17 January 2019
EMA/883815/2018

Overview of comments received on ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management (EMA/CHMP/ICH/804273/2017)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Kinapse, a Syneos Health™ Company
2	Gilead Sciences International Limited
3	Emergent BioSolutions
4	A3P Association
5	Indivior UK Limited
6	Janssen Pharmaceutical Research And Development, LLC
7	International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium)
8	AESGP + APIC + EFPIA/EBE/Vaccines Europe + Medicines for Europe
9	Shire Pharmaceuticals
10	CSL Behring
11	LEO Pharma A/S
12	International Plasma and Fractionation Association (IPFA)

Please note that comments will be sent to the **ICH Q12 EWG** for consideration in the context of Step 3 of the ICH process.

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1. General comments – overview

Stakeholder no.	General comment (if any)
1	This is a good initiative; defining established conditions (ECs) for a drug product should minimize number of variations based on critical risk assessment and scientific approach. The proposal (if adopted by a company) can pose a challenge for legacy products than newer products in terms of generating supplementary developmental studies for proposing ECs. Both the Established conditions (ECs) and Product Lifecycle Management (PLCM) are the core of the Q12 guideline. Incompatibility of these concepts with the established legal framework is a matter of concern at the moment.
2	**Comment:** Many of the lifecycle management concepts introduced in the Q12 draft are similar to the requirements of the JNDA M1.2 Application Form (e.g., pre-approval, notification, KPP, etc.). These concepts may not be familiar to other groups (e.g., those focused on FDA/EMA standards). By raising these concepts only in the context of guiding post-approval filing decisions, ICH misses an opportunity to describe how they may play a role in development and initial MAA content decisions. **Proposed change:** Consider adding text to Section 3 to better link these concepts to the development process described in ICH Q8(R2). Various sponsors may have useful suggestions on additional content.
3	The goal of ICH Q12 in achieving a harmonized approach regarding technical and regulatory considerations for lifecycle management to benefit patients, industry and regulatory authorities is commended. However, there is concern that in certain ICH regions the proposed guideline is not aligned or fully compatible with the established legal framework with regard to the use of Established Conditions (ECs) and Product Lifecycle Management (PLCM). In order to fully realize the impact of this document, ICH regions will need to make strides in addressing this to build the appropriate infrastructure and update existing guidance to point to the tools and enablers described in ICH Q12. Further, for established products, already marketed products, although Chapter 8 suggests that ECs can be proposed as a post-approval change and PACMPs can be used for proposed changes, it is not clear how the Market Authorization Holder (MAH) are to establish the ECs, the PLCM document, and/or PACMPs and have these negotiated and approved by the Regulatory Agencies in some jurisdictions. Specifically, these mechanisms are not discussed in current local regulations nor guidances. Each jurisdiction will need to work towards building infrastructure and amending

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	existing legislation and/or guidelines to enable the use of the tools described in ICH Q12 in order for the benefits of ICH Q12 to be realized. There needs to be a clear process on how to submit and gain agreement on ECs, PLCM and PACMP for already licensed products to avoid significant work for both regulators and industry. The scope of ICH Q12 includes "drug-device combination products" yet the content mostly addresses characteristics of drug development. It is recommended that a footnote be added to the scope, indicating that there may be specific aspects of drug-device combination products (i.e. device functionality and performance) that should be considered. Furthermore, it should be acknowledged that there are other systems available for device development, risk management and quality system management of devices and that it is up to the MAH to determine how best to integrate those processes with ICH Q8, Q9 and Q10 to apply to the combination products. The document reflects key considerations for managing changes to pharmaceuticals and focus mostly on changes to process. Drug delivery devices have additional considerations, specifically changes to the device design. Additionally, there are other systems that are used in the development of devices. The MAH should consider where these differences can be complementary to the corresponding ICH Q8, Q9 and Q10 guidelines to ensure a comprehensive approach for combination products. Provision of a template for PACMP. Although there are examples in the Q12 Annex, it would be useful for Industry to have a template for the PACMP as this would aid writing by Industry and Review by Agencies. Although there is an outline in Section 4.3, a detailed template would aid all parties. The importance of an established PQS as discussed in ICH Q10 is mentioned in chapter 6, however, the importance of establishing a robust and effective PQS should be emphasized throughout the document. It is suggested that the information in Appendix 2 be moved up the front of the document. MAH and regulators will only benefit from the tools and enablers described in ICH Q12 if the concepts originally intended in ICH Q8 through to ICH Q10 are realized and implemented in an effective manner across industry.
4	The concepts of ICH Q12 are fully supported by A3P Regulatory "Common Interest Group". The main concerns of the Group are the regional specificities and regional considerations that are listed throughout the guideline. A3P's request is to avoid as much as possible regional disparities that would limit the implementation of this guideline and its benefits.
	General comment on chapter 8. 8. POST-APPROVAL CHANGES FOR MARKETED PRODUCTS A3P proposes to place this chapter before chapter 7.

