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

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

Q12

ANNEX

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ANNEX

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

Q12

ICH Consensus Document

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ANNEX I: ECS – ILLUSTRATIVE EXAMPLES

Identification of Established Conditions for the Manufacturing Process

The examples provided below are intended for illustrative purposes and only suggest how the EC concept could be applied using the development approaches described in ICH Q12 Guideline Chapter 3.2.3.1.

The examples describe the relevant reporting categories for changes to the ranges of the manufacturing process parameters, controls or equipment referenced in the tables.

This demonstrates that increased knowledge and understanding (e.g., enhanced development approaches) leads 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 an initially determined CPP does not have a direct impact on a CQA. Therefore, it could be classified as either a KPP (impact on process consistency) or a process parameter (PP).

- Risk management activities could lead to downgraded reporting categories e.g., change to CPP could be downgraded from prior approval to notification.

- 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 is provided as supportive information. During manufacture, the process parameters may be adjusted to deliver the expected outcome. The risks related to the inline PAT (Process Analytical Technology) tests, e.g., NIR, should be appropriately managed throughout the lifecycle. The inline PAT tests are considered ECs.

For the parameter based approach where there is limited process understanding, if specific ECs were not proposed by the MAH then regional regulations would be followed for managing post-approval changes. This is illustrated in the examples for comparative purposes.

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

Change Reporting Categories:

Prior Approval (PA) – PAS, Type II, PCA, etc.

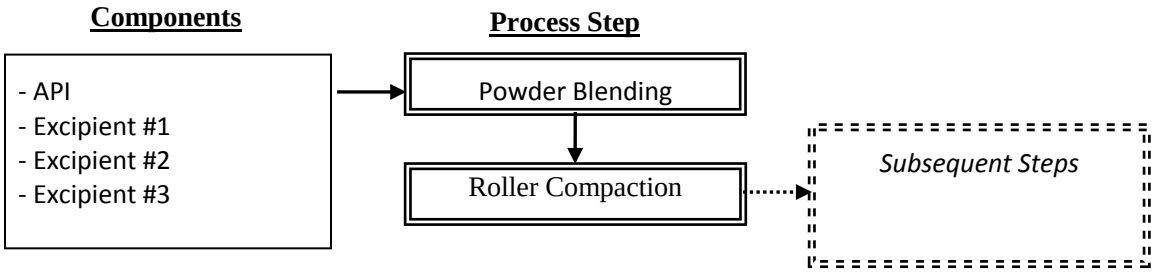
Notification Moderate (NM) – CBE 30, Type IB, MCN, etc.

Notification Low (NL) –AR, Type IA, MCN etc.

Not Reported (NR)

Annex I A: Chemical Product

Process Flow



Powder Blending Unit Operation

	Parameter	Acceptable ranges and reporting categories (White boxes are ECs and grey ones are not-ECs.)			Comments/Justification
		Parameter Based Approach	**Enhanced Approach**	**Performance Based Approach**	Refer to section 3.2.P.2. for detailed justification and experimental data
Input Materials	API PSD	20-50um **(PA)**	5-200um **(NM)**	5-200um **(NM)**	API moisture and Pharmacopoeial specifications for excipients 1-3 are ECs in all cases. Excipient specifications managed in line with the Pharmacopoeia. Equipment type is an EC in all cases. **Enhanced Approach** API Moisture has limited impact on quality demonstrated within the ranges explored. Particle size distribution (PSD) of API demonstrated no impact on dissolution or absorption. DoE studies showed no significant impact on blend uniformity for 5-200um PSD of API. This allows reduction in reporting type for API moisture or PSD. Understanding of variability of blending on product performance allows reduction in reporting type. Knowledge of the impact of scale on blending may allow downgrading of the reporting category (See 3.2.P.2). Homogeneity (blend uniformity <5%RSD) is required for assurance of quality in the next manufacturing step. Experimental studies identified the range of blend speeds and times utilised without significant impact on blend uniformity as confirmed by successful process demonstration. Blending parameters being defined as ECs means homogeneity is not routinely measured but confirmed by end-product testing **Performance Based Approach** Using a performance-based approach (online NIR analyser) in the control strategy allows homogeneity confirmation in real-time. Use of the NIR analyser with feedback to blending operating parameters minimizes the need to rely on blend speed and time to ensure process control. Therefore, these parameters 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 is supportive information and monitored to assure performance.
	API Moisture	<1.0% **(NM)**	<1.0% **(NL)**	<1.0% **(NL)**	
	Excipients #1-3 Specification	Pharmacopoeial	Pharmacopoeial	Pharmacopoeial	
Equipment and Parameters	Equipment type	Diffusion blender (V-blender) **(PA)**	Diffusion blender (V-blender) **(NM)**	Diffusion blender (V-blender) **(NM)**	
	Scale >10x	200kg **(NM)**	200kg **(NL)**	200-600kg **(NL)**	
	Blend Speed	20rpm CPP **(NM)**	10-20rpm KPP **(NL)**	**15 rpm (NR)**	
	Blend Time	20 minutes CPP **(NM)**	15-25 minutes KPP **(NL)**	**20 minutes (NR)**	
Output Performance Measure	Homogeneity method	**Not Tested**	**Not Tested**	NIR online analyser **(PA)**	
	Homogeneity	**Not Tested**	**Not Tested**	<5% RSD IPC **(NM)**	

