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4 **ICH guideline Q12 on technical and regulatory**
5 **considerations for pharmaceutical product lifecycle**
6 **management - Annexes**
7 **Step 2b**

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Comments should be provided using this [template](#). The completed comments form should be sent to ich@ema.europa.eu

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12 Document History

Code	History	Date
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15 ICH guideline Q12 on technical and regulatory
16 considerations for pharmaceutical product lifecycle
17 management - Annexes

18 **Table of contents**

19 **Annex I: ECs – Illustrative Examples..... 4**
20 Annex I A: Chemical Product5
21 Annex I B: Biological Product9
22 **ANNEX II: PACMP- Illustrative Examples 14**
23 Annex II A: PACMP Example 1 14
24 Annex II B: PACMP Example 2 16
25 **Annex III: Product Lifecycle Management Document - Illustrative Example**
26 **..... 19**

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29 **Annex I: ECs – Illustrative Examples**

30 **Identification of Established Conditions for the Manufacturing Process**

31 The examples provided below are intended for illustrative purposes and only suggest how the EC
32 concept could be applied using the development approaches described in ICH Q12 Guideline Chapter
33 3.2.3.1.

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

36 This demonstrates that increased knowledge and understanding (e.g., enhanced development
37 approaches) leads to reduction of uncertainty and improved management of risk. As a result, ECs
38 could become less extensive and reporting categories more flexible.

39 For example,

- 40 • Enhanced knowledge may lead to a reduction in uncertainty demonstrating that an initially
41 determined CPP does not have a direct impact on a CQA. Therefore, it could be classified as either
42 a KPP (impact on process consistency) or a process parameter (PP).
- 43 • Risk management activities could lead to downgraded reporting categories e.g., change to CPP
44 could be downgraded from prior approval to notification.
- 45 • Where the performance based approach is used, some process parameters may not be classified as
46 ECs due to assurance of quality being provided by online monitoring. In this circumstance the
47 typical operating conditions for process parameters is provided as supportive information. During
48 manufacture, the process parameters may be adjusted to deliver the expected outcome. The risks
49 related to the inline PAT (Process Analytical Technology) tests, e.g., NIR, should be appropriately
50 managed throughout the lifecycle. The inline PAT tests are considered ECs.

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

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

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57 **Change Reporting Categories:**

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

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

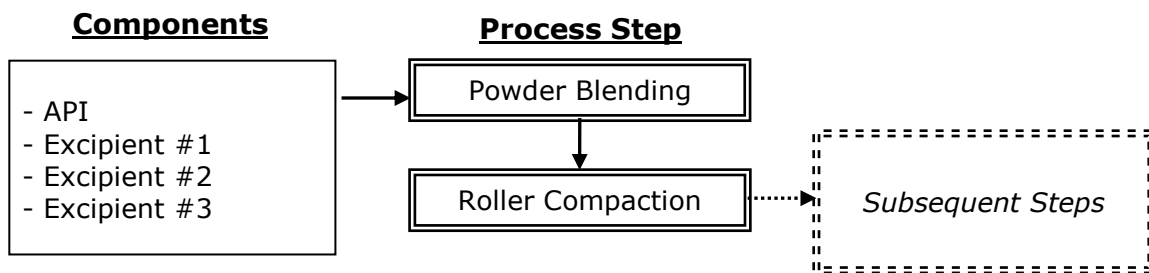
60 **Notification Low (NL) –AR, Type IA, MCN etc.**

61 **Not Reported (NR)**

62 ***Annex I A: Chemical Product***

63 **Process Flow**

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66 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	
Input Materials	API PSD	20-50um (PA)	5-200um (NM)	5-200um (NM)	<p>Refer to section 3.2.P.2. for detailed justification and experimental data</p> <p>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.</p> <p>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</p>
	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)	<p>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</p>
	Homogeneity	Not Tested	Not Tested	<5% RSD IPC (NM)	

					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.
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68 **Roller Compaction Unit Operation:**