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	This guideline can be useful for marketed products beyond analytical procedures and stability (site change, transfer to CMO). We propose to complete this chapter with other examples not focused on analytical methods and stability) Details are appreciated for analytical procedures and stability. Other examples would be appreciated for the product /process. Why is there a specific chapter focused on marketed products whereas the interpretation is that the ICHQ12 can be implemented both for new products and marketed products. Title of this chapter is confusing.
	The use of examples in the Annex to illustrate the guidance is very useful, the addition of other examples (an example of a sterile process, aseptic filling) would be appreciated.
	CTD sections should be defined in this guideline for the different tools/documents (e.g. PLCM document) for harmonization throughout all ICH regions.
5	Indivior acknowledges and welcome the new guidance for Industry and Regulators as a means towards incremental steps to improve transparency and potentially regulatory flexibility through more risk-based approaches to support predictable CMC changes. Steps for minimum requirements to introduce the concepts for ICHQ12 should be made clearer for the scenarios of existing dossiers, existing marketed products, should Industry wish to adopt these concepts moving forward. E.g. Need to update dossiers to include List of ECs, with proposed categories, PLCM document to be included, documented (tabulated) control strategy to be included etc.. Indivior consider the value in flexibility offered by this draft guidance may be further supported by an ICH regional alignment on assessment of change via the harmonized processes described with it e.g. PACMP. If Industry wish to apply this to their future changes, then it may be good to allow for a workshare-type assessment across regions (as applicable), for such a change requiring a PACMP, to really adopt any regional nuances within the scope of the protocol). Or at minimum some level of harmonization on timelines for assessment as they currently differ across countries/ regions. Otherwise the value may be substantially diminished, as Industry deals separately with some countries respective agencies across ICH regions. How will training for Assessors as well as Industry be completed. Especially for those Agencies new to ICH (e.g. ANVISA)? A recommendation may be to publish a metrics assessment so that Industry and Regulators can see how well the concepts of ICHQ12 are progressing applications with respect to timelines from submission of a PACMP to change approval, across the ICH regions in which it is implemented.
6	**Comment:** Separate from this guidance, it should be communicated by the ICH member's regulatory authorities if there are concrete dates when ICHQ12 will be reviewed through the appropriate legal frameworks (specifically US, EU, Canada, Japan). If there is not a harmonized approach to established conditions across regions after

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	the guidance is finalized, it will likely trigger confusion between the regulatory authority and industry when attempting to implement EC concepts and also considering existing regulatory guidances for post approval changes. **Comment:** Is there an expectation that concepts described in this guidance must be retrospectively applied to existing (legacy) marketing applications? If so, it should be clearly communicated by each regulatory authority the dates when the applications need to be updated. This exercise may be labor intensive for industry. **Comment:** Since KPPs are not directly linked to CQAs, we believe KPPs do not need to be listed as ECs but can be controlled just under GMP Quality Systems for process consistency.
7	The ICH EWG is thanked for this comprehensive guidance on pharmaceutical product lifecycle management. This document is welcomed by the industry and it is acknowledged as a significant step forward in the assessment of CMC changes across the product lifecycle.
	General Comment #1: **Established Legal Framework** The guideline states that in certain ICH regions, Q12 is not fully compatible with the established legal framework with regard to the use of explicit Established Conditions and the Product Lifecycle Management. We are concerned that this will impact the harmonization efforts and will not reduce the burden on both industry and regulators. Regulatory processes across the ICH regions need to be harmonized, and the purpose of ICH is to promulgate this harmonization across its regions. Additionally, allowing for this lack of harmonization may also be setting precedence in future new/revised ICH guidelines. We acknowledge that ICH Q12 concepts may necessitate legislative/guidance changes to fully implement in certain regions, but that through the ICH harmonization process regional authorities are agreeing that EC and PLCM concepts should be implemented. Since ECs and PLCMs are subject to RA review, revision and approval, it is ensured that regional requirements and product life cycle maintenance are fully incorporated and documented in the PLCM at the time of approval. Therefore, we recommend removing lines 81 through line 85 of the draft guidance. Absent that, it is recommended that local/national health authorities with legal frameworks currently conflicting with ICH Q12 put Q&As in place to guide the applicant in describing Established Conditions to avoid even greater complexity in regulatory submissions, which could lead to hindrance of innovation and continual improvement.
	General Comment #2: Key Process Parameters The current draft introduced new concepts that will need further clarification before this guideline can be adopted by industry. For example: • KPP: The term "KPP (Key Process Parameter)" is not a defined term or concept within ICH Q8 or ICH Q11, while Critical Process Parameters (CPP) and non-CPP have

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	been well defined and broadly adopted by industry and regulators. The KPP definition in this draft is not very distinctive with that of CPP and make it difficult to differentiate CPP, KPP and Non-CPP on the criticality spectrum. The introduction of this new KPP concept will increase the complexity and variability for categorization of CMC changes, which could cause confusion to both sponsors and regulators. We recommend removing the KPP concept completely and keeping the CPP/non-CPP framework, or at least give MAHs the option to continue with the CPP/non-CPP framework. If the term/concept of KPP is maintained within the guideline, examples of KPPs need to be included. Additionally, the definition of KPP states that these parameters "need to be tightly controlled to assure process consistency as it relates to product quality" This phrase is not defined within ICH Q8 or ICH Q11 and as such, it leaves this term open for industry/regulator interpretation. It is unclear whether this language refers only to ECs and not to business-specific criteria (cycle time for unit operations, for example).
	General Comment #3: Implicit and Explicit Established Conditions (ECs) The current draft introduced new concepts that that will need further clarification before this guideline can be adopted by industry. For example: • Implicit ECs and Explicit ECs: We strongly support the concept that "ECs provide a clear understanding between the MAH and regulatory authorities regarding the necessary elements to assure product quality and identify the elements that require a regulatory submission, if changed." The incorporation of the "implicit" and "explicit" EC terminology adds confusion and is recommended for removal from the guidance. Implicit ECs are defined as "elements that are not specifically proposed by the MAH but are derived from and revised according to regional regulation or guidance related to post-approval changes." The phrase "derived from and revised according to" implies that implicit ECs may change at any time and supersede the ECs aligned upon between the MAH and RA. We suggest removing the distinction between Implicit/Explicit ECs and maintain a single category of ECs within the guideline. However, if the concept of Implicit ECs are maintained in the guideline, then specific examples of Implicit ECs and Explicit EC should be included within the document.
	General Comment # 4: Chapter 8. Post-approval changes for marketed products Chapter 8 describes "a strategy for a structured approach for frequent CMC changes" (Line 530) and provides illustrative examples specific to analytical methods however, there are many other changes to marketed products that may occur post-approval, including changes to manufacturing process. We presume that the same structured approach would apply in these cases as well but question whether a comparable example for manufacturing changes might be necessary to avoid misinterpretation.
	General Comment # 5: Annex 1 There is no illustrative example for a drug-device combination product within the Annex. Since combination products are within the scope of ICH Q12, it is recommended that Annex I include a drug-device combination product.

