

Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Core Guideline

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

ICH HARMONISED GUIDELINE

Technical and Regulatory Considerations for Pharmaceutical
Product Lifecycle Management
Core Guideline

Q12

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

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1 **1. INTRODUCTION¹**

2 **1.1. Objectives**

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

12 A harmonised approach regarding technical and regulatory considerations for lifecycle
13 management will benefit patients, industry, and regulatory authorities by promoting innovation
14 and continual improvement in the biopharmaceutical sector, strengthening quality assurance and
15 improving supply of medicinal products.

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

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

31

32 **1.2. Scope**

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

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

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

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

38 **1.3. ICH Q12 Regulatory Tools and Enablers**

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

- 43 • Categorisation of Post-Approval CMC Changes ([Chapter 2](#))

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

- 47 • Established Conditions (ECs) ([Chapter 3](#))

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

- 54 • Post-Approval Change Management Protocol (PACMP) ([Chapter 4](#))

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

- 60 • Product Lifecycle Management (PLCM) ([Chapter 5](#))

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

- 65 • Pharmaceutical Quality System (PQS) and Change Management ([Chapter 6](#))

66 An effective PQS as described in ICH Q10 and compliance with regional GMPs are
67 necessary for implementation of this guideline. In particular, management of
68 manufacturing changes across the supply chain is an essential part of an effective
69 change management system. This guideline provides recommendations for robust
70 change management across multiple entities involved in the manufacture of a
71 pharmaceutical product.

72 • Relationship Between Regulatory Assessment and Inspection ([Chapter 7](#))
73 This guideline outlines the complementary roles of regulatory assessment and
74 inspection, and how communication between assessors and inspectors facilitates the
75 use of the tools included herein.

76 • Post-Approval Changes for Marketed Products ([Chapter 8](#))
77 Approaches to facilitate changes to marketed products are outlined. This guideline
78 provides detailed guidance to enable changes to analytical methods to be made with
79 immediate or other post-implementation notification. Science- and risk-based
80 approaches for stability studies in support of the evaluation of CMC changes are also
81 described.

82 The tools and enablers described above are complementary and are intended to link different
83 phases of the product lifecycle. Pharmaceutical development activities result in an appropriate
84 control strategy, elements of which are considered to be **Established Conditions**. All changes to
85 an approved product are managed through a firm’s **Pharmaceutical Quality System**; changes to
86 ECs must also be reported to the regulatory authority. Where the regulatory system provides for
87 **Categorisation of Post-approval CMC Changes** for reporting according to risk, the MAH may
88 propose reporting categories for changes to ECs based on risk and knowledge gained through
89 enhanced pharmaceutical development. A system with risk-based reporting categories also
90 facilitates the use of **Post-Approval Change Management Protocols**, which provide
91 predictability regarding planning for future changes to ECs. The **Product Lifecycle Management**
92 document is a summary that transparently conveys to the regulatory authority how the MAH plans
93 to manage post-approval CMC changes. The tools and enablers in this guideline do not change
94 the **Relationship Between Regulatory Assessment and Inspection**; however, collaboration and
95 communication between assessors and inspectors are necessary for the implementation of this
96 guideline. Finally, this guideline proposes approaches to facilitate **Post-Approval Changes to**
97 **Marketed Products** without the need for regulatory review and approval prior to implementation
98 of certain CMC changes.

99 2. CATEGORISATION OF POST-APPROVAL CMC CHANGES

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

106 In such a regulatory system, the types of changes in the drug substance, drug product, production
107 process, quality controls, equipment, and facility that invoke communication with regulatory
108 authorities are classified with regard to the potential to have an adverse effect on product quality
109 of the drug product. The regulatory communication category, supporting
110 information/documentation requirements, and associated time frame for evaluation are
111 commensurate with that potential risk.

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

117 • **Prior-approval:** Certain changes are considered to have sufficient risk to require
118 regulatory authority review and approval prior to implementation and are requested by the
119 MAH in a suitably detailed regulatory submission. An inspection may be associated with
120 such changes.

121 • **Notification:** Certain moderate- to low-risk changes are judged to not require prior
122 approval and generally require less information to support the change. These changes are
123 communicated to the regulatory authority as a formal notification that takes place within a
124 defined period of time before or after implementation, according to regional requirements.
125 A mechanism for immediate notification is useful when prior approval is not required, but
126 timely awareness of the change by the regulator is considered necessary.

127 In addition, the lowest risk changes are only managed and documented within the PQS and not
128 reported to regulators, but may be verified on routine inspection.

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

133 • Facilitating the use of tools and enablers described in this guideline by providing a range
134 of request and notification categories available as a target for a lowering of regulatory
135 submission requirements.

136
137 • The use of a lower category for request/notification if certain criteria/conditions are met
138 and the relevant supporting documentation is provided as described in regional regulatory
139 guidance; the need for regulatory inspection associated with the change may preclude the
140 ability to use a lower category.

141
142 • Options for possible regulatory convergence regarding the association of a certain type of
143 change with a particular category when reasons for being different from other regulatory
144 authorities are not clearly established.

145
146 A risk-based categorisation system may be accomplished by having the principles captured in
147 regulations with further details in guidance, which can provide additional flexibility to modify
148 expectations as science and technology evolve. For examples of risk-based categorisation systems,
149 refer to existing regulations and guidance of ICH members, and WHO guidelines and guidance on
150 changes to approved products.

151 **3. ESTABLISHED CONDITIONS (ECs)**

152 **3.1. Introduction**

153 Although the Common Technical Document (CTD) format has been defined for a marketing
154 application, there are no previously harmonised approaches to defining which elements in an
155 application are considered necessary to assure product quality and therefore would require a
156 regulatory submission if changed post-approval. These elements are being defined in this
157 guideline as “Established Conditions for Manufacturing and Control” (referred to as ECs
158 throughout this guideline).