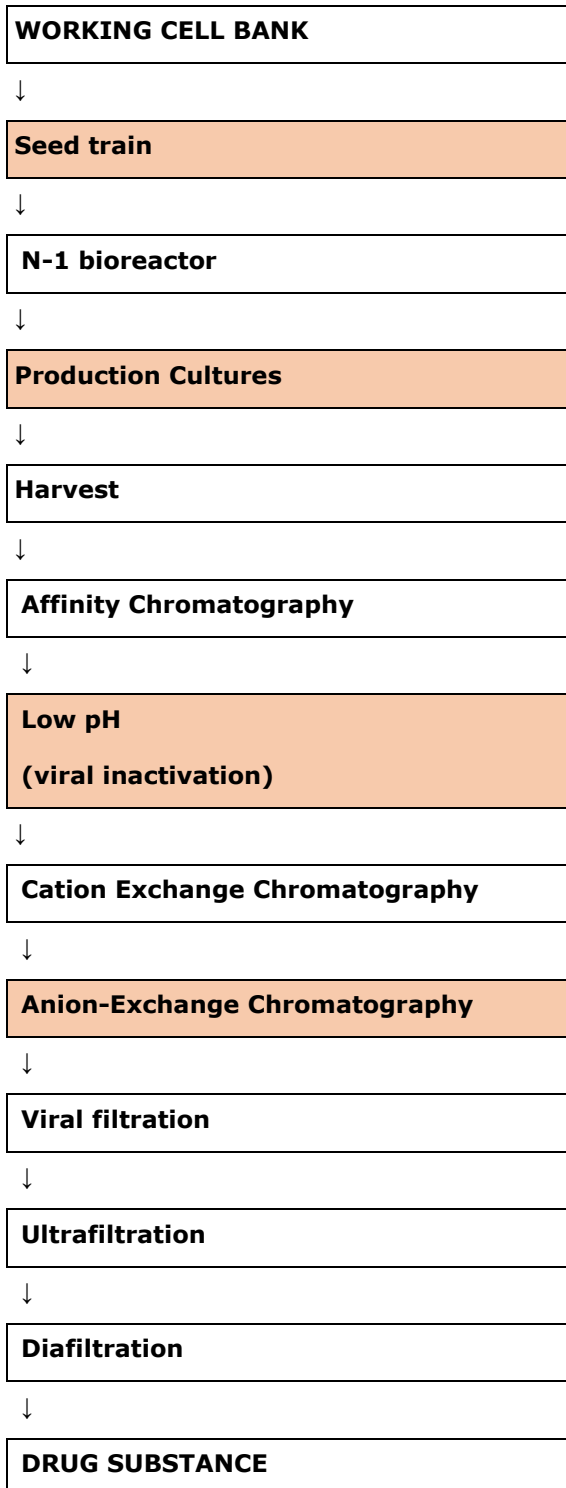
	Parameter	Acceptable ranges and reporting categories (White boxes are ECs and grey ones are not-ECs.)			Comments/Justification
		Parameter Based Approach	Enhanced Approach	Performance Based Approach	
Input Materials	Powder Blend	from blending operation	from blending operation	from blending operation	Enhanced Approach Refer to section 3.2.P.2. for detailed justification and experimental data
Equipment and Parameters	Equipment type	Roller compactor with 10cm rolls (PA)	Roller compactor with 10cm rolls (NM)	Roller compactor with 10cm rolls (NL)	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
	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	4-10rpm	7rpm	

		CPP (NM)	KPP (NL)	(NR)	<p>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.</p>
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)	

