspects of the product lifecycle (i.e., product development, registration, and launch). Experience with implementation of recent ICH guidelines has revealed technical and regulatory gaps that limit the full realisation of more flexible regulatory approaches to post-approval CMC changes as described in ICH Q8 (R2) and Q10 Annex I. This guideline addresses the commercial phase of the product lifecycle (as described in ICH Q10).

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 biopharmaceutical sector, strengthening quality assurance and improving supply of medicinal products.

This guideline provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner. It is also intended to demonstrate how increased product and process knowledge can contribute to a reduction in the number of regulatory submissions. Effective implementation of the tools and enablers described in this guideline should enhance industry's ability to manage many CMC changes effectively under the firm's Pharmaceutical Quality System (PQS) with less need for extensive regulatory oversight prior to implementation. The extent of operational and regulatory flexibility is subject to product and process understanding (ICH Q8 and Q11), application of risk management principles (ICH Q9), and an effective pharmaceutical quality system (ICH Q10).

In certain ICH regions, the current ICH Q12 guideline is not fully compatible with the established legal framework with regard to the use of explicit Established Conditions (ECs) referred to in Chapter 3 and with the Product Lifecycle Management (PLCM) referred to in Chapter 5 as outlined in this guideline. These concepts will, however, be considered when the legal frameworks will be reviewed and, in the interim, to the extent possible under the existing regulation in these ICH regions.[2]

1.2. Scope

This guideline applies to pharmaceutical drug substances (i.e., active pharmaceutical ingredients) and pharmaceutical drug products, including marketed chemical, and biotechnological/biological products. The guideline also applies to drug-device combination products that meet the definition

[1] This guidance is intended to be considered in conjunction with the ICH Q12 Annex document being simultaneously published for comment.

[2] Note: In the United States, the ICH Q12 guidance is fully compatible with the established legal framework. Therefore, the concept of Established Conditions and supporting Product Lifecycle Management document are fully supported by the U.S. FDA as described in this guidance.

of a pharmaceutical or biotechnological/biological product. Changes needed to comply with revisions to pharmacopeial monographs are not in scope of this guideline.

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, leading to innovation and continual improvement.

- Categorisation of Post-Approval CMC Changes (Chapter 2)

  Categorisation of Post-Approval CMC Changes is 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) (Chapter 3)

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

- Post-Approval Change Management Protocol (PACMP) (Chapter 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) (Chapter 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 (Chapter 6)

  An effective PQS as described in ICH Q10 and compliance with regional GMPs are necessary for implementation of 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 multiple entities involved in the manufacture of a pharmaceutical product.

- Relationship Between Regulatory Assessment and Inspection (Chapter 7)

  This guideline outlines the complementary roles of regulatory assessment and inspection, and how communication between assessors and inspectors facilitates the use of the tools included herein.

- Post-Approval Changes for Marketed Products (Chapter 8)

  Approaches to facilitate changes to marketed products are outlined. This guideline provides detailed guidance to enable changes to analytical methods to be made with immediate or other post-implementation notification. Science- and risk-based approaches for stability studies in support of the evaluation of CMC changes are also described.

The 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 changes to an approved product are managed through a firm'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. Finally, this guideline proposes approaches to facilitate **Post-Approval Changes to Marketed Products** without the need for regulatory review and approval prior to implementation of certain CMC changes.

2. CATEGORISATION OF POST-APPROVAL CMC CHANGES

Regulatory mechanisms that allow the timely and efficient introduction of CMC changes are important to drug quality, safety, and availability. There is a range of potential CMC changes for which communication between a firm and the regulatory authority is required. CMC changes vary from low to high potential risk with respect to product quality. 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 changes in the drug substance, drug product, production process, quality controls, equipment, and facility 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.

Regulatory authorities are encouraged to utilise a system that incorporates risk-based regulatory processes for (a) requesting 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. An inspection may be associated with such changes.

- **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 lowest risk changes are only managed and documented within the PQS and not reported to regulators, but may be verified on routine 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.

- Options for possible regulatory convergence regarding the association of a certain type of change with a particular category when reasons for being different from other regulatory authorities are not clearly established.

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 approved products.