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8	**Introduction – Compatibility of Q12 with legal frameworks (Ch 1.1, line 81)** The EU Trade Associations acknowledge that legal assessments have indicated that current regulatory framework in some regions/countries may not be fully compatible with some of the principles foreseen in ICH Q12, such as the use of explicit Established Conditions and the Product Lifecycle Management document. However, it is unclear how selective adoption of parts of ICH Q12 will consequently lead to harmonization and reduction of regulatory burden. It is critical that all ICH partners work together to develop a Step 4 document that omits the text added in the introduction of Step 2B draft Q12 document: *"In certain ICH regions, the current ICH Q12 guideline is not fully compatible with the established legal framework with regard to the use of explicit Established Conditions ('EC') referred to in Chapter 3 and with the Product Lifecycle Management ('PLCM') referred to in Chapter 5 as outlined in this guideline. These concepts will, however, be considered when the legal frameworks will be reviewed and, in the interim, to the extent possible under the existing regulation in these ICH regions."* The draft guideline allows for regional regulatory interpretations in several areas (the term 'region/regional' is mentioned multiple times). There is a real risk of divergence across countries/regions, for example in terms of approved ECs and reporting categories (which are by default regional), or in approval of a PACMP, and in even more divergence in regulatory documentation and approval timelines. In addition, the regulatory burden during implementation can be even greater due to different understanding from different authorities of old and new concepts. The original goal to harmonize and facilitate life cycle management across region will be compromised if the guideline allows a disharmonized approach on technical and regulatory considerations for lifecycle management. In addition, lines 552-555 (Chapter 8) include text allowing regional implementation of this chapter: the concept of harmonisation will be jeopardized if specific changes may require prior approval as defined in regional guidance. **Proposed change:** The Joint EU Trade Associations recommend that introductory text regarding the compatibility of Q12 with legal frameworks is removed from the guideline because the legal aspects of implementation of ICH guidelines are best addressed through the ICH Assembly and Management Committee. Such legal aspects are beyond the competence of an Expert Working Group and should not be addressed in a Guideline. Rather we believe that they are best addressed through the development of general principles and obligations concerning the timely implementation of ICH guidelines by existing and future members of ICH, that would be agreed by the ICH Assembly, and that would provide predictability for industry and regulators. In addition we recommend that the text in chapter 8 (lines 552 -555) is also deleted, for the same reason as the removal of the Introductory text discussed above.
	Established Conditions (Chapter 3)

Stakeholder no.	General comment (if any)
	For the EC concept to be a useful regulatory tool across the ICH regions it is desirable that regulatory agencies approve the same definition of ECs in a dossier and, the same reporting categories. We encourage dialogue between regulatory agencies to facilitate convergence and consistent outcomes in the review/approval of proposed ECs and change categories.
	Established conditions **Implicit ECs and Explicit ECs (Ch 3.2.2, line 215)** The concept of explicit and implicit ECs lacks clarity, and will likely lead to a difference in interpretation between regulators and industry about changes, introducing additional regulatory complexity. It does not seem necessary to create these categories of ECs, or make the distinctions between the approaches to define ECs. It would be useful if the guideline would clarify that inclusion of ECs in a Marketing Authorisation is not mandatory, and that a sponsor could propose ECs at the time of initial MAA, or during the product lifecycle after first approval via an appropriate post-approval regulatory mechanism. **Proposed change:** The Joint EU Trade Associations recommends that section 3.2.2 is revised to remove the concept of implicit and explicit ECs and to clarify that ECs may be proposed in the initial MAA or via an appropriate post-approval regulatory change, for example: **3.2.2. ECs in a regulatory submission** ECs in a regulatory submission may be proposed by the applicant in a Marketing Authorisation Application, or as a post-approval regulatory submission (according to regional requirements) in support of an existing marketed product. The applicant may choose to propose ECs for some or all of the sections of CTD Module 3 that may contain ECs as listed in
	Appendix 1. ECs are approved by the regulatory authority. Unless otherwise specified by regional requirement, identifying ~~explicit~~ ECs for a given product is not mandatory, and a Marketing Authorisation Holder may continue to follow regional regulatory requirements when introducing changes to the Marketing Authorisation dossier where ECs are not defined. ECs in a regulatory submission comprise: • a description of the EC, • values or ranges for the EC, and may include • the proposed reporting category (where this is different from regional guidelines) Defining ECs in a regulatory submission (see Chapter 3.2.3) enables the applicant to clearly differentiate the legally binding information considered necessary to assure product quality from supportive information. ~~All regulatory submissions contain a combination of ECs and supportive information (refer to Appendix 1).~~ Supportive

