Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Annexes
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2021
ICH

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Contains Nonbinding Recommendations

FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

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I. ILLUSTRATIVE EXAMPLES (ANNEX I)[2]

The examples provided in sections I.A through I.F of the ICH Q12 Annexes are mock examples provided for illustrative purposes. They only suggest how the tools described in sections III, IV, and V of the ICH Q12 guidance could be applied, and should not be used as a template or the sole basis for a regulatory submission. In addition, the reporting categories, as described in section II of the ICH Q12 guidance, may differ across regions depending on regional legislation; the nature of the product; and the Marketing Authorization Holder's (MAH's) demonstrated understanding of the product, process, and analytical procedure.

Table 1: Terminology Used in Examples

ICH Terminology	Regional Terminology
Prior approval (PA)	PAS, Type II, PCA, etc.
Notification moderate (NM)	CBE 30, Type IB, MCN, etc.
Notification low (NL)	CBE 0, AR, Type IA, MCN, etc.
Not reported (NR)	

[1] This guidance was developed within the Expert Working Group (Quality) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2019. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory members of the ICH regions.

[2] This guidance is intended to be considered in conjunction with the ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* ([May 2021), which is being simultaneously published as a final guidance. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Sections I.A and I.B: Identification of Established Conditions for the Manufacturing Process

The examples in sections I.A and I.B of the ICH Q12 Annexes illustrate how the development approaches described in section III.B.3.a of the ICH Q12 guidance could be applied. The examples describe different development approaches and resulting control strategies to illustrate how they influence the identification of Established Conditions (ECs) and reporting categories. Marketing Authorization Applications could consist of a combination of these approaches.

These examples demonstrate that increased knowledge and understanding gained from progressively more extensive development approaches lead to reduction of uncertainty and improved management of risk. As a result, ECs could become less extensive and reporting categories more flexible.

For example:

- Enhanced knowledge may lead to a reduction in uncertainty, demonstrating that a material attribute or process parameter initially considered potentially critical in a minimal approach is not actually critical—i.e., does not have an impact on product quality and, therefore, is not an EC.

- Risk management activities could lead to different reporting categories—e.g., a change from prior approval (PA) to a notification for a change to a critical process parameter (CPP). Where the performance-based approach is used, some process parameters may not be classified as ECs due to assurance of quality being provided by online monitoring. In this circumstance, the typical operating conditions for process parameters are provided as supportive information. During manufacture, the process parameters may be adjusted to deliver the expected outcome. The risks related to the in-line Process Analytical Technology (PAT) tests (e.g., near infrared (NIR)) should be appropriately managed throughout the lifecycle. In-line PAT tests used for quality control are considered ECs.

A holistic view of the manufacturing process and overall control strategy is necessary when considering ECs since the output of one unit operation is the input for a subsequent operation.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

A. Identification of Established Conditions for the Manufacturing Process—Chemical Medicinal Product (Annex IA)

Table 2: Powder Blending Unit Operation

	Parameter	Acceptable Ranges and Reporting Categories (White boxes are ECs and grey boxes are not ECs.)		
		Minimal Parameter-Based Approach	**Enhanced Parameter-Based Approach**	**Performance-Based Approach**
Input Materials	API PSD	20–50 um **Tighten (NL)** **Widen (PA)**	5–200 um **Tighten (NL)** **Widen (NM)**	5–200 um **Tighten (NL)** **Widen (NM)**
	API Moisture	<1.0% **(NM)**	**(NR)**	**(NR)**
	Excipients #1–3 Specification	Pharmacopoeial	Pharmacopoeial	Pharmacopoeial
Equipment and Parameters	Operating Principle	Diffusion mixing **(PA)**	Diffusion mixing **(PA)**	Diffusion mixing **(PA)**
	Equipment Type	V-blender **(NM)**	V-blender **(NL)**	**(NR)**
	Scale	200 kg **Increase >10x (NM)**	200 kg **Increase >10x (NL)**	200–600 kg **Increase >10x (NL)**
	Blend Speed	20 rpm CPP **(NM)**	Design space consisting of blend speed: 10–20 rpm blend time 15–25 minutes CPP **(NM)**	15 rpm CPP **(NR)**
	Blend Time	20 minutes CPP **(NM)**		20 minutes CPP **(NR)**

Continued

Table 2 continued: Powder Blending Unit Operation

	Parameter	Acceptable Ranges and Reporting Categories (White boxes are ECs and grey boxes are not ECs.)		
		Minimal Parameter-Based Approach	**Enhanced Parameter-Based Approach**	**Performance-Based Approach**
Output Performance Measure	Homogeneity Method Principle	HPLC **(NM)**	**Not tested**	NIR online analyzer **(PA)**
	Homogeneity Acceptance Criteria	<5% RSD IPC **(NM)**	**Not tested**	<5% RSD IPC **(NM)**

Comments/Justification

For this example, discussion and justification for selected parameters are provided to illustrate concepts in section III.B.3.a of the ICH Q12 guidance. *EC* refers to the identification of ECs; *reporting* refers to the assessment of the appropriate reporting category.