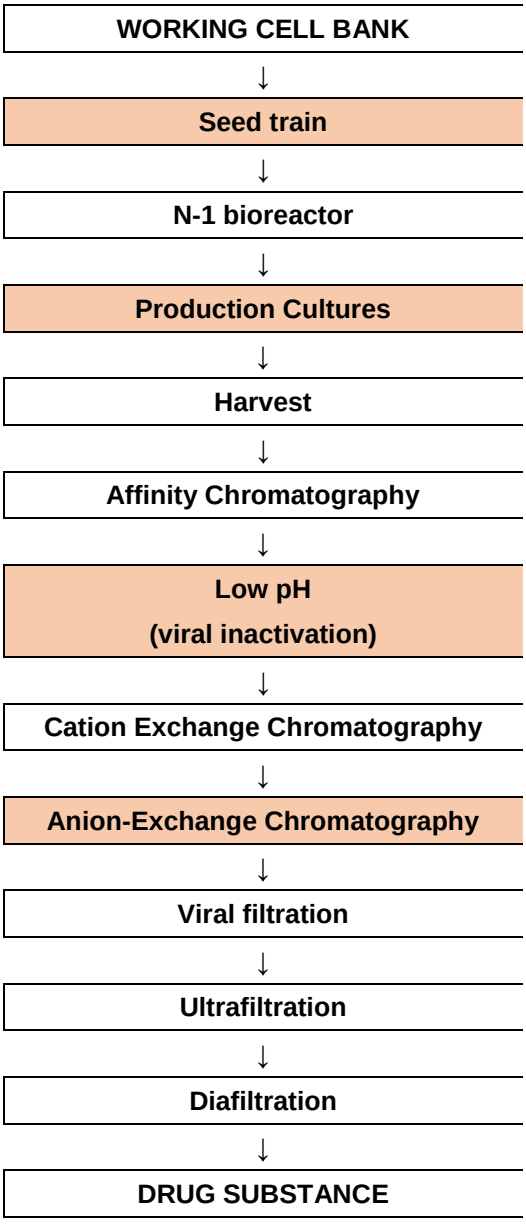
Roller Compaction Unit Operation:

	Parameter	Acceptable ranges and reporting categories (White boxes are ECs and grey ones are not-ECs.)			Comments/Justification Refer to section 3.2.P.2. for detailed justification and experimental data
		Parameter Based Approach	**Enhanced Approach**	**Performance Based Approach**	
Input Materials	Powder Blend	from blending operation	from blending operation	from blending operation	**Enhanced Approach** Understanding of the inter-relationship between roll force/gap and roll speed allows for consistent process operation in achieving a target ribbon density. This provides the optimal input for the subsequent milling operation. Following milling, granules with the desired particle size distribution, flow and compressibility characteristics are generated. These quality attributes verified following the milling operation minimise the need for output performance measurements in the roller compaction operation. Expanded knowledge from experimental studies allows definition of operating ranges and lower reporting categories to be proposed. **Performance Based Approach** Using a performance based approach (online NIR analyser) in the control strategy allows ribbon density to be confirmed in real-time. This allows more flexibility in the type of roller compactor equipment and operating conditions. These output measurements ensure process performance and acceptable ribbon quality attributes. Online measurement of a defined ribbon density with feedback to roller compactor operating parameters reduces variability and ensures lot to lot uniformity of granules for compression. Typical operating conditions are described in Module 3.2 as supportive information and monitored to assure performance.
Equipment and Parameters	Equipment type	Roller compactor with 10cm rolls **(PA)**	Roller compactor with 10cm rolls **(NM)**	Roller compactor with 10cm rolls **(NL)**	
	Roll gap	3mm CPP **(NM)**	2-4mm KPP **(NL)**	**3 mm** **(NR)**	
	Roller compaction force	8kNcm^{-1} CPP **(NM)**	5-10kNcm^{-1} KPP **(NL)**	**7.5kNcm^{-1}** **(NR)**	
	Roller Speed	8rpm CPP **(NM)**	4-10rpm KPP **(NL)**	**7rpm** **(NR)**	
Output performance measure	Ribbon Density Method	**Not Tested**	**Not Tested**	NIR online analyser **(PA)**	
	Ribbon density (solid fraction)	**Not Tested**	**Not Tested**	0.7-0.9 gcm^{-3} **IPC** **(PA)**	