159 **3.2. Definition of ECs and Their Role in the Regulatory Submission**

160 **3.2.1. ECs Definition**

161 ECs are legally binding information (or approved matters) considered necessary to assure product
162 quality. As a consequence, any change to ECs necessitates a submission to the regulatory
163 authority.

164 **3.2.2. ECs in a Regulatory Submission**

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

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

174 ECs in a submission are either implicit or explicit:

- 175 • Implicit ECs are elements that are not specifically proposed by the MAH but are derived
176 from and revised according to regional regulation or guidance related to post-approval
177 changes.
- 178 • Explicit ECs are specifically identified and proposed by the MAH together with their
179 proposed reporting category as part of a regulatory submission (see [Chapter 3.2.3](#)). This
180 guideline provides the opportunity to identify explicit ECs and associated reporting
181 categories. Unless otherwise specified by regional requirement, identifying explicit ECs
182 for a given product is not mandatory.

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

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

188 See [Appendix 1](#) for more information regarding sections of the marketing application that may
189 contain ECs and supportive information.

190 3.2.3. Identification of ECs

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

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

197 3.2.3.1. Identification of ECs for the Manufacturing Processes

198 In addition to the unit operation and the sequence of steps, and in considering the overall control
199 strategy, ECs proposed and justified in a manufacturing process description should be those inputs
200 (e.g., process parameters, material attributes) and outputs (that may include in-process controls)
201 that are necessary to assure product quality. These should include critical process parameters
202 (CPPs, as defined in ICH Q8(R2)), as well as key process parameters (KPPs), which are parameters
203 of the manufacturing process that may not be directly linked to critical product quality attributes,
204 but need to be tightly controlled to assure process consistency as it relates to product quality.
205

206 The details of ECs and the associated reporting category will depend on the extent to which the
207 firm can apply knowledge from product and process understanding (i.e., their development
208 approach) to manage the risks to product quality. Appropriate justification should be provided to
209 support the identification of ECs and proposed reporting categories. Different approaches can be
210 used alone, or in combination, to identify ECs for manufacturing processes; these include, but are
211 not limited to the following:
212

213 • A **parameter based approach**, in which product development prior to regulatory
214 submission provides a limited understanding of the relationship between inputs and
215 resulting quality attributes, will include a large number of inputs (e.g., process parameters
216 and material attributes) along with outputs (including in-process controls).

217 • An **enhanced approach** with increased understanding of interaction between inputs and
218 product quality attributes together with a corresponding control strategy can lead to
219 identification of ECs that are focused on the most important input parameters along with
220 outputs, as appropriate.

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

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

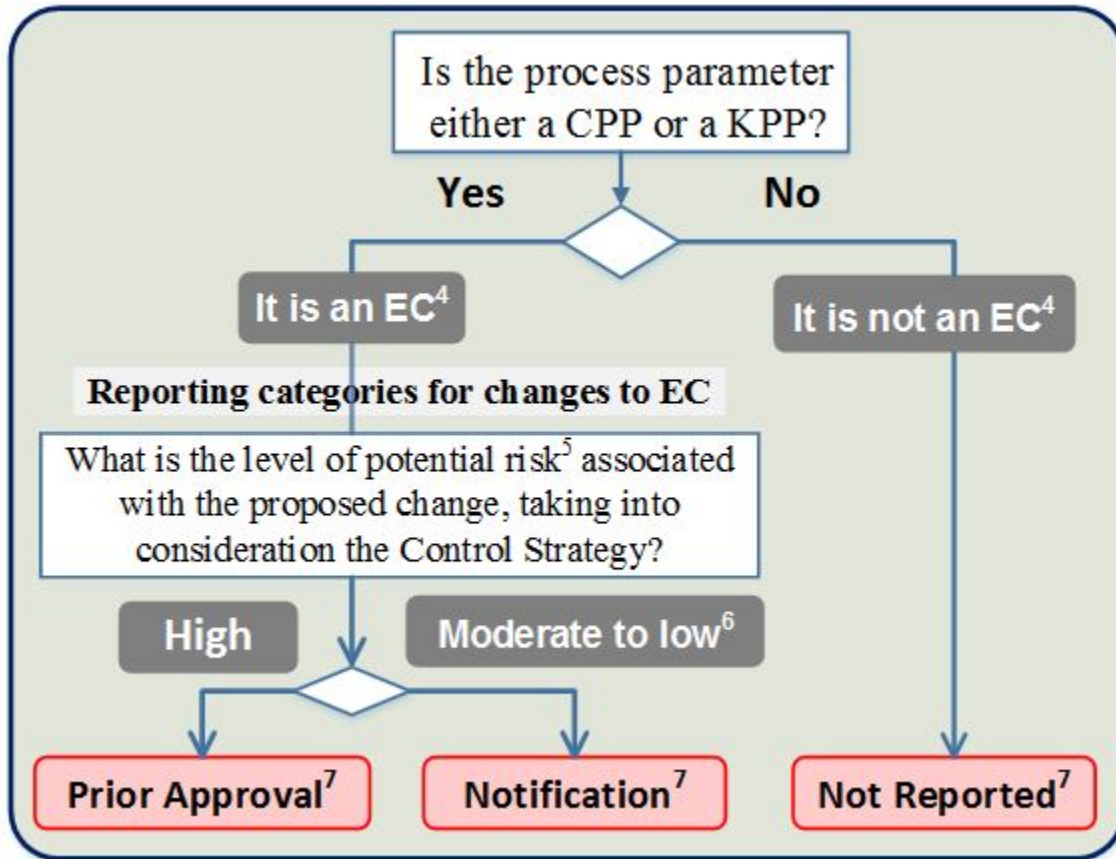
229 equipment used remains qualified in order to assure a stable process. In certain cases, such
230 as a path-dependent process where a specific outcome cannot be defined (e.g., fluid bed
231 granulation and drying), select parameters or attributes may need to be specified as ECs
232 (e.g., differences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

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

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

244

245 **Figure 1. Decision Tree for Identification of ECs and Associated Reporting Categories for**
 246 **Manufacturing Process Parameters³**



247
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249 Information regarding product-specific post-approval change activities, such as post-change
 250 monitoring, may be provided as supporting information to aid in the determination of ECs and
 251 associated reporting categories.