Excipient specifications are ECs and managed in line with the pharmacopoeia. Equipment operating principle is an EC in all cases.

Minimal Parameter-Based Approach

- Active pharmaceutical ingredient (API) particle size distribution (PSD)

  – EC: The impact of the PSD of the API on blend homogeneity and dissolution could not be excluded during development. PSD was not studied outside the range of 20–50 µm; this range is an EC.

  – Reporting: The impact of a change outside this range on blend homogeneity and dissolution is unknown, and the risk to product quality is potentially high. As a result, any future change outside the range would be reported as PA, supported by appropriate studies and data. Changes to tighten the EC range based on knowledge gained during the commercial phase (e.g., better process control observed at tighter ranges) are considered low-risk and reported as notification low (NL).

- API Moisture

  – EC: The impact of API moisture content on blend flowability, which impacts content uniformity, could not be reasonably excluded during development and has not been further studied in detail. The set point value is based on a limited amount of development and manufacturing data. API moisture content is therefore considered an EC.

  – Reporting: A change in this EC is considered moderate risk since downstream processing involves a power-assisted feeder in the tablet press which mitigates the risk of content uniformity failure. The change is reported as notification moderate (NM).

- Blend Equipment

  – EC: Only one type of blending equipment (V-blender) was considered in development. Due to limited knowledge, blender type is considered an EC.

  – Reporting: A change in this EC is considered moderate risk and therefore is reported as NM.

- Blend Speed and Time

  – EC: Blend speeds and times used have not been studied in detail beyond the set points described. The set point values are based on a limited amount of development and manufacturing data. Therefore, the set points and the homogeneity specification are considered ECs.

  – Reporting: When assessing the risk of changing set points for these parameters, it was demonstrated that detection mechanisms are sufficient to capture disturbances in homogeneity. Therefore, changes in these process parameters and specification are reported as NM.

Enhanced Parameter-Based Approach

- API PSD

  – EC: The impact of PSD of API on blend homogeneity and dissolution was well understood. Design of Experiments (DoE) studied PSD within 5–200 um. API PSD was confirmed as having no impact on dissolution. The proposed control range for PSD of 5–200 µm maintained adequate homogeneity. Compared to the minimal approach, a wider PSD range is the EC.

  – Reporting: Enhanced knowledge gained from studying a wider range led to a reduction in uncertainty regarding the impact of changing the EC and a better understanding of the risk related to homogeneity. A change to increase the range beyond that studied is considered a moderate risk and reported as NM. Changes to tighten the EC range based on knowledge gained during the commercial phase (e.g., better process control observed at tighter ranges) are considered low-risk and reported as NL.

- API Moisture

  – EC: API moisture has been studied in detail and demonstrated to have no impact on flowability and content uniformity within the ranges explored. API moisture content is not an EC.

- Blending Equipment

  – EC: The impact of different equipment types within the same operating principle on blend quality was studied and no significant impact was observed. Due to this enhanced knowledge, the EC is focused on blending principle rather than specific type of equipment.

  - Reporting: Enhanced understanding regarding the impact of different blending equipment reduced uncertainty regarding the impact of changing blender type on blend homogeneity. A change is considered low-risk and is reported as NL.

- Blend Speed and Time

  - EC: Enhanced understanding of blending parameter variability on homogeneity allows ranges for blend speed and blend time (i.e., design space established across these two parameters) that maintain adequate product quality and offer more operational flexibility than set points. The ranges studied for both parameters are considered to be ECs. The EC for blend homogeneity testing seen in the minimal approach is not an EC in this approach as a result of enhanced knowledge about the risk of blend segregation gained through homogeneity assessment and stratified sampling during development.

  - Reporting: Changes outside of the design space established for blend speed and time are considered moderate-risk and reported as NM.

Performance-Based Approach

It is assumed that a performance-based approach is developed on the basis of an enhanced approach. The same relationships among material attributes, equipment, process parameters, and product quality as outlined above for the enhanced parameter-based approach apply. However, some of the ECs are different as a result of a performance-based control strategy.

Using a performance-based approach (online NIR analyzer) in the control strategy allows homogeneity confirmation in real time. Use of the NIR analyzer with feedback to blending operating parameters minimizes the need to rely on blend speed and time to ensure blend homogeneity. Therefore, these CPPs are not ECs. The NIR method and blend homogeneity specification are ECs. Enhanced understanding of blending and output measurement allows for a wider range of manufacturing scale. Typical operating conditions for blend speed and time, described in Module 3.2, are supportive information and monitored to assure performance.

B. Identification of Established Conditions for the Manufacturing Process—Biological Medicinal Product (Annex IB)

The following monoclonal antibody example illustrates how ECs and reporting categories could be defined differently depending on the related risk and development approaches used.

This example will focus on two steps: production culture and anion-exchange chromatography.