3. ESTABLISHED CONDITIONS (ECS)

3.1. Introduction

Although the Common Technical Document (CTD) format has been defined for a marketing application, there are no previously harmonised approaches 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. Definition of ECs and Their Role in the Regulatory Submission

3.2.1. ECs Definition

ECs are legally binding information (or approved matters) 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 Submission

All regulatory submissions contain a combination of ECs and supportive information (refer to Appendix 1). Supportive information is not considered to be ECs, but is provided to share with regulators the development and manufacturing information at an appropriate level of detail, and to justify the initial selection of ECs and their reporting category.

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

ECs in a submission are either implicit or explicit:

- Implicit ECs are elements that are not specifically proposed by the MAH but are derived from and revised according to regional regulation or guidance related to post-approval changes.

- Explicit ECs are specifically identified and proposed by the MAH together with their proposed reporting category as part of a regulatory submission (see Chapter 3.2.3). This guideline provides the opportunity to identify explicit ECs and associated reporting categories. Unless otherwise specified by regional requirement, identifying explicit ECs for a given product is not mandatory.

An MAH may use one or both approaches as described above to define ECs and their associated reporting categories. If the MAH wishes to propose a different reporting category than provided in regional regulation and guidance for an implicit EC, the explicit EC approach should be used.

The MAH should provide rationales for the ECs and associated reporting categories in the appropriate CTD sections in Module 3.

See Appendix 1 for more information regarding sections of the marketing application that may contain ECs and supportive information.

3.2.3. Identification of ECs

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

The extent of ECs may vary based on the firm's development approach and potential risk to product quality.

3.2.3.1. Identification of ECs for the Manufacturing Processes

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. These should include critical process parameters (CPPs, as defined in ICH Q8(R2)), as well as key process parameters (KPPs), which are parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency as it relates to product quality.

The details of ECs and the associated reporting category will depend on the extent to which the firm can apply knowledge from product and process understanding (i.e., their development approach) to manage the risks to product quality. Appropriate justification should be provided to support the identification of ECs and proposed reporting categories. Different approaches can be used alone, or in combination, to identify ECs for manufacturing processes; these include, but are not limited to the following:

- A **parameter based approach**, in which product development prior to regulatory submission provides 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 controls).

- 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 certain cases, applying knowledge from a data-rich environment enables a **performance based approach** in which ECs could be primarily focused on control of unit operation outputs rather than process inputs (e.g., process parameters and material attributes). For example, a performance-based approach could be considered for manufacturing process steps with in-line continuous monitoring (e.g., using appropriate process analytical technologies such as NIR for the control of a blending process).

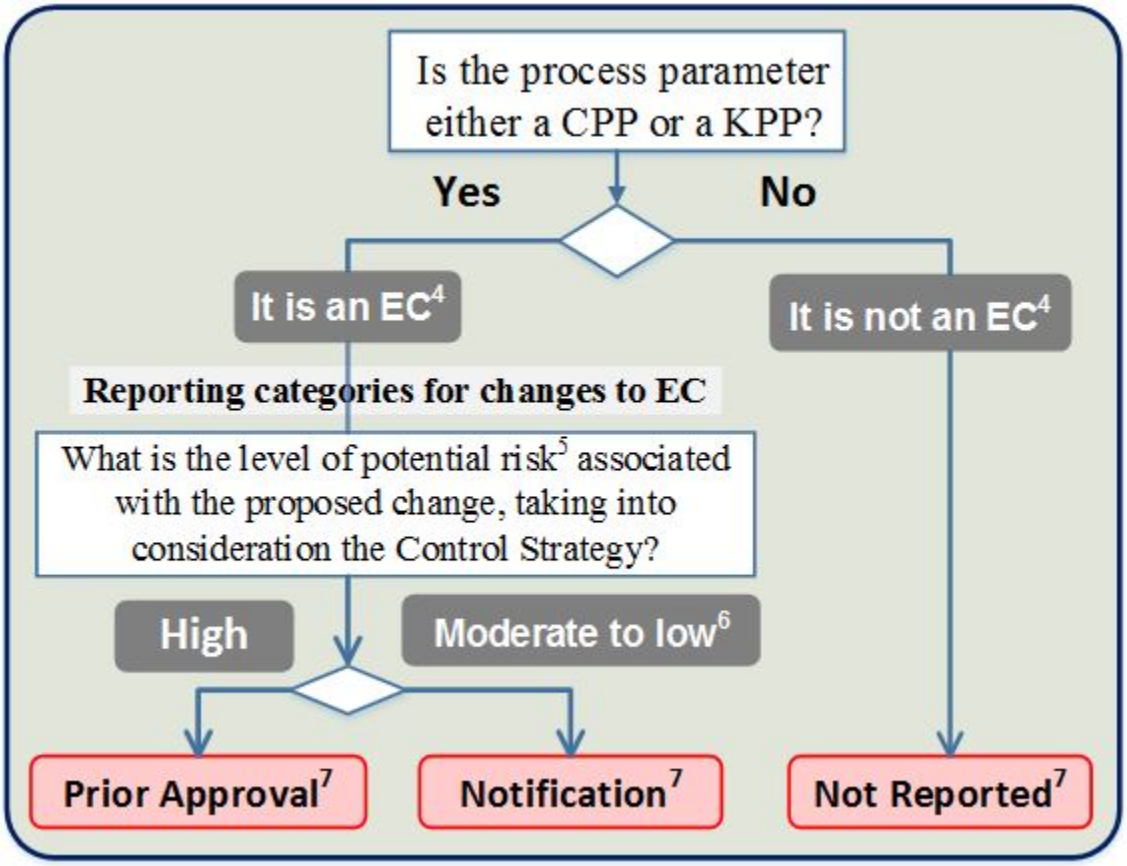
  When considering this approach, it is important to ensure that all relevant parameters and material attributes that have a potential to impact product quality are monitored and