Annex I B: Biological Product

EXAMPLE FOR BIOLOGICAL PRODUCT

FLOW DIAGRAM



The following monoclonal antibody example illustrates how, in a future state, established conditions could be defined differently in terms of for acceptable ranges, extent of parameters included in EC, and reported depending on their related risk and development approaches. This example will focus on 4 steps: seed train, production culture, low pH and anion-exchange chromatography.

Unit operation	Input/Output		Acceptable ranges and reporting categories (White boxes are ECs and **grey ones are not-ECs**.)			Comments
			Parameter Based Approach	**Enhanced Approach**	**Performance Based Approach**	
Seed train	**input**	Viable cell density at thaw	≥1.0 x10^6 cells/mL KPP **(NL)**	≥1.0 x10^6 cells/mL KPP **(NL)**	≥1.0 x10^6 cells/mL PP	**Parameter Based Approach**: The impact of inputs on outputs were not studied. Minimal value is needed to ensure proper seeding of subsequent bioreactors. Viable cell density, pH, duration and input X are considered KPP as they are important to ensure process consistency as it relates to product quality. Viable cell density is tested as output; lower reporting (NL) is proposed. **Enhanced Approach :** Interaction of inputs on outputs were studied through multivariate analyses. No product is produced at this step, and thus the direct impact of PP on CQA cannot be studied for this step (i.e., no CPP identified). Interaction studies shows that a viable cell density at thaw, pH and input X needs to be controlled within tight ranges to ensure proper output (classified as KPP). Duration does not require tight control. Based on the process understanding, outputs of this step are not considered EC, but are internally monitored. **Performance Based Approach:** In addition to the study performed for enhanced approach parameer based: - Outputs of this step were linked to subsequent steps, - Inline tests are used to control outputs in a real time manner; inline test equipment is considered EC (PA).
		pH	6.5 – 7.5 KPP **(NM)**	6.5 – 7.5 KPP **(NM)**	6.5 – 7.5 PP	
		Duration	20 - 28 hours KPP **(NM)**	12 - 48 hours PP (Monitored)	12 - 48 hours PP	
		Input X	### KPP **(NM)**	### KPP **(NM)**	### PP	
	output	Cell viability	≥ 70% IPC **(NM)**	⩾ 70% (Monitored)	≥ 70% IPC inline automatic counting **(NM)**	
		Cell density	≥ 5 x10^6 cells/mL IPC **(NM)**	⩾ 5 x10^6 cells/mL (Monitored)	≥ 5 x10^6 cells/mL IPC at-line NIR **(NM)**	
		Output Y	### IPC **(NM)**	### (Monitored)	### IPC **(NM)**	

Unit operation	Input/Output		Acceptable ranges and reporting categories (White boxes are ECs and **grey ones are not-ECs**.)			Comments
			Parameter Based Approach	**Enhanced Approach**	**Performance Based Approach**	
Production bioreactor (XXX L)	**Input**	Inoculum Cell Density	4.0-6.0 x10^5 cells/mL KPP **(NM)**	2.0-8.0 x10^5 cells/mL PP	Controlled by MSPC	**Enhanced Approach:** Similar DOEs as described for seed train step were performed. These studies showed that: - Temperature and input Z can impact CQAs (classified as CPP) - Inoculum cell density (tested at wider ranges than traditional parameter based approach) do not impact CQAs and process consistency. Downgraded reporting for Temperature is proposed (NM) because statistical models predict that when operating beyond the tested acceptable ranges, CQAs would remain within their acceptance criteria. **Performance Based Approach:** In addition to parameter based: - Outputs of this step were linked to subsequent steps - Inline tests are used to control outputs in a real time manner - Relevant inputs are monitored through Multivariate Statistical Process Control (MSPC) defining a process signature that is not considered EC. - Inputs are adjusted realtime based on a model accounting for the inline measurements of outputs.
		Temperature	37.0 – 38.0°C CPP **(PA)**	36.0 – 39.0°C CPP **(NM)**	Controlled by MSPC	
		Input Z	### CPP **(PA)**	### CPP **(PA)**	Controlled by MSPC	
	output	Viability at harvest	⩾ 70% IPC **(NM)**	⩾ 50% (Monitored)	≥ 50% IPC inline automatic counting **(NM)**	
		Titer	≥ 4.0 g/L IPC **(NM)**	≥ 4.0 g/L *Predicted through process model*	≥ 4.0 g/L IPC inline HPLC **(NM)**	
		G0-F oligosaccharide (CQA)	*Included in release specification*	*Included in release specification*	2.0-5.0% IPC inline UPLC UV/MS (CQA not included in specification) **(PA)**	
		Microbiological tests	### IPC **(PA)**	### IPC **(PA)**	### IPC **(PA)**	