Figure 2: Monoclonal Antibody Example

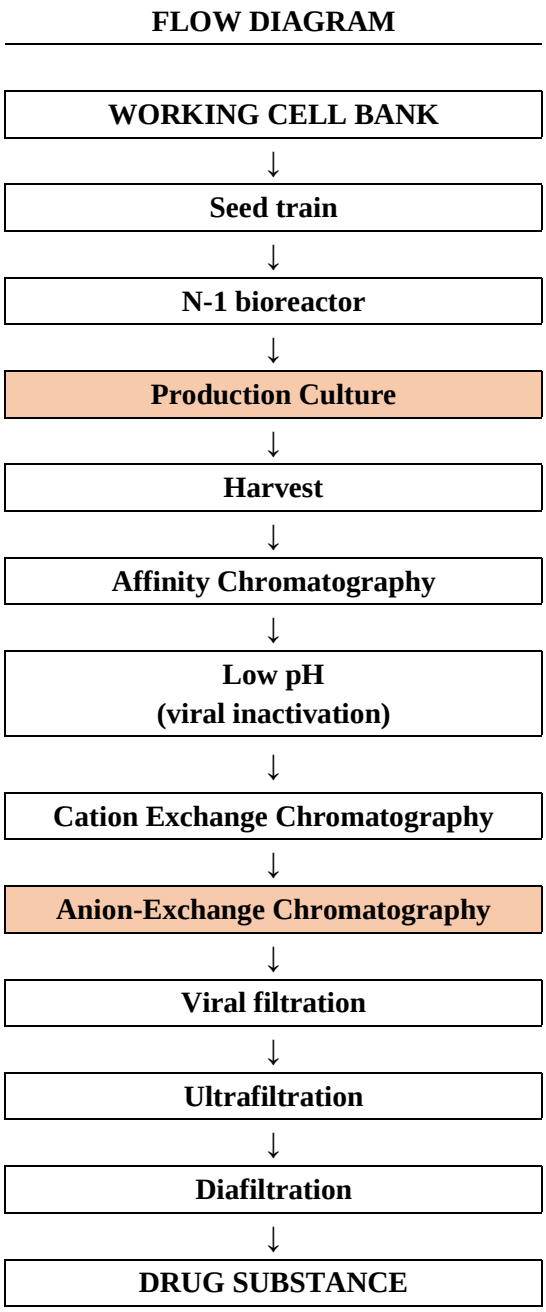

Table 3: Production Culture (XXX L)

Unit Operation	Input/Output	Acceptable Ranges and Reporting Categories (White boxes are ECs and **grey boxes are not ECs**.)		
		Minimal Parameter-Based Approach	**Enhanced Parameter-Based Approach**	**Performance-Based Approach**
Input	Inoculum Cell Density	4.0-6.0 x10^5 cells/mL PP **(NM)**	2.0-8.0 x10^5 cells/mL PP **(NR)**	Controlled by MSPC PP **(NR)**
	Temperature	37.0 – 38.0°C CPP **(PA)**	36.0 – 39.0°C CPP **(NM)**	Controlled by MSPC CPP **(NR)**
	Input Y	### CPP **(PA)**	### CPP **(PA)**	Controlled by MSPC CPP **(NR)**
Output	Viability at Harvest	≥ 70% IPC **(NM)**	≥ 50% (Monitored) **(NR)**	≥ 50% IPC in-line automatic counting **(NM)**
	Titre	≥ 4.0 g/L IPC **(NM)**	≥ 4.0 g/L *Predicted through process model* **(NR)**	≥ 4.0 g/L IPC in-line HPLC **(NM)**
	G0-F Oligosaccharide (CQA)	*Included in release specification*	*Included in release specification*	2.0-5.0% IPC in-line UPLC UV/MS (CQA not included in specification) **(PA)**
	Bioburden	## CFU/mL IPC **(PA)**	## CFU/mL IPC **(PA)**	## CFU/mL IPC **(PA)**

Minimal Parameter-Based Approach

- EC
  - Process development is minimal. Due to a lack of supporting justification, most parameters are considered ECs and ranges are narrow.
  - The bioburden test is considered an EC as the production culture step presents a known risk of microbial growth if contaminated.

- Reporting

  – A change of inoculum cell density is medium-risk, taking into account that control of viability and titre takes place for this step. The change is reported as NM.

  – Considering that the impact of temperature and input Y was not studied, and that literature suggests potential impact of these parameters on a critical quality attribute (CQA), changes to these parameters are considered high-risk. These changes are reported as PA.

  – A change in the bioburden test or results is considered high-risk, considering the severity of microbial contamination at that stage. The change is reported as PA.

Enhanced Parameter-Based Approach

- EC: CQAs have been identified and DoE studies for selected CQAs show that:

  – Temperature and input Y can impact the CQA G0-F at a different magnitude (high impact for input Y and low-to-moderate impact for temperature); these are considered ECs.

  – Inoculum cell density does not impact CQAs and is not considered an EC.

  – Linkage studies demonstrate the lack of impact of viability at harvest on CQAs when reduced to 50%. Process characterization studies demonstrate that viability at harvest is maintained above 70% when the CPPs (temperature and input Y) are maintained within the proposed ranges. Viability at harvest is not considered an EC.

  – Titre is predicted through a process model. With this knowledge, cell viability at harvest and titre are not considered ECs.