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

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

256 **3.2.3.2. Identification of ECs for Analytical Procedures**

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

³ This diagram does not apply as is for the performance-based approach.

⁴ Appropriate justification is expected for ECs and non-ECs

⁵ Assessment of risk to quality using tools and concepts found in ICH Q9

⁶ In some cases, moderate risk changes may require prior approval.

⁷ See [Chapter 2](#) for further guidance on reporting categories and see [Chapter 3.3](#) regarding roles and responsibilities related to managing changes and maintaining an approved application.

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

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

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

269 A suitably detailed description of the analytical procedures in Module 3 is expected to provide a
270 clear understanding regardless of the approach used to identify ECs for analytical procedures. Use
271 of this guideline should not lead to providing a less detailed description of analytical procedures
272 in the MAA.

273 **3.2.4. Revision of ECs**

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

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

279 • Submission of an appropriate post-approval regulatory submission describing and
280 justifying the proposed revision to the approved ECs. Justification may include information
281 such as validation data and batch analyses.

282 • Submitting a PACMP, in the original marketing application or as part of a post-approval
283 submission, describing a revision to ECs or reporting categories, and how the change will
284 be justified and reported.

285 • Revisions to ECs could also be made utilizing an approved post-approval regulatory
286 commitment, as appropriate.

287 **3.3. Roles and Responsibilities**

288 The management of all changes to and maintenance of the approved marketing application is the
289 responsibility of the MAH. There is a joint responsibility to share and utilise information between
290 the MAH and any manufacturing organizations to assure the marketing application is maintained,
291 reflects current operations, and that changes are implemented appropriately across relevant sites.
292 Maintenance of the marketing application (including aspects that are not identified as ECs) should
293 follow regional expectations. See [Chapter 6](#) for information related to interactions between an
294 MAH and any manufacturing organizations.

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

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

302 **4. POST-APPROVAL CHANGE MANAGEMENT PROTOCOL (PACMP)**

303 **4.1. Definition of a PACMP**

304 A PACMP is a regulatory tool that provides predictability and transparency in terms of the
305 requirements and studies needed to implement a change as the approved protocol provides an
306 agreement between the MAH and the regulatory authority. A protocol describes the CMC change
307 an MAH intends to implement during the commercial phase of a product, how the change would
308 be prepared and verified, including assessment of the impact of the proposed change, and the
309 suggested reporting category in line with regional requirements, i.e., a lower reporting category
310 and/or shortened review period as compared to similar change procedure without an approved
311 PACMP. The PACMP also identifies specific conditions and acceptance criteria to be met. A
312 PACMP can address one or more changes for a single product, or may address one or more changes
313 to be applied to multiple products (see [Chapter 4.5](#)). The PACMP may be submitted with the
314 original MAA or subsequently as a stand-alone submission. The PACMP requires approval by
315 the regulatory authority, and the conditions and acceptance criteria outlined in the protocol must
316 be met in order to implement the change(s).

317 A PACMP should describe changes with a level of detail commensurate with the complexity of
318 the change. Once approved, in cases where implementation (see “step 2” below) is pending, there
319 is an assumption that the proposed approach is re-evaluated by the MAH on a regular basis and its
320 validity reconfirmed prior to implementation of the change(s). Specifically, before implementing
321 the change(s), the risk assessment provided in the initial PACMP submission should be reviewed
322 by the MAH to ensure that the outcomes of that risk assessment as they pertain to the planned
323 change(s) are still valid. If the review of the initial risk assessment indicates an increased level of
324 risk associated with execution of the change, the previously approved reporting category should
325 no longer be considered appropriate. In such cases, existing guidance should be followed or a
326 consultation with the relevant regulatory authority should be sought. In addition, the MAH should
327 confirm that the control strategy continues to ensure that the product will be produced consistently
328 following implementation of the change(s).

329 Finally, the use of a PACMP is enabled through an effective PQS that incorporates quality risk
330 management principles (ICH Q9) and an effective change management system (ICH Q10,
331 Appendix 2). The MAH is responsible for ensuring that whenever a CMC change is to be
332 introduced under a PACMP, the facility meets the regulatory requirements of the regulatory
333 jurisdiction where the PACMP was approved with respect to GMP compliance, and inspection or
334 licensing status.

335 **4.2. Application of a PACMP**

336 A PACMP typically involves two steps:

337 Step 1: Submission of a written protocol that describes the proposed change(s), its rationale(s),
338 risk management activities, proposed studies and acceptance criteria to assess the impact of the
339 change(s), other conditions to be met (e.g., confirmation that there is no change to the approved
340 specification), the proposed reporting category for the change(s), and any other supportive
341 information (see also below). This protocol is reviewed and approved by the regulatory authority
342 in advance of execution of the protocol.

343 Step 2: The tests and studies outlined in the protocol are performed. If the results/data generated
344 meet the acceptance criteria in the protocol and any other conditions are met, the MAH submits
345 this information to the regulatory authority according to the categorisation (classification) in the
346 approved protocol for review by the regulatory authority as appropriate. Depending on the
347 reporting category, approval by the regulatory authority may or may not be required prior to
348 implementation of the change. If the acceptance criteria and/or other conditions in the protocol
349 (see step 1) are not met, the change cannot be implemented using this approach and should follow
350 existing regulation or guidance instead.

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

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

362 **4.3. Elements of a PACMP**

363 The development of the PACMP is informed by the application of process and product
364 understanding gained from product development and/or manufacturing experience. A PACMP
365 includes some, if not all, of the following elements:

366 • A detailed description of the proposed change(s), including a rationale. The differences
367 before and after the proposed change(s) should be clearly highlighted (e.g., in a tabular
368 format).