equipment used remains qualified in order to assure a stable process. In certain cases, such as a path-dependent process where a specific outcome cannot be defined (e.g., fluid bed granulation and drying), select parameters or attributes may need to be specified as ECs (e.g., differences in granular properties can affect the final product quality).

A suitably detailed description of the manufacturing process is important to provide a clear understanding of what is and is not necessary to assure product quality. Use of this guidance should not lead to a less detailed description of the manufacturing process in Module 3 of the CTD.

A decision tree to identify ECs and associated reporting categories for manufacturing process parameters is shown in Figure 1. This decision tree is intended to guide the identification of ECs based on an assessment of criticality (i.e., CPPs) or impact on the process consistency as it relates to product quality (i.e., KPPs). The corresponding reporting category is dependent on the potential risk to quality. Risk assessment activities should follow approaches described in ICH Q9. In assessing the risk and subsequent reporting category, an MAH should consider the overall control strategy and any possible concurrent changes. Appropriate justification should be provided in support of the identification of ECs and those aspects that are not ECs.

Figure 1. Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters[3]



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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 evaluated periodically during the lifecycle of the product and, using the decision tree, the ECs should be updated based on acquired knowledge.

Additionally, an MAH should consider the impact of concurrent changes when assessing the appropriate reporting category.

3.2.3.2. Identification of ECs for Analytical Procedures

ECs related to analytical procedures should include elements which assure performance of the procedure. Appropriate justification should be provided to support the identification of ECs for

[3] This diagram does not apply as is for the performance-based approach.
[4] Appropriate justification is expected for ECs and non-ECs
[5] Assessment of risk to quality using tools and concepts found in ICH Q9
[6] In some cases, moderate risk changes may require prior approval.
[7] See Chapter 2 for further guidance on reporting categories and see Chapter 3.3 regarding roles and responsibilities related to managing changes and maintaining an approved application.

analytical procedures. The extent of ECs could vary based on the method complexity, development and control approaches.

- Where the relationship between method parameters and method performance has not been fully studied at the time of submission, ECs will incorporate the details of operational parameters including system suitability.

- When there is an increased understanding of the relationship between method parameters and method performance defined by a systematic development approach including robustness studies, ECs are focused on method-specific performance criteria (e.g., specificity, accuracy, precision) rather than a detailed description of the analytical procedure.

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. Use of this guideline should not lead to providing a less detailed description of analytical procedures in the MAA.

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.

- Submitting a PACMP, in the original marketing application 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.

- Revisions to ECs could also be made utilizing 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 application is the responsibility of the MAH. There is a joint responsibility to share and utilise information between the MAH and any manufacturing organizations to assure the marketing application is maintained, reflects current operations, and that changes are implemented appropriately across relevant sites. Maintenance of the marketing application (including aspects that are not identified as ECs) should follow regional expectations. See Chapter 6 for information related to interactions between an MAH and any manufacturing organizations.