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	information is not considered to be ECs, but is provided to share with regulators the development and manufacturing information at an appropriate level of detail, and to justify the initial selection of ECs and their reporting category. ECs should not be confused with CMC regulatory commitments (e.g., stability and other commitments) made by a MAH to provide data or information to the regulatory agency in a marketing authorisation application (MAA). Such information, in the context of this guideline, is considered supportive information. Changes to CMC regulatory commitments are not addressed in this guideline, but are managed according to existing regional regulations and guidance. ~~ECs in a submission are either implicit or explicit:~~ • ~~Implicit ECs are elements that are not specifically proposed by the MAH but are derived from and revised according to regional regulation or guidance related to post-approval changes.~~ • ~~Explicit ECs are specifically identified and proposed by the MAH together with their proposed reporting category as part of a regulatory submission This guideline provides the opportunity to identify explicit ECs and associated reporting categories.~~ ~~An MAH may use one or both approaches as described above to define ECs and their associated reporting categories. If the MAH wishes to propose a different reporting category than provided in regional regulation and guidance for an implicit EC, the explicit EC approach should be used.~~ The MAH should provide rationales for the ECs and associated reporting categories in the appropriate CTD sections in Module 3. See Appendix 1 for more information regarding sections of the marketing application that may contain ECs and supportive information. Appendix 1 lists some ECs that are applicable to all kinds of products and notes that some ECs that are specific to the product and must be identified by the applicant (e.g. for the manufacturing process, see Section 3.2.3). In all cases the values or ranges for the ECs are specific to the product and must be proposed by the applicant. The reporting category for the changes to an EC may follow the regional regulatory requirements, or a lower reporting category/shortened review period may be proposed by the applicant with appropriate justification. The applicant may also propose different reporting categories for tightening or widening ranges of ECs, with appropriate justification.
	Established Conditions – **KPPs and Decision Tree (Figure 1, Ch 3.2.3.1)** Chapter 3.2.3.1 "Identification of ECs for manufacturing process" introduces a new concept of Key Process Parameters (KPPs) (line 240). We do not support the inclusion of this new term and the definition, particularly the final phrase "as it relates to product quality" is ambiguous. Industry historically has used the term KPP inconsistently in small and large molecule dossiers, and regulators discouraged the continued use of the term KPP. (see EMA/430501/2013). We acknowledge that there can be parameters which impact process performance and

Stakeholder no.	General comment (if any)

are important to control, but are not CPPs. However, it should not be necessary to automatically designate these parameters as ECs. For many products, inclusion of all parameters which impact consistency will mean including the majority of parameters as ECs and will not decrease the regulatory burden and therefore negatively impact the effectiveness of ICHQ12 in managing the product lifecycle. ECs should be identified using a risk-based approach, considering the level of control, process experience, and prior knowledge.

Footnote 4 to Figure 1: "In some cases, moderate risk changes may require prior approval" is potentially confusing and open to interpretation by regulators and industry: for Q12 to be a transformative guideline it is important the principle that only high risk changes should require prior approval is consistent in the guideline.

Proposed change:

References to KPPs should be removed from the text, the definition deleted from the Glossary, and the text at lines 239-242, 273-274, and the decision tree (Figure 1, line 279) be revised accordingly, for example:

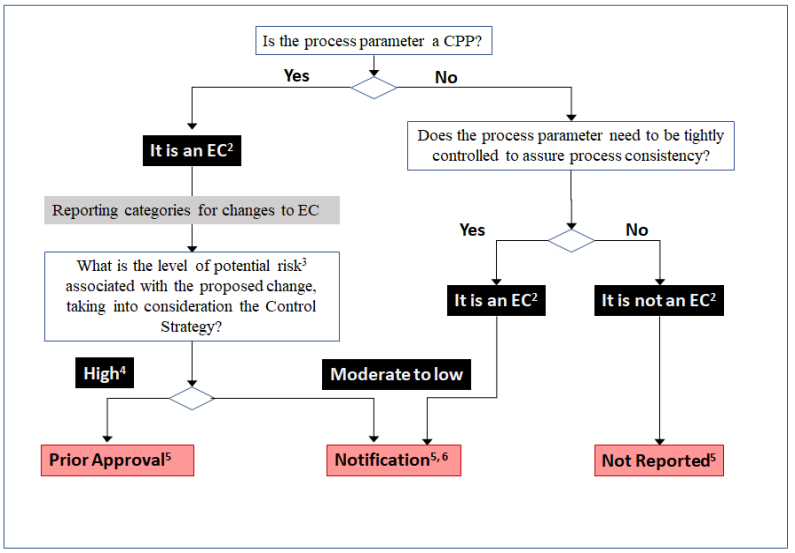
Lines 239-242:

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

Lines 273-274:

"This decision tree is intended to guide the identification of ECs based on an assessment of criticality (i.e., CPPs) or impact on the process consistency ~~as it relates to product quality (i.e., KPPs)~~."

Figure 1:



Add new footnote 6 to Figure 1:

"6 Low change reporting category for ECs that are not CPPs: Notification (Annual

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	Report, Type IA, MCN etc)." Delete footnote 4 to Figure 1: "~~In some cases, moderate risk changes may require prior approval~~"
	Identification of ECs for Analytical Procedures (Ch 3.2.3.2) More information is required to explain how established conditions for analytical procedures can be identified/defined, as the current text does not provide enough clarity (lines 290-304). **Proposed change:** **3.2.3.2. Identification of ECs for Analytical Procedures** ECs related to analytical procedures should include those elements which assure performance of the procedure. Appropriate justification should be provided to support the identification of ECs for analytical procedures. The extent of ECs could vary based on the method complexity, development and control approaches. Where the analytical procedure has been validated according to the requirements of ICH Q2(R1), including robustness studies, then ECs may be defined as: • method principle (e.g. chromatography, IR spectroscopy etc.) and • performance, defined by the acceptance criteria specified in the validation protocol (e.g., specificity, accuracy, precision) The procedure must contain system suitability or other suitable evaluations to confirm that the procedure is meeting the performance requirements. For some complex analytical procedures it may not be possible to sufficiently describe the performance of the procedure as described above, and some details of operational parameters may also be included as ECs. Other approaches, for example identifying the critical operational parameters of the procedure, may be used define the ECs for the analytical procedure. A suitably detailed description of the analytical procedures in Module 3 is expected to provide a clear understanding regardless of the approach used to identify ECs for analytical procedures. Use of this guideline should not lead to providing a less detailed description of analytical procedures in the MAA.
	Established Conditions for DMFs (Ch3.3 Line 327-331) Please clarify how the confidential information (proprietary information) related to ECs and included in the file can be managed. The DMF system in certain regions (e.g. EU-ASMF and USA-DMF) gives the opportunity to the DMF holder to provide the confidential information directly to Health Authorities (HA). Any questions that the reviewers may have during the DMF assessment are directed to the DMF holder. **Proposed change:** The guideline should explicitly state that all confidential information included in the