369 • Based on an initial risk assessment, a list of specific tests and studies to be performed to
370 evaluate the potential impact of the proposed change(s), such as characterisation, batch
371 release, stability (as appropriate, see [Chapter 8.2.1](#)), and in-process controls. The PACMP
372 should include an appropriate description of the analytical procedures and proposed
373 acceptance criteria for each test or study.

- 374 • Discussion regarding the suitability of the approved control strategy or any changes needed
375 to the control strategy associated with the planned change(s).
- 376 • Any other conditions to be met, such as confirmation that certain process qualification steps
377 will be completed before implementation.
- 378 • Where applicable, supportive data from previous experience with the same or similar
379 products related to: development, manufacturing, characterisation, batch release, and
380 stability to allow for risk mitigation.
- 381 • Proposed reporting category for the implementation of step 2 of the PACMP.
- 382 • Confirmation that ongoing verification will be performed under the PQS to continue to
383 evaluate and ensure that there is no adverse effect of the change(s) on product quality. In
384 cases where monitoring of the impact on product quality following implementation of the
385 change(s) is required, a summary of the quality risk management activities should be
386 provided to support the proposed PACMP. If multiple changes are to be implemented,
387 these activities should address the potential risk from the cumulative effect of multiple
388 changes and how they are linked.

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

393 **4.4. Modification to an Approved PACMP**

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

400 **4.5. Types of PACMPs**

401 There are different types of PACMPs:

- 402 • One or more changes to a single product – see above and Annex IIA, for content and
403 implementation. A PACMP can also be designed to be used repeatedly to make a specified
404 type of CMC change over the lifecycle of a product, applying the same principles.

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

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

- 411 ○ One or more changes to be implemented across multiple products (e.g., change in
412 stopper across multiple products that use the same container closure system): the
413 same risk mitigation strategy should be applicable across all impacted products;
- 414 ○ One or more changes to be implemented across multiple products and at multiple
415 sites (e.g., change in analytical method across multiple sites, change in
416 manufacturing site(s) across multiple products): the same risk mitigation strategy
417 should be applicable across all impacted products and/or sites (see Annex IIB).

418 5. PRODUCT LIFECYCLE MANAGEMENT (PLCM)

419 The PLCM document outlines the specific plan for product lifecycle management that is proposed
420 by the MAH, includes key elements of the control strategy, the ECs, proposed reporting categories
421 for changes to ECs, PACMPs (if used) and any post-approval CMC commitments. This will
422 encourage prospective lifecycle management planning by the MAH and facilitate regulatory
423 assessment and inspection. The PLCM document should be updated throughout the product
424 lifecycle as needed.

425 5.1. PLCM Document: Scope

426 The PLCM document serves as a central repository in the MAA for ECs and reporting categories
427 for making changes to ECs. It includes the key elements described in [Chapter 5.2](#) below and
428 references to the related information located elsewhere in the MAA (see Annex III). Submission
429 of the PLCM document is encouraged; however, the document is expected when the MAH
430 proposes explicit ECs.

431 The elements of the PLCM document are summarised below:

- 432 • **Summary of Product Control Strategy:** A high level summary of the product control
433 strategy should be included in the PLCM document to clarify and highlight which elements
434 of the control strategy should be considered ECs.
- 435 • **ECs** (refer to [Chapter 3](#)): The proposed ECs for the product should be listed in the PLCM
436 document. The identification and justification of ECs are located in the relevant sections of
437 the CTD.
- 438 • **Reporting category for making changes to approved ECs** (refer to [Chapter 3](#)): The
439 proposed reporting categories when making a change to an EC should be listed in the PLCM
440 document. The detailed justification of the reporting categories is located in the relevant
441 sections of the CTD. The reporting category may be based on regional regulations or
442 guidance, or MAH justification.
- 443 • **PACMPs** (refer to [Chapter 4](#)): PACMPs that are submitted to prospectively manage and
444 implement one or more post-approval changes should be listed along with the corresponding
445 ECs to be changed. The approval date of the PACMP should be noted in subsequent
446 submissions. If the PACMP is submitted and approved after approval of the original MAA,
447 an updated PLCM document should accompany the PACMP.

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

451 **5.2. Submitting the PLCM Document**

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

456 **5.3. Maintenance of the PLCM Document**

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

461 **5.4. Format and Location of PLCM Document**

462 A tabular format is recommended to capture certain elements of PLCM described in [Chapter 5.2](#),
463 but other appropriate formats can be used. See Annex III for an example PLCM table.

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

466 **6. PHARMACEUTICAL QUALITY SYSTEM (PQS) AND CHANGE MANAGEMENT**

467 **6.1. General Considerations**

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

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

476 Consistent with the basic requirements of ICH Q10, an effective change management system is
477 necessary for implementation of this guideline and is summarised in
478 [Appendix 2](#).

479 **6.2. Management of Manufacturing Changes in the Supply Chain**

480 In many cases, a firm has to manage communication of information and interactions of PQSs
481 across multiple entities (internal and external). Therefore, the implementation of robust change
482 management across multiple sites (outsourced or not) is necessary. In conjunction with change
483 control principles in [Appendix 2](#), the following change management activities should be
484 considered to support the approaches defined in this guideline:

- 485 • Changes to ECs should be communicated in a timely fashion between the MAH and the
486 regulators, and between the MAH and the manufacturing chain (and vice versa).
- 487 • The timeliness of communication is driven by the impact of any change related to ECs and
488 should be targeted to those entities in the chain that need to be aware of or to implement
489 the change over the lifecycle of the product.
- 490 • Process knowledge and continual improvement are drivers for change. For example, a
491 Contract Manufacturing Organization (CMO) may be in a position to propose process
492 improvements which significantly improve control and product consistency. These data
493 can be utilised to revise the ECs and associated PLCM document. The organization
494 responsible for batch release should be aware of all relevant changes and where applicable,
495 be involved in the decision making.
- 496 • The communication mechanisms regarding MAA changes and GMP issues should be
497 defined in relevant documentation, including contracts with CMOs.