For any referenced submission (e.g., Type II Drug Master File, Active Substance Master File, etc.) in a marketing application, the holder of the referenced submission has a responsibility to report 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, 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 requirements, 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 Chapter 4.5). The PACMP may be submitted with the original MAA or subsequently as a stand-alone submission. The PACMP requires approval by the regulatory authority, and the conditions and acceptance criteria outlined in the protocol must be met 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, in cases where implementation (see "step 2" below) is pending, there is an assumption that the proposed approach is re-evaluated by the MAH on a regular basis and its validity reconfirmed prior to implementation of the change(s). Specifically, before implementing the change(s), the risk assessment provided in the initial PACMP submission should be reviewed by the MAH 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. In such cases, existing guidance should be followed or a consultation with the relevant regulatory authority should be sought. In addition, the MAH should confirm that the control strategy continues to ensure that the product will be produced consistently following implementation of the change(s).

Finally, the use of a PACMP is enabled through an effective PQS that incorporates quality risk management principles (ICH Q9) and an effective change management system (ICH Q10, Appendix 2). 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

A PACMP typically involves 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). 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 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 follow existing regulation or guidance instead.

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 generally 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 includes some, if not all, of the following elements:

- 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 Chapter 8.2.1), and 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 the implementation of step 2 of the PACMP.

- Confirmation 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. Such changes would normally require 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 changes to a single product – see above and Annex IIA, 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:

- 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;

- 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 IIB).

5. PRODUCT LIFECYCLE MANAGEMENT (PLCM)

The PLCM document outlines the specific plan for product lifecycle management that is proposed by the MAH, includes key elements of the control strategy, the ECs, proposed reporting categories for changes to ECs, PACMPs (if used) and any post-approval CMC commitments. This will encourage prospective lifecycle management planning by the MAH and 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 in Chapter 5.2 below and references to the related information located elsewhere in the MAA (see Annex III). Submission of the PLCM document is encouraged; however, the document is expected when the MAH proposes explicit ECs.

The elements of the PLCM document are summarised below:

- **Summary of Product Control Strategy:** A high level summary of the product control strategy should be included in the PLCM document to clarify and highlight which elements of the control strategy should be considered ECs.

- **ECs** (refer to Chapter 3)**:** The proposed 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 proposed 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. The reporting category may be based on regional regulations or guidance, or MAH justification.

- **PACMPs** (refer to Chapter 4)**:** PACMPs that are submitted to prospectively manage and implement one or more post-approval changes should be listed along with the corresponding ECs to be changed. The approval date of the PACMP should be noted in subsequent submissions. If the PACMP is submitted and approved after approval of the original MAA, an updated PLCM document should accompany the PACMP.

- **Post-approval CMC commitments:** CMC commitments (e.g., specific process monitoring, revisions to ECs) that will be implemented during the commercial phase should be listed in the PLCM document.

5.2. Submitting the PLCM Document

The initial PLCM document is submitted with the original MAA or with a supplement/variation for marketed products where defining ECs (Chapter 3.2.3) may facilitate regulatory change management. Following regulatory review and approval of the MAA, the PLCM document will contain ECs and associated reporting categories.

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 Chapter 5.2, but other appropriate formats can be used. See Annex III for an example PLCM table.

The PLCM document can be located in either the CTD Module 1, 2, or 3 based on regional recommendations.

6. PHARMACEUTICAL QUALITY SYSTEM (PQS) AND CHANGE MANAGEMENT

6.1. General Considerations

An effective PQS as established in ICH Q10 and in compliance with regional GMPs is the responsibility of a firm (manufacturing sites and MAH where relevant) and it is not the intent of this guideline to require a specific inspection assessing the state of the PQS before the firm can use the principles in this guideline. The conduct of routine inspections in connection with submitted marketing applications and surveillance will nevertheless continue as foreseen by regional regulatory requirements.

In the event that the PQS is found not to be compliant, it may result in restrictions on the ability to utilise flexibility in this guideline.

Consistent with the basic requirements of ICH Q10, an effective change management system is necessary for implementation of this guideline and is summarised in Appendix 2.

6.2. Management of Manufacturing Changes in the Supply Chain

In many cases, a firm 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 Appendix 2, 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 Contract Manufacturing Organization (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 organization 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.

7. RELATIONSHIP BETWEEN REGULATORY ASSESSMENT AND INSPECTION

Regulatory assessment and inspection are complementary activities and their fundamental roles remain unchanged by this guideline. Facility-related information obtained on inspection should be available to assessors and the most recent PLCM document, when applicable, should be available to inspectors.