69 **Annex I B: Biological Product**

70 **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 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	<p>Parameter Based Approach:</p> <p>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.</p> <p>Viable cell density is tested as output; lower reporting (NL) is proposed.</p>
		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)	<p>Enhanced Approach :</p> <p>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).</p> <p>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.</p> <p>Based on the process understanding, outputs of this step are not considered EC, but are internally monitored.</p>
		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)	<p>Performance Based Approach:</p> <p>In addition to the study performed for enhanced approach parameter based:</p> <ul style="list-style-type: none"> - 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).
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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	<p>Enhanced Approach:</p> <p>Similar DOEs as described for seed train step were performed. These studies showed that:</p> <ul style="list-style-type: none"> - 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. <p>Downgraded reporting for Temperature is proposed (NM) because statistical models predict that when operating beyond the tested acceptable ranges, CQAs would remain</p>
		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 <i>Predicted through process model</i>	≥ 4.0 g/L IPC inline HPLC (NM)	within their acceptance criteria.
	G0-F oligosaccharide (CQA)	<i>Included in release specification</i>	<i>Included in release specification</i>	2.0-5.0% IPC inline UPLC UV/MS (CQA not included in specification) (PA)	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.
	Microbiological tests	### IPC (PA)	### IPC (PA)	### IPC (PA)	- Inputs are adjusted realtime based on a model accounting for the inline measurements of outputs.

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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	<p>Enhanced Approach:</p> <ul style="list-style-type: none"> - 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. <p>Performance Based Approach:</p> <p>In addition to parameter based:</p> <ul style="list-style-type: none"> - 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)	<i>Tested in DS specification</i>	<i>Predicted through process model</i>	≤ 100 ppm IPC inline UPLC UV/MS (PA)	
		CQA XXX	<i>Tested in DS specification</i>	<i>Predicted through process model</i>	Inline IPC (PA)	

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76 **ANNEX II: PACMP- Illustrative Examples**

77 The examples provided below are intended to illustrate the range of PACMPs that are possible
78 for a given type of change. They are not intended to serve as a binding template and other
79 approaches may also be acceptable. The first example below outlines a protocol for a single
80 change (a manufacturing site change) to a single product. The second example outlines a
81 protocol for multiple changes (multiple manufacturing site changes) that could be
82 implemented for multiple products. These examples are not intended to suggest that the only
83 type of change appropriate for inclusion in a PACMP is a manufacturing site change. As
84 described in ICH Q12 Guideline Chapter 4, in order to meet expectations regarding continuous
85 improvement of the product and process, many other quality-related changes may be suitable
86 for inclusion in a PACMP.

87 ***Annex II A: PACMP Example 1***

88 *Alternative manufacturing site for a small molecule drug substance*

89 *Outline for Step 1 Submission*

90 1. Introduction and Scope

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

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

98 2. Quality Risk Management (QRM) Activities

99 QRM is conducted for the proposed alternative site and includes:

- 100 • Identification and assessment of the potential risks associated with the proposed change,
101 as well as the activities proposed to mitigate each risk;
- 102 • Accounting for known elements of the process, such as robustness, existing controls, and
103 potential impact on product quality; and
- 104 • Incorporating prior knowledge gained from development and commercial manufacturing
105 experience.

106 3. Acceptance criteria

107 Based on the risk assessment, the following acceptance criteria should be met:

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

111 Other conditions to be met prior to implementation:

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

- 117 • Alternative manufacturing site to have acceptable compliance status for small molecule
- 118 drug substance manufacturing; depending on the region, this may be indicated by the last
- 119 GMP inspection with acceptable outcome, through a valid GMP certificate, or other
- 120 appropriate documentation (e.g., Qualified Person declaration)

- 121 • Alternative manufacturing site to use similar manufacturing equipment or equipment with
- 122 the same type of material of construction

- 123 • Technology transfer and process qualification to be completed

- 124 • No change to synthetic route, control strategy, impurity profile, or physicochemical
- 125 properties

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

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

- 129 • Any additional regional requirements.

130 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.
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131 **Annex II B: PACMP Example 2**

132 *Manufacturing Site Transfers of Biotech Drug Substances*

133 *Proposed Outline for Step 1 Submission*

134 1. Introduction and Scope

135 The primary objective of this expanded PACMP is to support the mobility across biologic drug
136 substance manufacturing sites, i.e., the transfer of one or multiple products from one donor
137 site to one or more recipient site(s) including CMOs (sites already licensed with appropriate
138 inspection record) thereby reducing the number of regulatory submissions of similar content
139 and driving consistency. The expanded PACMP effectively leverages concepts of Quality Risk
140 Management and ICH Q9. Typical process adaptations linked to scale and equipment
141 differences at the donor and recipient site(s) are in scope of the protocol (e.g., change in raw
142 material sourcing) whereas the scope excludes opportunistic significant process changes (e.g.,
143 changes to increase productivity/yield).