498 **7. RELATIONSHIP BETWEEN REGULATORY ASSESSMENT AND INSPECTION**

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

503
504 Communication between assessors and inspectors can facilitate regulatory review of a specific
505 product submission. When required, information relating to GMP and marketing authorization
506 compliance may be communicated from inspectors to assessors, and vice-versa, via established
507 mechanisms. The communications can also occur between regulators across regions in accordance
508 with appropriate bilateral/multilateral arrangements.

509 **8. POST-APPROVAL CHANGES FOR MARKETED PRODUCTS**

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

516 **8.1. Structured Approach to Analytical Procedure Changes**

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

524 The following situations are out of scope of this chapter:

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

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

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

541 **8.1.1. Principles**

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

- 543 • The high-level description of the original method and the revised method should be the
544 same (e.g., chromatography with spectroscopic detection).
- 545 • Validation results should demonstrate that the revised method is equivalent to or better than
546 the original method.
- 547 • Test results obtained using the original method and revised method should be equivalent
548 to each other. This should be assessed in two ways: First, the revised method should give
549 an equivalent outcome, i.e., the same quality decision will be made regardless of whether
550 the data was obtained by the original or the revised method. Second, the validation protocol
551 should contain explicit criteria that compare results obtained using the new and revised
552 method. See step 2 below for further details.
- 553 • System suitability requirements should be established for the revised method. System
554 suitability ensures the day-to-day performance of the method during routine use.
- 555 • Specification changes (e.g., total impurities, potency) cannot be introduced using this
556 mechanism unless allowed by existing regional regulations.
- 557 • This approach may not be used if toxicological or clinical data are required as a result of
558 the method change.
559
560

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

563 **8.1.2. Structured Approach**

564 • Step 1: Evaluate the high-level method description. Examples include:

565 ○ Gravimetric analysis

566 ○ Volumetric analysis

567 ○ Atomic absorption

568 ○ Microscopy

569 ○ Thermal analysis

570 ○ Electrochemical analysis

571 ○ Column chromatography (e.g., HPLC, UPLC)

572 ○ Plate chromatography (e.g., TLC); if used as an ID test or limit test a change to another
573 type of method description may be made if the criteria in this chapter are met.

574 ○ Electrophoresis

575 ○ Changes to spectroscopic procedures should remain within same specific technology, e.g.,
576 UV to UV, NMR to NMR.

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

579

580 • Step 2: A prospective analytical validation protocol should be prepared and approved
581 internally by the firm. It should be based on a comparison of the current and proposed method
582 and knowledge of the original validation protocol. The validation should assure that the
583 revised method will be fit for its intended purpose and should contain at least the following:

584 ○ The principles of ICH Q2 should be followed to validate the change. All validation
585 characteristics relevant to the type of method being validated should be executed as
586 described in ICH Q2.

587 ○ The validation protocol should include, at minimum, the tests used to validate the existing
588 method and all other relevant tests in ICH Q2. For example, if specificity, linearity,
589 precision, and accuracy were assessed during validation of the original method, then
590 specificity, linearity, precision, and accuracy should also be included in the validation of
591 the revised method. The protocol acceptance criteria should reflect appropriate
592 expectations for method performance and be justified scientifically. They should also be
593 developed in the context of the validation acceptance criteria for the original method to
594 assure that the revised method is fit for purpose.

- 595 ○ The validation should assess equivalency of the results of the revised method to those of
596 the original method using parallel testing of an adequate number of samples of appropriate
597 concentration based on the intended use of the method. The assessment of equivalency
598 should include the requirement that the new method does not lose any meaningful
599 information provided by the old method. Also the same quality decision should result
600 when assessing data from the same samples tested using the original and revised methods.
- 601 ○ If there is a switch from manual to automated methods, the validation should also assess
602 the impact of any related changes in critical reagents, reference standards or software.
- 603 ○ The protocol should also contain the detailed operating conditions of both the original
604 method and the revised method to assure the changes being made are clear. The description
605 of the method may be included by attachment.
- 606 ● Step 3: Consider the system suitability criteria that exist in the current method, if any, and
607 determine, based on method development data and any additional knowledge gained from
608 commercial production, the system suitability criteria aspects that should be part of the new
609 method. System suitability in this context includes all criteria used to evaluate the day-to-day
610 performance of the method when used for routine testing.
- 611 ● Step 4: Execute the validation protocol and compare the results to the predetermined
612 acceptance criteria. If any criterion is not met, an assessment should be performed to evaluate
613 the impact of the failure to meet the criterion on the validity of the method. If all criteria are
614 met, the method is considered acceptable for its intended use.
- 615 ● Step 5: Consider new product information, if any, identified as a result of a change in the
616 context of the current regulatory filing. If new or revised specifications (e.g., total impurities,
617 potency) are required based on results obtained during method validation, this structured
618 approach may not be used unless allowed by existing regional regulations. In addition, this
619 approach may not be used if toxicological or clinical data are required as a result of the method
620 change. Thus, the method change should have no impact on safety, efficacy, purity, strength,
621 identity, or potency of the product.
- 622 ● Step 6: Prepare a written summary report documenting the outcome of the validation versus
623 the protocol criteria.
- 624 ● Step 7: Follow the internal change process as defined within the firm's PQS to implement the
625 change.
- 626 ● Step 8: Unless new information is identified as a result of this process (see step 5), provide a
627 post-implementation notification of the method change to the regulatory authority after the
628 change is implemented as per regional reporting requirements. This may include the updated
629 method description, the protocol, and the summary report of the validation.
- 630 ● Step 9: Complete post-change monitoring. The firm's change control system (refer to
631 Appendix 2) should explicitly identify and document a mechanism to assure the change was