Unit operation	Input/Output		Acceptable ranges and reporting categories (White boxes are ECs and **grey ones are not-ECs**.)			Comments
			Parameter Based Approach	**Enhanced Approach**	**Performance Based Approach**	
Low pH	Input	Operating temperature	18°C – 23°C CPP **(PA)**	15°C – 25°C CPP **(PA)**	15°C – 25°C CPP **(PA)**	Performance based approach is not applicable due to intrinsic viral safety risk (i.e., meaningful output cannot be tested); Such situation should follow parameter based or enhanced approach.
		pH	2.0 – 4.0 CPP **(PA)**	2.0 – 4.0 CPP **(PA)**	2.0 – 4.0 CPP **(PA)**	
		Incubation time	120 -240 min CPP **(PA)**	120 -360 min CPP **(PA)**	120 -360 min CPP **(PA)**	
Anion-Exchange Chromatography	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 PP	**Enhanced Approach:** - Scale down studies demonstrate that feedstocks conductivity, pH, resin age and input XX can impact CQA and are considered CPP. - Ongoing validation protocol includes time points beyond the claim of 100 cycles up to 3 years for the resin age. A downgraded reporting (NL) is proposed to extend the maximum number of cycle / lifetime in accordance to validation protocol. **Performance Based Approach:** In addition to parameter based: - Outputs of this step were linked to subsequent steps - Inline tests are used to control outputs in a real time manner - Inputs are adjusted realtime based on a model accounting for the inline measurements of outputs.
		Feedstock pH	4.8 – 5.2 CPP **(PA)**	4.5-5.5 CPP **(PA)**	4.0-6.0 PP	
		Resin age	≤ 20 cycles, ≤ 3 yrs CPP **(PA)**	≤ 100 cycles, ≤ 3 yrs CPP **(NL)**	≤ 100 cycles, ≤ 3 yrs PP	
		Input XX	### CPP **(PA)**	### CPP **(PA)**	XX PP	
	output	Bioburden	≤ 10 CFU/10 mL IPC **(PA)**	≤ 10 CFU/10 mL IPC **(PA)**	≤ 10 CFU/10 mL IPC **(PA)**	
		Endotoxin	≤ 5 EU/mL IPC **(NM)**	≤ 5 EU/mL Monitored	≤ 5 EU/mL Monitored	
		HCP (CQA)	*Tested in DS specification*	*Predicted through process model*	≤ 100 ppm IPC inline UPLC UV/MS **(PA)**	
		CQA XXX	*Tested in DS specification*	*Predicted through process model*	Inline IPC **(PA)**	

ANNEX II: PACMP- ILLUSTRATIVE EXAMPLES

The examples provided below are intended to illustrate the range of 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 ICH Q12 Guideline Chapter 4, in order to meet expectations regarding continuous improvement of the product and process, many other quality-related changes may be suitable for inclusion in a PACMP.

Annex II A: PACMP Example 1

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; and
- 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 will be 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.
- Alternative manufacturing site to have acceptable compliance status for small molecule drug substance manufacturing; depending on the region, this may be indicated by the last GMP inspection with acceptable outcome, through a valid GMP certificate, or other appropriate documentation (e.g., Qualified Person declaration)
- Alternative manufacturing site to use similar manufacturing equipment or equipment with the same type of material of construction
- Technology transfer and process qualification to be 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.

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 requirements of scope are 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 is 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 are met. Updated CTD sections for S.2.1 Manufacturer(s) of Drug Substance and S.4.4 Batch Analyses for Drug Substance.