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	DMF be reported directly to the HAs in all ICH regions by the DMF holder, and not to the MAH. This is also applicable to annual reportable changes (notifications), which should be submitted by the DMF holder, who is then responsible to inform all MAH with whom a letter of access was granted. In the case of changes with impact on the product quality, strength, purity, safety and/or regulatory filing, the DMF holder is responsible to inform MAHs of the planned changes, and to provide enough information to support the MAH's impact evaluation of the change(s) proposed. However, this information provided by the DMF holder normally will not contain confidential information (proprietary information).
	Post-Approval Change Management Protocol (PACMP) – Chapter 4 As noted for other Q12 tools, for the PACMP to be a useful regulatory tool across the ICH regions it is often desirable that regulatory agencies approve the same PACMP, and we encourage dialogue between regulatory agencies to facilitate harmonization across ICH regions on approval of PACMPs. Certain aspects of this chapter can be improved to reduce the potential for disharmony and confusion during implementation: • Ch 4.1: Can a PACMP be used without defining the ECs? - Clarify that PACMPs and ECs are independent • Ch 4.1 (para 2, lines 348-350): Do not state that PACMPs need to be revaluated on a regular basis, but only that their validity should be confirmed before use. • Ch 4.3: This section should be clear on what is expected as a minimum for a PACMP, rather than state that "some, if not all" of all the bullets are applicable: we propose "would typically include the following e.g." • Ch 4.5: This section should also clarify how a PACMP applicable to active substances is handled in referenced submissions (e.g. EU-ASMF, US-DMF). The PACMP contains confidential information, and other supportive information that could also be considered confidential. To guarantee confidentiality, the holder of the referenced submission should be able to submit the PACMP directly to the Heath Authorities (HAs) following the same procedure of the DMF clarifications requested by HAs related to the confidential information of the DMF or the annual report submitted by the DMF holder itself. **Proposed change:** A DMF holder should be able to submit a DMF-related PACMP to the HAs and provide the reference to the MAH, for all types of submissions. • Ch 4.5: For 'Broader Protocols' could the PACMP have to be filed as a stand-alone request to HAs, or could it still be linked to a particular MAA submission?
	Product Lifecycle Management (PLCM) – Chapter 5 Certain aspects of this chapter can be improved to reduce the potential for disharmony and confusion during implementation:

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	Ch 5.1: We acknowledge that the PLCM document is currently proposed as optional and the decision of the company; however, it states in line 450 that submission of the PLCM is 'encouraged' but also that the document is 'expected' when the MAH proposes explicit ECs. Making the PLCM document part of the regulatory filing could potentially add unnecessary duplication and administrative regulatory burden considering the submission and maintenance of ECs, PLCM and PACMP without significant added benefit. An additional complexity lies in the difficulties inherent to long-term planning in a rapidly changing environment. We recommend the PLCM is a communication tool provided for use by the CMC reviewer alongside the assessment of Module 3 (in Europe). The PLCM document could include additional information if the company felt this would be helpful, for example describing those planned changes to registered detail that the applicant may be considering at the point of file and how the company proposes to manage these changes. Revision of the example in Annex 3 could help to clarify these points. **Proposed change:** (Lines 449-450): Submission of the PLCM document is optional but recommended ~~encouraged; however, the document is expected~~ when the MAH proposes ~~explicit~~ ECs. **Ch 5.1 (lines 452-454):** A summary of control strategy is already proposed in ICH Q8 3.3 as part of P.5.6 and in ICH Q11 6.2 as part of S.4.5. or other appropriate CTD section. Therefore requiring this in a PLCM document is redundant. **Proposed change:** Lines 452-454 (Summary of Product Control Strategy) should be deleted. **Ch 5.1(lines 461-465):** References to PACMPs in the PLCM should be simplified to reduce the administrative burden. Furthermore a PACMP need not contain references to ECs as they may be used where ECs are not specified, so this requirement should be removed. **Proposed change:** Lines 461-465: PACMPs that are submitted to prospectively manage and implement one or more post-approval changes ~~should~~ are recommended to be listed in the PLCM document.~~along with the corresponding ECs to be changed. The approval date of the PACMP should be noted in subsequent submissions~~. ~~If the PACMP is submitted and approved after approval of the original MAA, an updated PLCM document should accompany the PACMP~~ **Ch 5.3 (Lines 475-478):** Maintenance of the PLCM document contains a proposal to include an updated PLCM with every post-approval submission for CMC changes – this is an unnecessary, impractical and onerous requirement that should be removed. **Proposed change:** It is recommended that An updated PLCM document ~~should~~ be provided ~~included in post-approval submissions for CMC changes. The updated PLCM document will capture the~~ when there are changes in ECs and other associated elements (reporting category, commitments, PACMP etc.) ~~The MAH should follow regional expectations for~~