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

634

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

637 **8.2. Data Requirements to Support CMC Changes**

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

643 **8.2.1. Stability Data Approaches to Support the Evaluation of CMC Change**

644 Unlike the formal stability studies recommended in ICH Q1A(R2), whose objective is to establish
645 a useful shelf-life and storage conditions for a new, never-marketed drug substance/drug product,
646 the purpose of stability studies, if needed, to support a post-approval CMC change is to confirm
647 the previously approved shelf-life and storage conditions. The scope and design of such stability
648 studies are informed by the knowledge and experience acquired for the drug product and drug
649 substance. Approaches to the design of such studies should be appropriately justified and may
650 include:

- 651 • Identifying the stability-related quality attributes and shelf-life limiting attributes
- 652 • Stability risk assessments to determine what factors can affect stability relative to the
653 proposed CMC changes
- 654 • Use of appropriate tools to evaluate the impact of the proposed change. These may include:
 - 655 ○ Drug substance and/or drug product accelerated and/or stress studies on
656 representative material (which may be pilot or laboratory scale rather than full
657 scale)
 - 658 ○ Pre-and post-change comparability studies on representative material
 - 659 ○ Statistical evaluation of informal and formal stability studies or other relevant data
 - 660 ○ Predictive degradation and other empirical or first-principles kinetic modelling
 - 661 ○ Application of relevant institutional knowledge and knowledge from the scientific
662 literature
 - 663 ○ Use of confirmatory studies post-change instead of submission of data as part of a
664 regulatory change submission

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

668 **9. GLOSSARY**

Term	Definition
CAPA	Corrective Action and Preventive Action – System that focuses on investigating, understanding, and correcting discrepancies while attempting to prevent their occurrence
CMO(s)	Contract Manufacturing Organization(s)
CPP	Critical Process Parameter – process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to assure the process produces the desired product quality. (Q8R2)
CQA	Critical Quality Attribute – a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to assure the desired product quality. (Q8R2)
CTD	Common Technical Document
ECs	Established Conditions
Firm	Manufacturing sites and MAH where relevant
KPP	Key Process Parameter – parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency as it relates to product quality
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
Notification	The submission of a change in ECs that does not require approval prior to implementation.

Term	Definition
PACMP	Post-Approval Change Management Protocol
PLCM	Product Lifecycle Management
Post-approval CMC commitments	Commitment by the MAH to undertake specific CMC activities to be implemented during the commercial phase.
Prior-approval	Change to an approved established condition that requires regulatory review and approval prior to implementation
PQR	Periodic Quality Review – regular periodic review of API or drug products with the objective to verify process consistency, to highlight any trends and to identify product and process improvements
PQS	Pharmaceutical Quality System
QRM	Quality Risk Management

669 **10. REFERENCES**

670 ICH *M4: The CTD – Quality*

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

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

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

675 ICH *Q8(R2) Pharmaceutical Development*

676 ICH *Q9 Quality Risk Management*

677 ICH *Q10 Pharmaceutical Quality System*

678 ICH *Q11 Development and Manufacture of Drug Substances*

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

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

682 **APPENDIX 1: CTD SECTIONS THAT CONTAIN ECs**

683 Notes:

- 684 • This table does not contain a complete list of ECs for a product. The intention of the table is to provide general guidance about the
685 elements of manufacture and control that constitute ECs and their location within the CTD structure.
- 686 • White rows indicate CTD sections where ECs are generally located. Grey rows indicate CTD sections where supportive
687 information is generally located.
- 688 • CTD sections containing ECs may contain elements of supportive information.
- 689 • B – applicable to biotechnological/biological products
- 690 • For delivery system information, the location or the relevant content within the CTD structure may vary depending on the design
691 of the particular product and region

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.S	DRUG SUBSTANCE	
3.2.S.1	General Information	
3.2.S.1.1	Nomenclature	Drug Substance Name, Structure
3.2.S.1.2	Structure	
3.2.S.1.3	General properties	Supportive information
3.2.S.2	Manufacture	
3.2.S.2.1	Manufacturer(s)	Drug Substance Manufacturing Site(s) (including testing)
3.2.S.2.2	Description of manufacturing process and process controls	Individual unit operations and their sequence in the manufacturing process For levels/details of ECs for inputs (process parameters and material attributes) and outputs of individual unit operations, reference is made to Chapter 3.2.3.1 – <i>Identification of ECs for the Manufacturing Processes</i>

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.S.2.3	Control of Materials	Starting material specifications (test, elements of analytical procedure and acceptance criteria) Raw material/reagent/solvent critical controls Source of materials (e.g., cell and seed source, raw materials) and control of critical materials of biological origin Generation and control of Master - Working Cell Bank / Master, Working Seed Lot, etc. (B)
3.2.S.2.4	Control of critical steps and intermediates	Specifications (e.g., test, elements of analytical procedure and acceptance criteria) for critical steps and intermediates including storage conditions of critical intermediates
3.2.S.2.5	Process validation and/or evaluation	Supportive information
3.2.S.2.6	Manufacturing process development	Supportive information
3.2.S.3	Characterisation	Supportive information
3.2.S.3.1 3.2.S.3.2	Elucidation of structure and other characteristics Impurities	Supportive information
3.2.S.4	Control of Drug Substance	
3.2.S.4.1	Specification	Drug Substance Specification For each Quality Attribute on the specification <ul style="list-style-type: none"> • Test Method • Acceptance Criteria
3.2.S.4.2	Analytical Procedures	Reference is made to Chapter 3.2.3.2 . – <i>Identification of ECs for Analytical Procedures</i>
3.2.S.4.3	Validation of analytical procedure	Supportive information