  – Bioburden test is considered an EC as the production culture step presents a known risk of microbial growth if contaminated.

- Reporting: Risk management activities have been performed and concluded that:

  – A change to input Y is considered high-risk because input Y has been shown to have a high impact on G0-F. The change is reported as PA.

  – A change in temperature is considered moderate-risk given the low-to-moderate impact on G0-F. The change is reported as NM.

  – A change in bioburden test or limit is considered high-risk given the severity of microbial contamination at that stage. The change is reported as PA.

Performance-Based Approach

- EC
  - In-line tests are used to control outputs in real time. In-line tests are considered to be ECs.
  - Relevant inputs are monitored through Multivariate Statistical Process Control (MSPC) defining a process signature that is not considered an EC.
  - Inputs are adjusted in real time based on a model accounting for the in-line measurements of outputs. Inputs are not considered ECs as the outputs of the step (titre and G0-F level) are assured by in-line testing.
  - The bioburden test is considered an EC as the production culture step presents a known risk of microbial growth if contaminated.
- Reporting
  - Changes of viability and titre tests are assessed as moderate-risk since CQAs are not directly impacted. These changes are reported as NM.
  - A change to G0-F test or ranges is assessed as high-risk because this attribute is not tested in the drug substance specification. The change is reported as PA.
  - A change in the bioburden test or results is considered high-risk given the severity of microbial contamination at that stage. The change is reported as PA.

Table 4: Anion Exchange Chromatography

Unit Operation	Input/Output	Acceptable Ranges and Reporting Categories (White boxes are ECs and **grey boxes are not ECs**.)		
		Minimal Parameter-Based Approach	**Enhanced Parameter-Based Approach**	**Performance-Based Approach**
Input	Feedstock Conductivity	6.0 – 8.0 mS/cm CPP **(PA)**	6.0 – 8.0 mS/cm CPP **(PA)**	6.0 – 8.0 mS/cm CPP **(NR)**
	Feedstock pH	4.8 – 5.2 CPP **(PA)**	4.5-5.5 CPP **(PA >5.5)** **(NM <4.5)**	4.0-6.0 CPP **(NR)**
	Resin Age	≤ 20 cycles, ≤ 3 yrs CPP **(PA)**	≤ 100 cycles, ≤ 3 yrs PP **(NL)**	≤ 100 cycles, ≤ 3 yrs PP **(NR)**
	Input Z	CPP **(PA)**	CPP **(NM)**	CPP **(NR)**
Output	Bioburden	≤ 10 CFU/10 mL IPC **(NL)**	≤ 10 CFU/10 mL (Monitored) **(NR)**	≤ 10 CFU/10 mL (Monitored) **(NR)**
	Endotoxin	≤ 5 EU/mL IPC **(NL)**	≤ 5 EU/mL (Monitored) **(NR)**	≤ 5 EU/mL (Monitored) **(NR)**
	Host Cell Protein (HCP) (CQA)	*Tested in DS specification*	*Predicted through process model*	≤ 100 ppm IPC in-line UPLC UV/MS **(PA)**
	CQA X	*Tested in DS specification*	*Predicted through process model*	In-line IPC **(PA)**

Minimal Parameter-Based Approach

- EC

  – Process development is minimal. The impact of inputs on CQAs has not been studied. Due to the lack of knowledge, all inputs are considered to be ECs as they can potentially have impact on CQAs.

  – Output (i.e., bioburden and endotoxin) are considered ECs as they have potential impact on product quality.

  - HCP and CQA X are part of drug substance specifications and are not tested at this stage. HCP and CQA X are not considered ECs for this step.

- Reporting

  - Considering the lack of understanding of the impact of inputs (feedstock conductivity and pH, resin age, and input Z) on CQAs, changes to these inputs are considered high-risk. These changes are reported as PA.

  - Changes to bioburden and endotoxin limits are considered low-risk as these are further tested in subsequent steps. These changes are reported as NL.

Enhanced Parameter-Based Approach

- EC

  - Studies on scale-down models demonstrate that feedstock conductivity and pH as well as input Z can impact CQAs (HCP and CQA X) and are considered CPPs.

  - Resin age, which has been studied for up to 100 cycles and up to 3 years, did not show any impact on CQAs. Impact on CQAs cannot be excluded when the range is further extended. Resin age is considered an EC.

  - HCP and CQA X are not considered ECs as multivariate studies demonstrated that they remain within their acceptance criteria when feedstock conductivity and pH as well as input Z are maintained within the studied ranges.

  - Bioburden and endotoxin are not considered ECs for this step, taking into consideration testing of the attributes in several of the subsequent process steps, but are monitored.

- Reporting: Risk management activities have been performed and concluded that:

  - Extension of resin age is considered low-risk, taking into account the ongoing validation protocol, which includes time points beyond the claim of 100 cycles/3 years. This change is reported as NL.

  - Change to feedstock conductivity is considered high-risk because it can impact HCP and CQA X. This change is reported as PA.

  - Change to feedstock pH is considered high-risk when increased beyond 5.5 and is reported as PA. This change is considered moderate-risk below 4.5 and is reported as NM.