Communication between assessors and inspectors can facilitate regulatory review of a specific product submission. When required, information relating to GMP and marketing authorization compliance may be communicated from inspectors to assessors, and vice-versa, via established mechanisms. The communications can also occur between regulators across regions in accordance with appropriate bilateral/multilateral arrangements.

8. POST-APPROVAL CHANGES FOR MARKETED PRODUCTS

Marketed products can benefit from the application of ECs and PACMPs as described in this guideline. Specifically, ECs and reporting categories can be proposed for a marketed product via a post-approval regulatory submission; a PACMP can also be proposed for planned change(s) to a marketed product. In addition, such products would also benefit from additional approaches to facilitate changes. This chapter describes a strategy for a structured approach for frequent CMC changes (e.g., analytical methods) and data requirements for CMC changes (e.g., stability).

8.1. Structured Approach to Analytical Procedure Changes

Marketed products have existing analytical procedures that may benefit from advances made in analytical sciences. The intent of this chapter is to incentivize structured implementation of equivalent analytical procedures that are fit for purpose. An approach wherein specific criteria are defined for changes to analytical procedures used to test marketed products is described below. If this approach is followed and all criteria are met, the analytical procedure change can be made with immediate or other post-implementation notification, as appropriate, to the relevant regulatory authorities.

The following situations are out of scope of this chapter:

- Procedures where the specification does not adequately reflect the complex information provided by the method. In particular, procedures for which only a subset of the peaks are identified and specified (e.g., assay for identity by peptide map, assay for complex drug substances), or where the specification acceptance criteria include a general comparison to a reference standard beyond specified peaks (e.g., "comparable to reference standard" such as for naturally derived products, biotechnology products made in living systems).
- Change(s) to a test method based on a biological/immunological/immunochemical principle or a method using a biological reagent (e.g., bioassay, binding assay, ELISA, testing for viral adventitious agents).
- Changes to predictive models used with multivariate methods.

It is important to note that with the exception of the above exclusion criteria, all other methods are in scope including those used for biotechnological/biological products.

Making use of Chapter 8.1 is dependent on the regional implementation of ICH guidelines (e.g., ICH Q2, Q9 and Q10) and routine application of these guidelines by industry. The flexibility provided in Chapter 8.1 may not be available in all regions and in all situations; some specific changes may require prior approval as defined in regional guidance.

8.1.1. Principles

In order for this approach to be used, the following should be met:

- The high-level description of the original method and the revised method should be the same (e.g., chromatography with spectroscopic detection).

- Validation results should demonstrate that the revised method is equivalent to or better than the original method.

- Test results obtained using the original method and revised method should be equivalent to each other. This should be assessed in two ways: First, the revised method should give an equivalent outcome, i.e., the same quality decision will be made regardless of whether the data was obtained by the original or the revised method. Second, the validation protocol should contain explicit criteria that compare results obtained using the new and revised method. See step 2 below for further details.

- System suitability requirements should be established for the revised method. System suitability ensures the day-to-day performance of the method during routine use.

- Specification changes (e.g., total impurities, potency) cannot be introduced using this mechanism unless allowed by existing regional regulations.

- This approach may not be used if toxicological or clinical data are required as a result of the method change.

If these criteria are met, the methods are equivalent and changes can be made with immediate or other post-implementation notification, as appropriate, to regulatory authorities.

8.1.2. Structured Approach

- Step 1: Evaluate the high-level method description. Examples include:
  - Gravimetric analysis
  - Volumetric analysis
  - Atomic absorption
  - Microscopy
  - Thermal analysis
  - Electrochemical analysis
  - Column chromatography (e.g., HPLC, UPLC)
  - Plate chromatography (e.g., TLC); if used as an ID test or limit test a change to another type of method description may be made if the criteria in this chapter are met.
  - Electrophoresis
  - Changes to spectroscopic procedures should remain within same specific technology, e.g., UV to UV, NMR to NMR.

When two techniques are used together (e.g., HPLC with UV detection), both would be part of the method description (i.e., column chromatography with spectroscopic detection).