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	~~maintaining a revision history for the PLCM document~~ **Ch 5.4 (lines 482-483):** If included in a dossier, the location of the PLCM document should be harmonized to avoid creation of multiple dossiers across ICH regions. **Proposed change:** Since documents that are similar to the proposed PLCM such as the Japan Application Form/Approved Matters and the Canadian CPID are included in CTD module 1, we suggest the Q12 EWG consider recommending that the PLCM be included in module 1 unless another location is specified in regional regulatory requirements.
	Chapter 8 Post-approval changes for marketed products and Section 8.1 Structured approach to analytical procedure changes The opening sentences of this chapter potentially create confusion by discussing ECs and PACMPs – this section would fit better in the Introduction chapter and the chapter title should be revised to clarify that the chapter discusses Additional approaches to facilitate post-approval changes to marketed products. The scope of section 8.1 needs clarification. It has no relation to the application of ECs and therefore it should be clear that section 8.1 is only applicable to existing marketed/approved products which do not have ECs defined in the dossier. **Proposed change:** **8. Additional approaches to facilitate post-approval changes to marketed products** ~~Marketed products can benefit from the application of ECs and PACMPs as described in this guideline. Specifically, ECs and reporting categories can be proposed for a marketed product via a post-approval regulatory submission; a PACMP can also be proposed for planned change(s) to a marketed product. In addition, such products would also benefit from~~ This chapter describes additional approaches to facilitate changes to marketed products: ~~This chapter describes~~ a strategy for a structured approach for frequent CMC changes (e.g., analytical methods) and data requirements for CMC changes (e.g., stability). 8.1. Structured approach to analytical procedure changes Marketed products have existing analytical procedures that may benefit from advances made in analytical sciences. The intent of this chapter is to incentivize structured implementation of equivalent or better analytical procedures that are fit for purpose, by providing another approach to change analytical procedures in the MA that does not require the use of the EC or PACMP tools described earlier. To use the ~~An~~ approach described below ~~wherein specific criteria are defined~~ for changes to analytical procedures used to test marketed products, the specified criteria must be met and the step-by-step procedure used to manage the change. ~~is described below~~. If this approach is followed ~~and all criteria are met,~~ then the analytical procedure change can be made with immediate or other post-implementation notification, as appropriate, to the relevant regulatory authorities
	Ch 8.1. Structured approach to analytical procedure changes The scope for changes that could follow the approach described in 8.1 is unnecessarily

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	narrow. Additional changes that could reasonably be in scope of this structured approach could include: • Model maintenance activities for multivariate methods • Changes which result in a tighter specification **Proposed change:** Line 549: • Changes to predictive models used with multivariate methods, except model maintenance activities Line 570: Specification changes (e.g., total impurities, potency) cannot be introduced using this mechanism unless tighter/more restrictive acceptance criteria are introduced or they are allowed by existing regional regulations
	Addition to Annex As Q12 also applies to Vaccines, it would be very helpful to include a new Annex which describes common post-approval changes for Vaccines and which show how changes to some process parameters would be managed. A proposal for an additional Annex 1C is included here:  ICH Q12 Vaccine Annex final.docx
9	Shire commends all stakeholders, including regulatory authority (e.g. EMA, FDA, MHLW/PMDA, Health Canada, Swissmedic, ANVISA, etc.) and industry (e.g. EFPIA, PhRMA, BIO and JPMA) members for their ongoing regulatory harmonization and convergence efforts. In consideration of the importance and impact of the Q12 guideline for new and marketed pharmaceutical drug substances and drug products (e.g. post-approval chemistry, manufacturing, and controls changes), we are particularly pleased with the opportunity to contribute to these efforts as well as provide recommendations that we believe will further enhance the guideline. As some topics and sections are insufficiently covered, Shire believes that the finalized guideline would greatly benefit from expanding the content as well as clarifying recommendations in certain instances; Specific issues and our proposed recommendations are detailed in the "Specific Comments" section. Most importantly, Shire notes significant discrepancies between this guideline and other related ICH guidelines, specifically "ICH Q8 – Pharmaceutical Development" and "ICH Q11 – Development and Manufacture of Drug Substances". Given our substantial concerns regarding potential challenges to proper and timely adoption and implementation due to apparent misalignment, Shire urges the EMA and the ICH Expert Working Group to consider expanding, clarifying and specifying the linkage of this document to existing ICH guidelines. We believe that this will result in ensuring

Stakeholder no.	General comment (if any)
	closer convergence with ICH Q8 and Q11, among others. Should there be a need, Shire would be pleased to provide additional input or clarification of our comments.

10	• Established Conditions
	  • While during the transition phase from *status quo* to full implementation of ICH Q12 the dualism of implicit and (not mandatory) explicit ECs seems to be of a certain value, the benefit of maintaining this distinction on a permanent basis is not evident.
	  • Any kind of guidance for the implementation period should be separated from the "permanent" parts of the guideline and clearly defined as being temporary in nature (i.e. until national/regional legal framework has been reviewed accordingly).
	  • In addition, the guideline should better clarify the expectations for "legacy" products" (already approved and marketed products) to overcome the uncertainty that was raised with ICH Q8 – 11.

	• Training documents should be available for implementation of ICH Q12, which should include amongst other items examples of different stability data requirements for changes related to marketed products.
11	LEO Pharma A/S welcomes the opportunity to comment on this very relevant ICH document. We broadly agree with the document; our detailed comments can be found below. In general, it is not clear if the introduction of ECs (Chapter 3) either in the original dossier or post approval should cover the whole dossier or if ECs can be introduced to parts of the dossier, e.g. manufacturing CTD documents only. LEO proposes to specify this more clearly in the introduction of Chapter 3. The PLCM document (Chapter 5) outlines planned changes during life cycle management. In practice unexpected events arise during life cycle management LEO proposes that ICH Q12 also addresses how this type of urgent changes in case of unforeseen events should be managed within or outside the framework of ICH Q12. Chapter 8 describes a strategy for a structured approach for frequent CMC changes (e.g., analytical methods) and data requirements for CMC changes (e.g., stability). LEO finds that the regulatory procedures for the structured Approach to Analytical Procedure Changes (8.1) and the Stability Data Approaches to Support the evaluation of CMC Change (8.2) are not clearly described, and therefore suggests to describe more clearly in the introduction to Chapter 8: • if the structured approach for frequent CMC changes (e.g., analytical methods) and data requirements for CMC changes (e.g., stability) can be used in general without introduction of Established Condition in Module 3 and by use of a PACMP • if the use of the structured approach may lead to a lower reporting category