– A change to input Z has a moderate impact on HCP and CQA X. This change is reported as NM.

Performance-Based Approach

- EC: In-line tests are used to control outputs (i.e., HCP and CQA X) in real time. Inputs are adjusted in real time based on a model accounting for the in-line measurements of outputs. In-line tests are considered ECs.

- Reporting: The control strategy relies on the in-line tests to ensure that HCP and CQA X remain within acceptable ranges. Changes to these in-line tests or ranges are assessed as high-risk and are reported as PA.

C. Identification of Established Conditions for Analytical Procedures (Annex IC)

The following is an example to illustrate how ECs could be presented for an analytical procedure, acceptance criteria, and testing facility, along with their suggested reporting categories. This example considers an analytical procedure (capillary electrophoresis) for a biological drug substance (non-glycosylated recombinant protein) referred to as *Illustropin*, using a minimal development approach validated in accordance to ICH Q2. To better illustrate the example, the change categories, conditions, and data requirements are according to the World Health Organization (WHO) guidelines on procedures for changes to approved biotherapeutic products. The actual reporting categories and data requirements may differ for a particular product and by region.

The information summarized in the table below provides guidance on:

- The conditions to be fulfilled for a given change to be classified as moderate or minor (if any of the conditions outlined for a given change are not fulfilled, the change is assessed and, if appropriate, the next higher reporting category may be used—for example, if any conditions recommended for a low-quality change are not fulfilled, the change may be considered to be a moderate-quality change).

- Adequate scientific data and justification should be provided to support a given change.

Table 5: Moderate or Minor Changes

	All Items Listed are ECs	**Reporting (as example referring to WHO)**
Method	Measurement of Purity: Determination of charged variants of active substance by capillary electrophoresis (nonreduced) and corrected relative-area %.	NM Conditions: None Supporting Data:1–5

Continued

Table 5 continued: Moderate or Minor Changes

	All Items Listed are ECs	Reporting (as example referring to WHO)
Test Solutions	Illustropin Reference Standard: Concentration of test solutions and reference standards: 1 mg/ml Illustropin in water	NL Conditions 1–4 Supporting Data:1, 4, 5
Equipment	Suitable capillary electrophoresis system Suitable spectrophotometric detector Capillary: Material: Uncoated fused silica capillary diameter Ø = 50 µm Size: Effective length = at least 70 cm	
Condition	**Chemicals (pharmacopoeial quality)** Separation buffer (CZE): 13.2 g/l solution of ammonium phosphate adjusted to pH 6.0 with phosphoric acid filtered Rinsing agents: 1M sodium Hydroxide, water, 0.1M sodium hydroxide **Instrument parameters** Detection: 200 nm (UV) Electric field strength: 217 V/cm Temperature: 30 °C **Sample analysis** Injection test solution (a) and the reference solution; injection for at least 3 s then CZE buffer injection for 1 s Separation: Separation buffer at both ends of the capillary Sample storage at 4°C during analysis **System conditioning** Preconditioning: At least 20 min. 1M sodium hydroxide At least 10 min. water At least 20 min. separation buffer Between-run rinsing: 0.1M sodium hydroxide at least 2 min. Separation buffer at least 6 min.	NL Conditions 1–4 Supporting Data:1, 4, 5
System Suitability	Specificity: The electropherogram obtained is similar to the electropherogram of Illustropin supplied with Illustropin reference; 2 peaks (I1, I2) eluting prior to the principal peak and at least 2 peaks (I3, I4) eluting after the principal peak are clearly visible	NL Conditions 1-4 Supporting Data:1, 4, 5

Continued

Table 5 continued: Moderate or Minor Changes

	All Items Listed are ECs	Reporting (as example referring to WHO)
Acceptance Criteria	Deamidated forms: Maximum 5.0% Any other impurity: For each impurity, maximum 2.0% Total: Maximum 10.0%.	Widening: NM Conditions: None Supporting Data:1, 5, 6 Narrowing: NL Conditions: 2, 7 Supporting Data:1
Site Transfer		NM Conditions: None Supporting Data: 7, 8 NL Conditions: 4-6 Supporting Data: 7, 8

Table 6: Conditions To Be Fulfilled To Implement the Change at the Corresponding Reporting Category

1	There is no change in the limits/acceptance criteria outside the approved limits for the approved assays used at release/stability.
2	The method of analysis is the same and is based on the same analytical technique or principle (for example, change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
3	The modified analytical procedure maintains or improves the performance parameters of the method.
4	The change does not concern potency testing.
5	No changes made to the test method.
6	The transfer is within a facility approved in the current marketing authorization for the performance of other tests.
7	The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, change in total impurity limits).