144 2. Quality Risk Management (QRM)

145 QRM is performed for each individual site transfer, and includes:

- 146 • Identification, scoring, and documentation of the potential hazard and harm associated
147 with each manufacturing unit operation and process change, as well as the prevention and
148 detection controls
- 149 • Accounting for known elements of the process, such as robustness, existing controls, and
150 potential impact on product quality

151 3. Comparability/ Acceptance Criteria

152 The overall comparability plan in line with ICH Q5E comprises the following elements:

- 153 • The drug substance meets all release and in-process specifications, as well as
154 comparability acceptance criteria (e.g., tolerance intervals [TI, 95/99]) derived from the
155 entire manufacturing history
- 156 • Analytical profiles from selected characterisation tests of post-change material are
157 consistent with pre-change material in side-by-side comparison
- 158 • Process performance attributes, e.g., cell culture performance, purification process yields,
159 and impurities levels are comparable between donor and recipient site
- 160 • Planned process validation at the recipient site
- 161 • Drug Substance degradation studies consistent with pre-change material

162 4. Site specific Considerations

163 a) Site Risk

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

171 b) Process Validation

172 An overview of the process validation project plan and validation master plan for the site
173 transfer in accordance to the current PQS system should be provided (at step 1). A summary
174 of validation studies performed to support the site transfers, e.g., studies adopted from donor
175 site and new studies at the recipient site are part of the step 2 implementation submission.

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

180 c) Stability

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

185

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

188 **Annex III: Product Lifecycle Management Document -**
189 **Illustrative Example**

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

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

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

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

200 **Summary of Product Control Strategy**

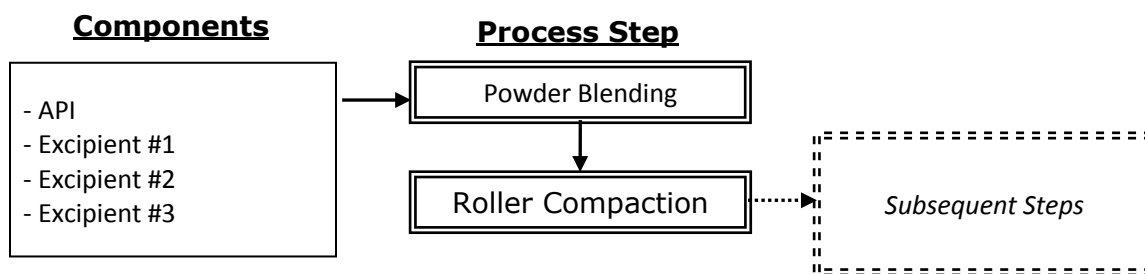
201 Tablet X is an immediate release, film coated tablet containing 100 mg of API Y, manufactured
202 via a standard batch manufacturing process. Description of Manufacturing Process and Process
203 Controls is typically described in section P.3.3 of Module 3.

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

206

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

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209

210

CTD Section	Section Title	Established Conditions <u>Note that identification and justification of EC is presented in the relevant section of CTD</u>	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	
		Equipment Type Diffusion blender (V-blender)	Notification Moderate	

CTD Section	Section Title	Established Conditions <u>Note that identification and justification of EC is presented in the relevant section of CTD</u>	Reporting Category when making a change to the Established Condition	PACMP or Post-approval CMC Commitment, if applicable
		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).
	Roller Compaction Operation	Equipment Type Roller compactor with 10cm rolls	Notification Moderate	
		Roll Gap 2-4mm	Notification Low	
		Roller Compaction Force	Notification Low	

CTD Section	Section Title	Established Conditions <u>Note that identification and justification of EC is presented in the relevant section of CTD</u>	Reporting Category when making a change to the Established Condition	PACMP or Post-approval CMC Commitment, if applicable
		5-10kNcm ⁻¹		
		Roller Speed 4-10rpm	Notification Low	

211