Stakeholder no.	General comment (if any)
12	IPFA acknowledges and welcomes the concepts covered by ICH Q12 enhancing industry's ability to manage many CMC changes effectively under the firm's Pharmaceutical Quality System with less need for extensive regulatory oversight prior to implementation.
	ICH has been conceived to implement International Harmonisation of Technical Requirements for Pharmaceuticals for Human Use to achieve greater regulatory harmonisation worldwide and serve as reference for regional guidance. However, the draft Guideline provides many provisions for regional specificities and considerations. IPFA would like to warn ICH that these provisions would allow regional discrepancies with a potential neutralisation of the international benefit of harmonious implementation. In addition, the draft Guideline foresees effective implementation of the tools in order to enhance this industry's ability to manage many CMC changes effectively under the PQS with less need for extensive regulatory oversight prior to implementation. Harmonious implementation throughout the regions is needed to allow MAHs to effectively implement post-marketing changes via PQS and optimize regulatory oversight. *In certain ICH regions, the current ICH Q12 guideline is not fully compatible with the established legal framework with regard to the use of explicit Established Conditions ('EC') referred to in Chapter 3 and with the Product Lifecycle Management ('PLCM') referred to in Chapter 5 as outlined in this guideline. These concepts will, however, be considered when the legal frameworks will be reviewed and, in the interim, to the extent possible under the existing regulation in these ICH regions.* IPFA praises ICH Q12 to firmly recommend the revision of regional legal and regulatory frameworks to be aligned with its model. In this spirit, PLCM submission and Reporting categorisation (pre-approval, notification, PQS) as well as PACMP strategy for products submitted through regional procedures, should be in regulatory convergence in all regions. Please refer to lines: 28-33; 154-156; 181-186; 197; 428; 436; 461-462; 481-482; 501; 589-593; 705-706.
	ICH has issued its M4 to assemble all the Quality, Safety and Efficacy information in a common format throughout all ICH regions, the CTD. Therefore, IPFA suggests ICH Q12 to define in the draft Guideline CTD sections for the PLCM and PACMP documents as well as for the different descriptions using the tools recommended by the guideline. Please refer to lines: 28-33; 201-202; 364; 458; 480.
	The draft Annex provides examples of Established Conditions (ECS) and Post-Approval Change Management Protocol (PACMP) for both chemical and biological products. The guideline should be clearer with regards to the Established Conditions Definition, especially - examples could be enriched and cover other scopes of the manufacturing process as well as analytical methods

Stakeholder no.	General comment (if any)
	- and on reporting categories The link between ECS and the control strategy with regards to CPPs and KPPs is not clear enough. IPFA suggests to clearly define KPPs (as CPPs are defined by ICH Q8(R2). Please refer to lines: 28-33; 162-169; 213-221; 218; 270.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
17–27	2	**Comment:** The impact of this guidance on previous guidances (ex. SUPAC-IR) currently used to implement post-approval CMC changes is not clear. **Proposed change:** Clearly state in the introduction the impact of this guidance on previous guidances such as SUPAC-IR.
59	6	**Comment:** If ICH Q12 is adopted by the FDA, the impact on the current US Comparability Protocol guidance will need to be evaluated.
60-68	1	**Comment:** Please clarify that for mature products, applicants can utilise the historical data (i.e. data obtained over commercial life span of the drug product) with some supplementary developmental studies to propose ECs and other tools as defined in this guidance.
63-68	9	**Comment:** The guideline indicates that: "*ICH Q8 and Q11 guidelines focus mostly on early stage aspects of the product lifecycle (i.e., product development, registration, and launch). Experience with implementation of recent ICH guidelines has revealed technical and regulatory gaps that limit the full realisation of more flexible regulatory approaches to post-approval CMC changes as described in ICH Q8 (R2) and Q10 Annex I. This guideline addresses the commercial phase of the product lifecycle (as described in ICH Q10).*" Shire agrees that there are regulatory gaps between ICH guidelines and supports the approach which allows application and use of the methods and documents established in the development phase to be utilized for changes in commercial phases as well. **Proposed change:** Shire suggests that the draft guideline be expanded to provide additional clarity with regard to the linkage of ICH Q12 with ICH Q8, Q11 and Q10, specifically addressing the concept of application and use of methods as well as documents in the development phase to the commercial phase as part of a product lifecycle approach.
69-72	3	**Comment:** As outlined in Section 1.2 Scope (lines 87-91), this guidance is applicable to NCEs and biopharmaceuticals. However, this 2nd paragraph on Page 5 (starting at line 69) only currently refers to the biopharmaceutical sector