- Step 2: A prospective analytical validation protocol should be prepared and approved internally by the firm. It should be based on a comparison of the current and proposed method and knowledge of the original validation protocol. The validation should assure that the revised method will be fit for its intended purpose and should contain at least the following:
  - The principles of ICH Q2 should be followed to validate the change. All validation characteristics relevant to the type of method being validated should be executed as described in ICH Q2.
  - The validation protocol should include, at minimum, the tests used to validate the existing method and all other relevant tests in ICH Q2. For example, if specificity, linearity, precision, and accuracy were assessed during validation of the original method, then specificity, linearity, precision, and accuracy should also be included in the validation of the revised method. The protocol acceptance criteria should reflect appropriate expectations for method performance and be justified scientifically. They should also be developed in the context of the validation acceptance criteria for the original method to assure that the revised method is fit for purpose.

- The validation should assess equivalency of the results of the revised method to those of the original method using parallel testing of an adequate number of samples of appropriate concentration based on the intended use of the method. The assessment of equivalency should include the requirement that the new method does not lose any meaningful information provided by the old method. Also the same quality decision should result when assessing data from the same samples tested using the original and revised methods.

- If there is a switch from manual to automated methods, the validation should also assess the impact of any related changes in critical reagents, reference standards or software.

- The protocol should also contain the detailed operating conditions of both the original method and the revised method to assure the changes being made are clear. The description of the method may be included by attachment.

- Step 3: Consider the system suitability criteria that exist in the current method, if any, and determine, based on method development data and any additional knowledge gained from commercial production, the system suitability criteria aspects that should be part of the new method. System suitability in this context includes all criteria used to evaluate the day-to-day performance of the method when used for routine testing.

- Step 4: Execute the validation protocol and compare the results to the predetermined acceptance criteria. If any criterion is not met, an assessment should be performed to evaluate the impact of the failure to meet the criterion on the validity of the method. If all criteria are met, the method is considered acceptable for its intended use.

- Step 5: Consider new product information, if any, identified as a result of a change in the context of the current regulatory filing. If new or revised specifications (e.g., total impurities, potency) are required based on results obtained during method validation, this structured approach may not be used unless allowed by existing regional regulations. In addition, this approach may not be used if toxicological or clinical data are required as a result of the method change. Thus, the method change should have no impact on safety, efficacy, purity, strength, identity, or potency of the product.

- Step 6: Prepare a written summary report documenting the outcome of the validation versus the protocol criteria.

- Step 7: Follow the internal change process as defined within the firm's PQS to implement the change.

- Step 8: Unless new information is identified as a result of this process (see step 5), provide a post-implementation notification of the method change to the regulatory authority after the change is implemented as per regional reporting requirements. This may include the updated method description, the protocol, and the summary report of the validation.

- Step 9: Complete post-change monitoring. The firm's change control system (refer to Appendix 2) should explicitly identify and document a mechanism to assure the change was

effective with no unintended consequences. The outcome of the assessment should be documented with a conclusion indicating the acceptability of the change.

- Step 10: All information related to the method change should be available for verification during routine regulatory inspection.

8.2. Data Requirements to Support 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 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 proposed in a PACMP (see Annex IIB).

8.2.1. Stability Data Approaches to Support the Evaluation of CMC Change

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, never-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 acquired for the drug product and drug substance. 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
- Stability risk assessments to determine what factors can affect stability relative to the proposed CMC changes
- Use of appropriate tools to evaluate the impact of the proposed 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 informal and formal stability studies or other relevant data
    - Predictive degradation and other empirical or first-principles kinetic modelling
    - Application of relevant institutional knowledge and knowledge from the scientific literature
    - Use of confirmatory 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.

9. 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(s)	Contract Manufacturing Organization(s)
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. (Q8R2)
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. (Q8R2)
CTD	Common Technical Document
ECs	Established Conditions
Firm	Manufacturing sites and MAH where relevant
KPP	Key Process Parameter – parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency as it relates to product quality
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
Notification	The submission of a change in ECs that does not require approval prior to implementation.

Term	Definition
PACMP	Post-Approval Change Management Protocol
PLCM	Product Lifecycle Management
Post-approval CMC commitments	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	Periodic 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

10. 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, and Q10 Questions and Answers -- Appendix: Q&As from Training Sessions (Q8, Q9, and 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 contain elements of supportive information.
- B – applicable to biotechnological/biological products
- For delivery system information, 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)
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 3.2.3.1 – *Identification of ECs for the Manufacturing Processes*

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
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. (**B**)
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 including 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
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 3.2.3.2. –*Identification of ECs for Analytical Procedures*
3.2.S.4.3	Validation of analytical procedure	Supportive information