Table 7: Supporting Data (Documentation to Be Submitted)

1	Updated drug substance specifications
2	Copies or summaries of analytical procedures if new analytical procedures are used
3	Validation/qualification results if new analytical procedures are used
4	Comparative results demonstrating that the approved and proposed analytical procedures are equivalent

Continued

Table 7 continued: Supporting Data (Documentation to Be Submitted)

5	Justification for the proposed drug substance specification (for example, tests, acceptance criteria, analytical procedures)
6	Documented evidence that consistency of quality is maintained
7	Information demonstrating technology transfer qualification for the non-pharmacopoeial assay or verification for the pharmacopoeial assay
8	Evidence that the new company/facility is compliant with good manufacturing practices (GMPs)

D. PACMP Example 1 (Annex ID)

The examples in sections I.D and I.E are intended to illustrate the range of Postapproval Change Management Protocols (PACMPs) that are possible for a given type of change. They are not intended to serve as a binding template, and other approaches may also be acceptable. The first example below outlines a protocol for a single change (a manufacturing site change) to a single product. The second example outlines a protocol for multiple changes (multiple manufacturing site changes) that could be implemented for multiple products. These examples are not intended to suggest that the only type of change appropriate for inclusion in a PACMP is a manufacturing site change. As described in section IV of the ICH Q12 guidance, in order to meet expectations regarding continual improvement of the product and process, many other quality-related changes may be suitable for inclusion in a PACMP.

Alternative Manufacturing Site for a Small Molecule Drug Substance

Outline for Step 1 Submission

(1) Introduction and scope

This PACMP is intended to allow for the addition of an alternative manufacturing site for the manufacture, testing, and release of the drug substance for a small-molecule, solid oral drug product.

Based on the risk management activities described below, the implementation of this change in step 2 is proposed to be reported in a submission type that is a lower category than currently provided for in existing regulations or guidance, or a submission type eligible for accelerated review timelines, depending on regional requirements.

(2) Quality risk management (QRM) Activities: QRM is conducted for the proposed alternative site and includes:

- Identification and assessment of the potential risks associated with the proposed change as well as the activities proposed to mitigate each risk

- Accounting for known elements of the process, such as robustness, existing controls, and potential impact on product quality

- Incorporating prior knowledge gained from development and commercial manufacturing experience

(3) Acceptance Criteria: Based on the risk assessment, the following acceptance criteria should be met:

- In a comparative batch analysis, three consecutive batches of drug substance manufactured at the alternative manufacturing site should meet approved specification to demonstrate equivalence to batches manufactured at the currently approved site.

- Other conditions to be met prior to implementation:

  - Stability studies are initiated immediately on a suitable number of commercial-scale batches of drug substance manufactured at the alternate manufacturing site and drug product manufactured with drug substance produced at the alternate manufacturing site. Stability data are to be reported to the regulatory authority subsequent to implementation of the new site according to regional requirements.

  - The alternative manufacturing site has acceptable compliance status for small-molecule drug substance manufacturing; depending on the region, this may be indicated by the last GMP inspection with an acceptable outcome, through a valid GMP certificate, or other appropriate documentation (e.g., Qualified Person declaration).

  - The alternative manufacturing site uses similar manufacturing equipment or equipment with the same type of material of construction.

  - The technology transfer and process qualifications are completed.

  - No change to synthetic route, control strategy, impurity profile, or physicochemical properties.

  - No change to any specification or analytical method for starting material or intermediates.

  - No change in analytical methods or specification for release and stability testing for drug substance manufactured at the alternative site.

  - Any additional regional requirements.

Table 8: Summary of Step 1 and Step 2 Submissions

PACMP Component	PACMP Step 1 Contents (Registration/Approval of Protocol)	PACMP Step 2 Contents (Change Implementation)
Overall Strategy (Scope and Limitations of Proposed Change)	Defined scope and limitations	Demonstrate that the requirements of the scope have been met
QRM	Description of QRM activities and summary of risk assessment	Confirmation that previously conducted risk assessment has not changed—or, if new information is available that impacts the risk assessment, an updated risk assessment has been provided
Acceptance Criteria	Tests and studies to be performed; description of any other criteria to be met, including plans to report outcomes from ongoing stability testing	Data demonstrating that acceptance criteria are met; confirmation that other criteria have been met; updated information in Common Technical Document (CTD) S.2.1, Manufacturer(s) of Drug Substance, and S.4.4, Batch Analyses for Drug Substance

E. PACMP Example 2 (Annex IE)

Manufacturing Site Transfers of Biotechnological Drug Substances

Proposed Outline for Step 1 Submission

(1) Introduction and scope

The primary objective of this expanded PACMP is to support mobility across drug substance manufacturing sites—i.e., the transfer of one or multiple products from one donor site to one or more recipient site(s), including Contract Manufacturing Organizations (sites already licensed with appropriate inspection records), thereby reducing the number of regulatory submissions of similar content and driving consistency. The expanded PACMP effectively leverages concepts of QRM and ICH Q9. Typical process adaptations linked to scale and equipment differences at the donor and recipient site(s) are within the scope of the protocol (e.g., change in raw material sourcing), whereas the scope excludes opportunistic significant process changes (e.g., changes to increase productivity/yield).

(2) Quality Risk Management (QRM) Activities: QRM is performed for each individual site transfer, and includes:

- Identification, scoring, and documentation of the potential hazard and harm associated with each manufacturing unit operation and process change as well as the prevention and detection controls

- Accounting for known elements of the process, such as robustness, existing controls, and potential impact on product quality

(3) Comparability/Acceptance Criteria: The overall comparability plan in line with ICH Q5E comprises the following elements:

- The drug substance meets all release and in-process specifications as well as comparability acceptance criteria (e.g., tolerance intervals (TI, 95/99)) derived from the entire manufacturing history.