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.S.4.4	Batch analyses	Supportive information
3.2.S.4.5	Justification of specification	Supportive information
3.2.S.5	Reference Material	Reference Material qualification (e.g., test, elements of analytical procedure, where appropriate, and acceptance criteria)
3.2.S.6	Container Closure	Material of construction and specification
3.2.S.7	Stability	
3.2.S.7.1	Stability Summary and Conclusions	Drug Substance storage conditions and shelf-life (or Retest period for chemicals)
3.2.S.7.2	Post-approval stability protocol and stability commitments	Supportive information (also see Chapter 3.2.2.)
3.2.S.7.3	Stability data	Supportive information
3.2.P	DRUG PRODUCT	
3.2.P.1	Description and Composition of Drug Product	Drug Product qualitative and quantitative composition
3.2.P.2	Pharmaceutical development	
3.2.P.2.1	Components of the drug product	Supportive information
3.2.P.2.2	Drug product	
3.2.P.2.3	Manufacturing process development	
3.2.P.2.4	Container closure system	
3.2.P.2.5	Microbiological attributes	
3.2.P.2.6	Compatibility	
3.2.P.3	Manufacture	

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.P.3.1	Manufacturer(s)	Drug Product Manufacturing (including: testing, primary packaging, device assembly for drug product-device combination products) sites
3.2.P.3.2	Batch Formula	Drug Product Batch Formula (Qualitative and Quantitative)
3.2.P.3.3	Description of manufacturing process and process controls	Individual unit operations and their sequence in the manufacturing process For levels/details of ECs for inputs (process parameters and material attributes) and outputs of individual unit operations, reference is made to Chapter 3.2.3.1 – Identification of ECs for the Manufacturing Processes
3.2.P.3.4	Controls of Critical Steps and Intermediates	Specifications (e.g., test, elements of analytical procedure and acceptance criteria) for critical steps and intermediates including storage conditions of critical intermediates
3.2.P.3.5	Process validation and/or evaluation	Supportive information
3.2.P.4	Control of Excipients	
3.2.P.4.1	Specifications	Excipient Specification For each Quality Attribute on the specification <ul style="list-style-type: none"> • Test Method • Acceptance Criteria Or, if applicable, Reference to Pharmacopeial monograph
3.2.P.4.2	Analytical Procedures	Reference to Pharmacopeial monograph and if none exists, refer to Chapter 3.2.3.2 – Identification of ECs for Analytical Procedures
3.3.P.4.3	Validation of analytical procedures	Supportive information
3.3.P.4.4	Justification of specifications	Supportive information

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.P.4.5	Excipients of Human or Animal Origin	Excipient source and controls should be specified (for human- or animal-derived excipients only)
3.2.P.4.6	Novel excipients	(If Novel excipient specification is not described in 3.2.P.4.1) Novel Excipient Specification For each Quality Attribute on the specification <ul style="list-style-type: none"> • Test Method • Acceptance Criteria
3.2.P.5	Control of Drug Product	
3.2.P.5.1	Specification(s)	Drug product specification For each Quality Attribute on the specification <ul style="list-style-type: none"> • Test Method • Acceptance Criteria
3.2.P.5.2	Analytical Procedures	Reference is made to Chapter 3.2.3.2 – <i>Identification of Established Conditions for Analytical Procedures</i>
3.2.P.5.3	Validation of analytical procedures	Supportive information
3.3.P.5.4	Batch analyses	Supportive information
3.2.P.5.5	Characterisation of impurities	
3.2.P.5.6	Justification of specification(s)	
3.2.P.6	Reference Materials	Reference material qualification (e.g., test, elements of analytical procedure, where appropriate, and acceptance criteria)
3.2.P.7	Container Closure System	Supplier/manufacturer of container closure Material of construction and specification

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.P.8	Stability	
3.2.P.8.1	Stability Summary and Conclusion	Drug product storage conditions and shelf-life (or retest period for chemicals) Where applicable, in-use storage conditions and shelf-life
3.2.P.8.2	Post-approval stability protocol and stability commitment	Supportive information (also see Chapter 3.2.2.)
3.3 P.8.3	Stability data	Supportive information
3.2.A	APPENDICES	
3.2.A.1	Facilities and equipment	Regional regulation and guidance apply
3.2.A.2	Adventitious agents safety evaluation	Supportive information
3.2.A.3	Excipients	Supportive information
3.2.R	REGIONAL INFORMATION	
	Not Applicable	Regional regulation and guidance apply. For EU, Medical Device information or CE mark confirmation

693 **APPENDIX 2: PRINCIPLES OF CHANGE MANAGEMENT**

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

- 696 1. Captures stimuli for change including those that can improve product performance
697 or process robustness;
- 698 2. Ensures full understanding of the scope of the change and its implications for all
699 aspects of the process and control strategy including the impact on ECs and aspects
700 that are not ECs in affected marketing authorisations;
- 701 3. Leverages existing process performance and product quality knowledge;
- 702 4. Requires a science and data based risk assessment and risk categorisation of the
703 proposed change including the management of risk in the event the proposed
704 change is not implemented;
- 705 5. Determines data (existing and/or to be newly generated) needed to support the
706 change and accordingly develops study protocols describing the methods,
707 prospective acceptance criteria as well as additional post-implementation process
708 performance and/or product quality monitoring as necessary;
- 709 6. When required, ensures that a regulatory submission is developed (e.g.,
710 supplement/variation, PACMP) and submitted;
- 711 7. Uses a defined change control process to approve or reject the change and involve
712 appropriate stakeholders, including but not restricted to Manufacturing, Quality,
713 and Regulatory personnel;
- 714 8. Ensures implementation of the change is based on:
- 715 a. Review that the change as implemented remains aligned with the relevant
716 protocols, any PLCM document and/or any PACMP;
- 717 b. Assessment of data generated to demonstrate that the change objective and
718 acceptance criteria were met;
- 719 9. Ensures that risk-mitigating steps are developed in case of deviations from
720 acceptance criteria, or identification of unanticipated risks;
- 721 10. Captures new product/process knowledge gained during implementation of the
722 change;
- 723 11. Verifies, post-implementation, that changes have been effective in achieving the
724 desired outcome with no unintended consequences;
- 725 a. If deviations associated with post-approval changes are detected, ensures
726 that the issue is managed via the firm's deviation management process and

- 727 appropriate corrective and/or preventive actions are identified and
728 undertaken via the firm's corrective and preventive action (CAPA) system
- 729 b. Where applicable, ensures that regulatory filings are updated and an
730 assessment is made as to whether updates to the PLCM document are
731 needed
- 732 c. Requires a post-implementation lessons-learned exercise to build on the
733 product and process knowledge gained with a view to continual
734 improvement, including improvement of the PQS
- 735 d. Ensures that the change is included and assessed as part of the Product
736 Quality Review (PQR)
- 737 12. The change management system should be organised and available for review
738 during audit/inspection.