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
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 qualification (e.g., test, elements of analytical procedure, where appropriate, and acceptance criteria)
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 3.2.2.)
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	Supportive information
3.2.P.2.2	Drug product	
3.2.P.2.3	Manufacturing process development	
3.2.P.2.4	Container closure system	
3.2.P.2.5	Microbiological attributes	
3.3.P.2.6	Compatibility	
3.2.P.3	Manufacture	

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.P.3.1	Manufacturer(s)	Drug Product Manufacturing (including: testing, primary packaging, device assembly for drug product-device combination products) sites
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 3.2.3.1 – *Identification of ECs for the Manufacturing Processes*
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 including 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 For each Quality Attribute on the specification • Test Method • Acceptance Criteria Or, if applicable, Reference to Pharmacopeial monograph
3.2.P.4.2	Analytical Procedures	Reference to Pharmacopeial monograph and if none exists, refer to Chapter 3.2.3.2 – *Identification of ECs for Analytical Procedures*
3.3.P.4.3	Validation of analytical procedures	Supportive information
3.3.P.4.4	Justification of specifications	Supportive information

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.P.4.5	Excipients of Human or Animal Origin	Excipient source and controls should be specified (for human- or animal-derived excipients only)
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 • 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 3.2.3.2 – *Identification of Established Conditions for Analytical Procedures*
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)	
3.2.P.6	Reference Materials	Reference material qualification (e.g., test, elements of analytical procedure, where appropriate, and acceptance criteria)
3.2.P.7	Container Closure System	Supplier/manufacturer of container closure Material of construction and specification

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.P.8	Stability	
3.2.P.8.1	Stability Summary and Conclusion	Drug product storage conditions and shelf-life (or retest period for chemicals) 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 3.2.2.)
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
3.2.A.3	Excipients	Supportive information
3.2.R	**REGIONAL INFORMATION**	
	Not Applicable	Regional regulation and guidance apply. For EU, Medical Device information or CE mark confirmation

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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 a science and data based risk assessment and risk categorisation of the proposed change including the management of risk in the event the proposed 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. When required, ensures that a regulatory submission is developed (e.g., supplement/variation, PACMP) and submitted;

7. Uses a defined change control process to approve or reject the change and involve appropriate stakeholders, including but not restricted to Manufacturing, Quality, and Regulatory personnel;

8. Ensures implementation of the change is based on:

    a. Review that the change as implemented remains aligned with the relevant protocols, any PLCM document and/or any 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 case of deviations from acceptance criteria, or identification of unanticipated risks;

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

11. Verifies, post-implementation, that changes have been effective in achieving the desired outcome with no unintended consequences;

    a. If deviations associated with post-approval changes are detected, ensures that the issue is managed via the firm's deviation management process and

appropriate corrective and/or preventive actions are identified and undertaken via the firm's corrective and preventive action (CAPA) system

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. Requires a post-implementation lessons-learned exercise to build on the product and process knowledge gained with a view to continual improvement, including improvement of the PQS

d. Ensures that the change is included and assessed as part of the Product Quality Review (PQR)

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

Management Review

Details of Management Review are extensively described in ICH Q10 including the use of appropriate performance indicators as a means to assess the effectiveness of a PQS. These should be meaningful, simple and data-driven. In addition to the requirements of ICH Q10 in the context of ensuring an effective change management system, the following could 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 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 proposed changes that are not approved for implementation upon first submission;

- 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);

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 A1.

As indicated in ICH Q10 and shown in Figure A1, these sources can include, but are not limited to, developmental studies, process understanding documents, product or process trending, and product-specific CAPA outcomes. They should be comprehensive across the product lifecycle, including all relevant stakeholders (R&D, manufacturing, CMOs,

suppliers, etc.). With respect to sharing knowledge between the firm and suppliers, and between the firm and CMOs, considerations for sharing knowledge that relates to product and process robustness or otherwise informs changes should be built into quality agreements and/or contracts.

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 PQR and shown in Figure A1. This should include steps taken to identify and manage variability introduced from raw materials and the manufacturing process that could impact on product quality during its lifecycle. This allows for the identification of further need for change not apparent when the data are viewed in isolation.

Use of knowledge is the responsibility of the firm and should be described in the PQS (for more detailed information reference is made to ICH Q8, Q9, Q10, Q11, Q/IWG Q&A). As described in ICH Q10, there is no added regulatory requirement for a formal knowledge management system.

Figure A1 Connection Between Knowledge Management and Change Management Process