- Analytical profiles from selected characterization tests of post-change material are consistent with pre-change material in side-by-side comparison.

- Process performance attributes (e.g., cell culture performance, purification process yields, impurity levels) are comparable between donor and recipient site.

- Process validation is planned at the recipient site.

- Drug substance degradation studies are consistent with pre-change material.

(4) Site-specific considerations

- Site risk

A risk assessment for the receiving site will be conducted by the MAH at the time of implementation. The risk assessment includes the GMP compliance status and should also include factors such as facility experience, process knowledge, and any additional regional assessments (e.g., QP declaration). The outcome of the risk assessment will indicate to the MAH whether a site inspection by the competent regulatory authority may be needed and whether additional data to support the change should be generated (e.g., site-specific stability data).

- Process validation

An overview of the process validation project plan and validation master plan for the site transfer in accordance with the current Pharmaceutical Quality System should be provided (at step 1). A summary of validation studies performed to support the site transfers—e.g., studies adopted from the donor site and new studies at the recipient site—are part of the step-2 implementation submission.

The number of proposed validation batches should be based on the variability of the process, the complexity of the process/product, process knowledge gained during development, supportive data at commercial scale during the technology transfer, and the overall experience of the MAH.

– Stability

Stability studies are traditionally rate-limiting to site transfer timelines; following successful demonstration of comparability by analytical characterization methods, including accelerated and/or stress-stability studies (see section IX of the ICH Q12 guidance) can leverage tiered regulatory submission reporting categories and commitments.

Table 9: Summary Expanded PACMP Step 1 Submission and Proposed Outline for Step 2 Submission

Component	Step 1 Contents (Registration of Protocol)	Step 2 Contents (Change Implementation)
Overall Strategy (Scope and Limitations)	Defined scope and limitations	Demonstrate that the requirements of the scope have been met, including process changes associated with the transfer
QRM	Description of QRM program and approach to site transfer risk assessment	Documented risk control strategy and executed risk management report summary
Comparability and Stability	Comparability plan, real-time stability commitments and acceptance criteria (product-specific)	Data demonstrating that acceptance criteria are met
Process Validation	Overview of validation program	Summary of facility/equipment differences and applicable validation; validation summary data support the process, facility/equipment, and method transfer
Site Risk	Description of site inspection risk assessment	Outcome of site inspection risk assessment defines actual change submission requirements

F. Product Lifecycle Management Document—Illustrative Example (Annex IF)

The following example for drug product illustrates how an MAH can present the elements of section V of the ICH Q12 guidance in an initial Product Lifecycle Management (PLCM) document. Other approaches and formats can be used as appropriate. This example follows the Enhanced Parameter-Based Approach from section I.A of the ICH Q12 Annexes—specifically, the example for identifying ECs for a Solid Dosage Form Tablet X (small molecule).

ECs defined in section I.A of the ICH Q12 Annexes are presented in the table below with additional illustrative ECs; a PACMP; and a postapproval chemistry, manufacturing, and controls (CMC) commitment. This table should not be seen as an exhaustive list of ECs. It is

recognized that other Common Technical Document (CTD) sections containing ECs, or ECs within a CTD section, as outlined in Appendix 1 of the ICH Q12 guidance may be included in a PLCM document. Additional unit operations (roller compaction, tabletting, and film-coating) are listed for illustrative purposes, but their ECs and reporting categories are not described. Similarly, although only the PSD attribute is included in this table, the entire drug substance specification would be provided in an application.

In this example, where the MAH proposes to follow regional regulations and guidance for a change to a particular EC, the reporting category has been left blank.

Table 10: Presentation of the Elements of Section V of the ICH Q12 guidance in an Initial PLCM Document

CTD Section	Established Conditions *(Note that identification and justification of EC is presented in the relevant section of CTD)*	Reporting Category When Making a Change to the Established Condition
3.2.S.4.1	Input material—API PSD (5 – 200 um)	**Tighten (NL)** **Widen (NM)**
3.2.P.3.1	*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	*Drug product batch formula (qualitative and quantitative)*	
3.2.P.3.3	The manufacturing process consists of the following sequence of unit operations: 1. Powder blending 2. Roller compaction 3. Tablet compression 4. Film-coating	
	1. Powder blending The active substance and three excipients are mixed together. The following process parameter are defined as ECs.	
	Operating principle: Diffusion mixing	PA
	Equipment type: V-blender	NL
	Scale: 200kg	NL

Continued

Table 10 continued: Presentation of the Elements of Section V of ICH Q12 guidance in an Initial PLCM Document