739 *Management Review*

740 Details of Management Review are extensively described in ICH Q10 including the use of
741 appropriate performance indicators as a means to assess the effectiveness of a PQS. These
742 should be meaningful, simple and data-driven. In addition to the requirements of ICH Q10
743 in the context of ensuring an effective change management system, the following could be
744 considered in the Management Review:

- 745 • Monitoring the timeliness of the change management system to assure that changes
746 are implemented in a timely manner commensurate with the urgency identified for
747 the change. When implementation is delayed, an assessment and mitigation of any
748 risks associated with the delay should be made;
- 749 • Monitoring the performance of the change management system, such as assessing
750 the frequency of proposed changes that are not approved for implementation upon
751 first submission;
- 752 • Ensuring that post-implementation verification occurs and reviewing the results of
753 that verification as a measure of change management effectiveness (e.g., to identify
754 improvements to the change management system);

755 *Use of Knowledge in Change Management*

756 An effective change management system includes active knowledge management, in
757 which information from multiple sources is integrated to identify stimuli for changes
758 needed to improve product and/or process robustness. The connection between knowledge
759 management and change management is illustrated in Figure A1.

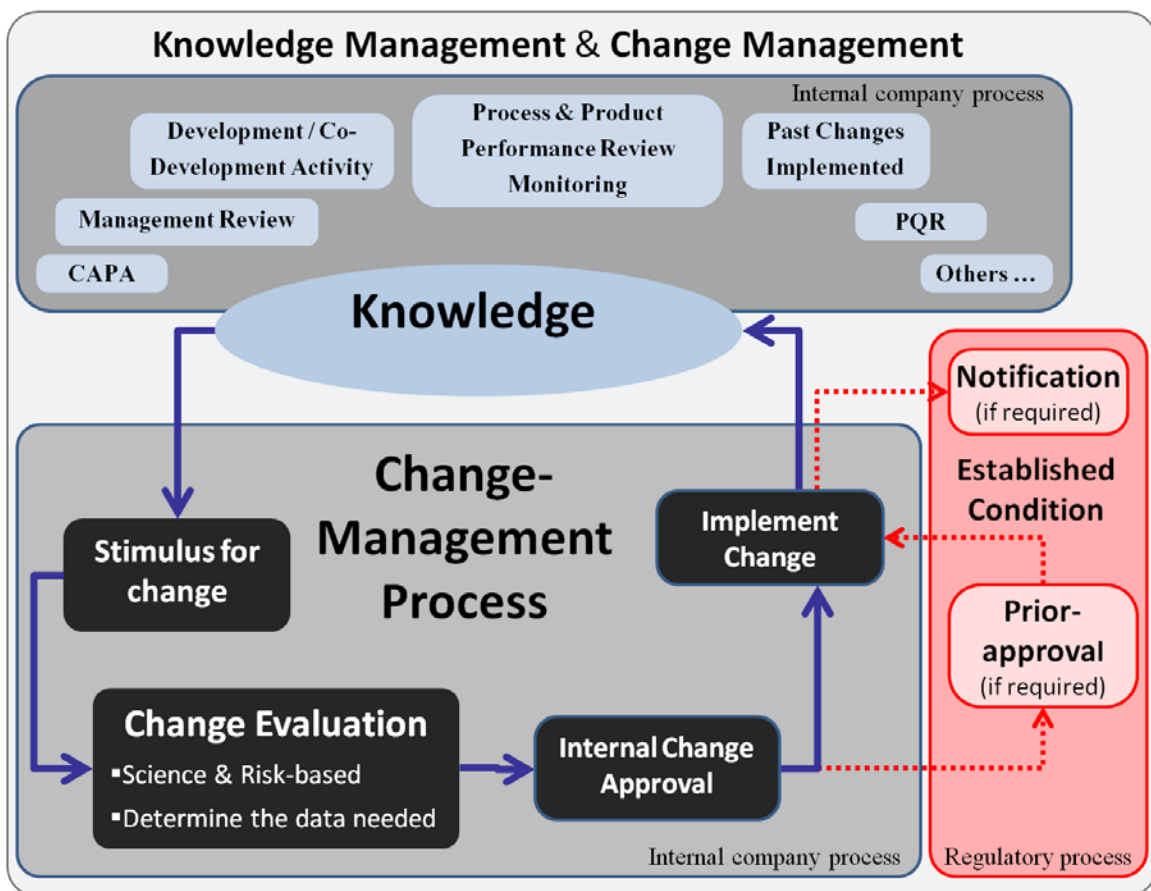
760 As indicated in ICH Q10 and shown in Figure A1, these sources can include, but are not
761 limited to, developmental studies, process understanding documents, product or process
762 trending, and product-specific CAPA outcomes. They should be comprehensive across the
763 product lifecycle, including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

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

768 In addition to individual sources of information, there should be a mechanism to provide a
 769 holistic view of quality performance for a specific product or product family on a regular
 770 basis, as captured in the PQR and shown in Figure A1. This should include steps taken to
 771 identify and manage variability introduced from raw materials and the manufacturing
 772 process that could impact on product quality during its lifecycle. This allows for the
 773 identification of further need for change not apparent when the data are viewed in isolation.

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

778 **Figure A1 Connection Between Knowledge Management and Change Management**
 779 **Process**



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