Annex II B: PACMP Example 2

Manufacturing Site Transfers of Biotech Drug Substances

Proposed Outline for Step 1 Submission

1. Introduction and Scope

The primary objective of this expanded PACMP is to support the mobility across biologic 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 CMOs (sites already licensed with appropriate inspection record) thereby reducing the number of regulatory submissions of similar content and driving consistency. The expanded PACMP effectively leverages concepts of Quality Risk Management and ICH Q9. Typical process adaptations linked to scale and equipment differences at the donor and recipient site(s) are in 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)

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 characterisation 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, and impurities levels are comparable between donor and recipient site

- Planned process validation at the recipient site

- Drug Substance degradation studies consistent with pre-change material

4. Site specific Considerations

a) 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 such as 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).

b) Process Validation

An overview of the process validation project plan and validation master plan for the site transfer in accordance to the current PQS system should be provided (at step 1). A summary of validation studies performed to support the site transfers, e.g., studies adopted from 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.

c) Stability

Stability studies are traditionally rate-limiting to site transfer timelines; following successful demonstration of comparability by analytical characterisation methods, including accelerated and/ or stress stability studies (see ICH Q12 Guideline Chapter 8.2.) can leverage tiered regulatory submission reporting categories and commitments.

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 requirements of scope met, including process changes associated with transfer
QRM	Description of QRM program and approach to site transfer risk assessment	Documented risk control strategy and executed risk management report summary
Comparability & 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

ANNEX III: PRODUCT LIFECYCLE MANAGEMENT DOCUMENT - ILLUSTRATIVE EXAMPLE

Example for a Solid Dosage Form Tablet X (small molecule)

The following example for drug product illustrates how MAH can present the elements of ICH Q12 Chapter 5 in the PLCM document. Other approaches and formats can be used as appropriate.

Figure 1 presents the current Flow Diagram the drug product Manufacturing Process for Tablet X. For purposes of this example, the flow diagram is limited to the dry blending and roller compaction operations within the manufacturing process using an enhanced approach. The table elaborates the details of the specific established conditions for these operations, the change reporting categories, and associated PACMPs and commitments.

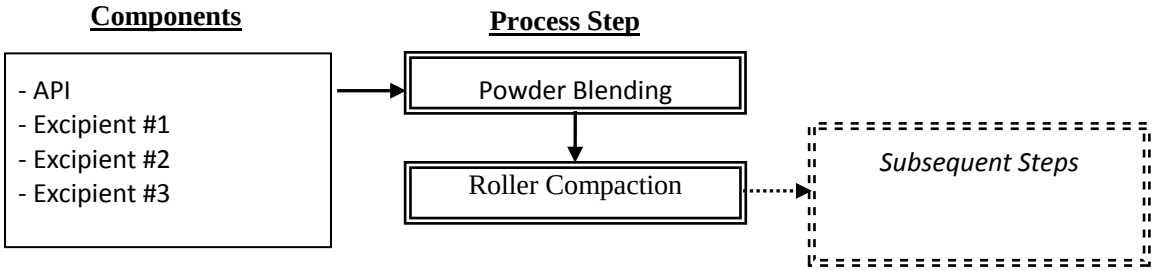
Note: This example is not intended to describe the EC identification process.

Summary of Product Control Strategy

Tablet X is an immediate release, film coated tablet containing 100 mg of API Y, manufactured via a standard batch manufacturing process. Description of Manufacturing Process and Process Controls is typically described in section P.3.3 of Module 3.

The drug product has been developed following an enhanced development approach, using the science- and risk-based principles described in ICH Q8(R2), Q9, and Q10.

Figure 1 Partial Flow Diagram of the Manufacturing Process for Tablet X



CTD Section	Section Title	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	PACMP or Post-approval CMC Commitment, if applicable
3.2.P				
3.2.P.3.3	**Description of Manufacturing Process and Process Controls - Unit Operations**			
	Powder Blending Operation	Input Material - API PSD 5-200um	Notification Moderate	
		Input Material – API Moisture <1.0%	Notification Low	
		Excipients Specification Pharmacopeial	By regional requirement	

CTD Section	Section Title	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	PACMP or Post-approval CMC Commitment, if applicable
		Equipment Type Diffusion blender (V-blender)	Notification Moderate	
		Scale 200kg	Notification Low	PACMP included in the MAA for expanded range for scale to be submitted as a Notification Low
		Blend speed 10-20rpm	Notification Low	
		Blend time 15-25 minutes	Notification Low	CMC commitment to monitor dissolution performance for 10 batches manufactured at upper end of blend time range due to potential over lubrication at the proposed commercial scale (200kg).
		Equipment Type Roller compactor with 10cm rolls	Notification Moderate	

CTD Section	Section Title	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	PACMP or Post-approval CMC Commitment, if applicable
	Roller Compaction Operation	Roll Gap 2-4mm	Notification Low	
		Roller Compaction Force 5-10kNcm^{-1}	Notification Low	
		Roller Speed 4-10rpm	Notification Low	