CTD Section	Established Conditions *(Note that identification and justification of EC is presented in the relevant section of CTD)*	Reporting Category When Making a Change to the Established Condition
	Design space for blending process parameters Blend speed: 10–20 rpm Blend time: 15–25 minutes	NM
	2. Roller compaction	
	3. Tablet compression	
	4. Film-coating	
3.2.P.3.4	Design space for blending process parameters Blend speed: 10–20 rpm Blend time: 15–25 minutes	NM
3.2.P.4	Input material—Excipients #1 specification (pharmacopeial)	
3.2.P.4	Input material—Excipients #2 specification (pharmacopeial)	
3.2.P.4	Input material—Excipients #3 specification (pharmacopeial)	

Table 11: PACMP and Postapproval CMC Commitment

CTD Section Referenced	PACMP or Postapproval CMC Commitment (If Applicable)
3.2.P.3.3	PACMP included in the Marketing Authorization Application for expanded range for scale
3.2.P.3.3	CMC commitment to monitor dissolution performance for 10 batches manufactured at upper end of blend-time range due to potential overlubrication at the proposed commercial scale (200 kg)

II. STRUCTURED APPROACH TO ANALYTICAL PROCEDURE CHANGES (ANNEX II)

Principles for Analytical Procedure Changes

MAHs are expected to maintain existing analytical procedures for authorized products and ensure that these are kept up-to-date. These analytical procedures can relate to the drug substance(s) and drug product. The intent of this approach is to incentivize structured implementation of at least 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.

This approach does not apply in the following situations:

- Procedures where the acceptance criteria do not adequately reflect the complex information provided by the method; in particular, procedures for which only a subset of the characteristics are identified and specified (e.g., test for identity by peptide map, assay for complex drug substances) or where the specified acceptance criteria include a general comparison to a reference standard beyond specified characteristics (e.g., "comparable to reference standard," such as for naturally derived products, biotechnology products)

- 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, enzyme-linked immunosorbent assay (ELISA), testing for viral adventitious agents)

- Changes to models and multivariate methods (model maintenance for multivariate models is not considered to be a change)

- Changes to analytical procedures (methods) described in pharmacopoeial monographs

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.

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

- The physicochemical basis and the high-level description of the current method and the intended method should be the same (e.g., reversed-phase chromatography with ultraviolet (UV) spectroscopic detection).

- The acceptance criteria of the validation protocol of the current method can be applied to the proposed method as well.

- Validation results should demonstrate that the intended method is equivalent to or better than the current method.

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

  - System suitability requirements should be established for the revised method to ensure the same effectiveness and day-to-day performance of the revised method compared to the current method.

- Acceptance criteria changes (e.g., total impurities, potency) should not be introduced using this mechanism unless tighter/more restrictive acceptance criteria are introduced, or they are allowed by existing regional regulations.

- Toxicological or clinical data are not warranted 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.

Structured Approach for Analytical Procedure Changes

- Step 1: Evaluate the physicochemical basis of the method (the mode) and the method description. When two or more techniques are used together (e.g., high-performance liquid chromatography (HPLC) with UV and mass spectrometry (MS) detection), each technique should be included in the method description. The current and intended method (and its mode(s)) should have the same scientific basis and principles. Changes between different modes (e.g., reversed phase to normal phase liquid chromatography) are not in the scope of this guidance.

  - By way of example, the following changes could be acceptable:

    - A change to a liquid column chromatography method where the mode of separation remains the same (e.g., reversed phase to reversed phase, size exclusion to size exclusion, etc.)

    - A change to an electrophoretic method where the mode of separation and method description remains the same (e.g., reduced to reduced, nonreduced to nonreduced, etc.)

    - A change to a pure spectroscopic or chemical/physical property method where principle remains the same (e.g., UV to UV, refractive index to refractive index, differential scanning calorimetry (DSC) to DSC)

  - This approach can be applied to other methods as appropriate.

- Step 2: A prospective analytical validation protocol should be prepared and approved internally by the company. It should be based on a comparison of the current and intended method, knowledge of the original validation protocol, and regulatory expectations. The validation should assure that the intended 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 intended method. 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 current method and all other relevant tests in ICH Q2 or as required for the analytical method type. For example, if specificity, linearity, precision, and accuracy were assessed during validation of the current method, then specificity, linearity, precision, and accuracy should also be included in the validation of the intended method. The protocol acceptance criteria should reflect current expectations for method performance, be justified scientifically, and not be less stringent than those used for the validation of the current method.

- The validation should demonstrate that the intended method is at least equivalent to the current 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 not lose any meaningful information provided by the current method. In addition, the same conclusion should result when assessing data from the same samples tested using the current and intended 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 current method and the intended method to assure the changes being made are clear.

- 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 intended 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 all criteria are met, the method is considered acceptable for its intended use. If any criterion is not met, the change in method is outside the scope of this approach and should not be implemented.

- 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 acceptance criteria (e.g., total impurities, potency) are required based on results obtained during method validation, this structured approach may not be used, unless it is allowed by existing regional regulations. In addition, this approach may not be used if toxicological or clinical data are needed as a result of the method change. Thus, the method change should have no impact on the 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 company's Pharmaceutical Quality System 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 company's change control system (refer to Appendix 2 of the ICH Q12 guidance) should explicitly identify and document a mechanism to assure the change was effective and had 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 regulatory inspection.