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		which could be misleading to readers **Proposed change:** Promoting innovation and continual improvement in the pharmaceutical and biopharmaceutical sector, strengthening quality assurance and improving supply of medicinal products
74	4	**Comment:** It is also intended to demonstrate how increased product and process knowledge can contribute to a reduction in the number of regulatory submissions. **Proposed change:** It is also intended to demonstrate how increased product and process knowledge can contribute to a reduction in the number of regulatory submissions, and/or associated corresponding review/approval timelines.
81-85	1	**Comment:** Kinapse understands *Variation guidelines (as laid down as per Commission Regulation [EC] No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations)* would be revised in future to be compatible with elements built in draft ICHQ12 i.e. EC or PLCM. Please elaborate how to apply these concepts in the interim. **Proposed change:** Specific instructions could be provided on how to introduce ECs for marketed products.
81-85	4	**Comment:** In certain ICH regions, the current ICH Q12 guideline is not fully compatible with the established legal framework with regard to the use of explicit Established Conditions ('EC') referred to in Chapter 3 and with the Product Lifecycle Management ('PLCM') referred to in Chapter 5 as outlined in this guideline. These concepts will, however, be considered when the legal frameworks will be reviewed and, in the interim, to the extent possible under the existing regulation in these ICH regions. To allow the efficient use and implementation of this guideline, in all ICH regions, legal framework needs to endorse ICHQ12 and support the concepts described in this guideline, to have the same interpretation and avoid regional disparities. Alignement is needed to allow the MAH to effectively implement some changes via PQS and optimize regulatory variations. A3P supports a rewording of paragraph lines 28-33 which limits the full implementation of ICH Q12 concepts and limits its benefits. Rewording of this paragraph and removal of all regional considerations throughout the guideline

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		would be preferred. A3P proposes the following rewording (refer to "proposed change" section) **Proposed change:** In certain ICH regions, the current ICH Q12 guideline is not currently fully compatible with the established legal framework with regard to the use of explicit Established Conditions ('EC') referred to in Chapter 3 and with the Product Lifecycle Management ('PLCM') referred to in Chapter 5 as outlined in this guideline. To allow the efficient use of this guideline, in all ICH regions, legal framework needs to be reviewed to align with the concepts of ICH Q12 and become compatible with the concept of Established Conditions and supporting Product Lifecycle Management document as described in ICHQ12. The goal is to have the same interpretation in ICH regions and avoid regional disparities, to allow the MAH to implement some changes via PQS. ~~These concepts will, however, be considered when the legal frameworks will be reviewed and, in the interim, to the extent possible under the existing regulation in these ICH regions.~~
81-85	5	**Comment:** The sentence "In certain ICH regions, the current ICHQ12 guideline is not fully compatible with the established legal framework with regards to the use of explicit Established conditions ('EC') referred to in Chapter 3 and with Product Life Cycle management ('PLCM') referred to in Chapter 5 as outlined in this guideline. These concepts will, however, be considered, when the legal frameworks will be reviewed and, in the interim, to the extent possible under the existing regulation in these regions." Indivior finds this sentence contradictory with the objectives of the new guideline. If the concepts are not compatible and may not be harmonised due to the regions legal framework, we consider more detail should be made clear to Industry on what this means and the consequences of any incompatibilities with respect to views from the regulators in the "certain regions".
81-85	9	**Comment:** The guideline states: "*In certain ICH regions, the current ICH Q12 guideline is not fully compatible with the established legal framework with regard to the use of explicit Established Conditions (ECs) referred to in Chapter 3 and with the Product Lifecycle Management (PLCM) referred to in Chapter 5 as outlined in this guideline. These concepts will, however, be considered when the legal frameworks will be reviewed and, in the interim, to the extent possible under the existing regulation in these ICH regions*" Shire notes that the disclaimer significantly reduces the value of the guideline, since it effectively diminishes regulatory harmonization/convergence aspects implied by ICH guidelines (i.e. acceptance of regulatory submissions for post approval changes throughout ICH regions). While it is clear that the guideline has applicability for US FDA, it neither states which jurisdictions don't have

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		requisite legal frameworks nor which aspects are incompatible, introducing regulatory uncertainty regarding applicability of the guideline within the ICH region. **Proposed change:** In the interim, in the interest of regulatory clarity and certainty, Shire recommends that the draft guideline be expanded to specify the level of regulatory acceptance/non-acceptance matched to specific ICH regions (e.g. a table or other appropriate format in the appendix).
83	2	**Comment:** Chapter 8 title is not descriptive of contents and may be confused with Chapter 2. **Proposed change:** Change title to "Post-Approval Changes to Analytical Methods for Marketed Products".
90-91	4	**Comment:** Changes needed to comply with revisions to Pharmacopoeial monographs are not in scope of this guideline. A3P recommends to keep in the scope the changes in monographs (managed through PQS) A3P suggests to delete the sentence. **Proposed change:** ~~Changes needed to comply with revisions to Pharmacopoeial monographs are not in scope of this guideline.~~
90-91	7	**Comment:** The intended implications of the following statement are not well understood: "Changes needed to comply with revisions to Pharmacopoeial monographs are excluded from the scope of the guideline". If this statement was meant to imply that changes made by the Market Authorization Holder to comply with revisions to Pharmacopoeial monographs will not require any type of regulatory filing, please comment or clarify in the draft text.
90-91	8	**Comment:** Ch 1.2 (lines 90-91) states: "Changes needed to comply with revisions to Pharmacopoeial monographs are not in scope of this guideline". It is not clear why changes to comply with revisions to pharmacopoeias are excluded from the scope of the guideline, even if in some cases they are not harmonized between the regions. On the contrary, pharmacopoeial changes could be regarded as minor changes to be reported as a notification only, and are often managed internally under the Pharmaceutical Quality System as long as the registration dossier refers to the "current pharmacopoeial

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		monograph". **Proposed change:** Either: Delete the sentence "Changes needed to comply with revisions to Pharmacopoeial monographs ….guideline" Or: Provide additional clarifying text, for example: "Where the registration dossier refers to the current pharmacopoeial monograph, changes to comply with revisions to the monograph are managed under the Pharmaceutical Quality System, without any regulatory notification."
96	4	**Comment:** Categorisation of Post-Approval CMC Changes (Chapter 2) Please add "reporting" categorisation. A3P suggests to add "reporting" before "categorisation of Post approval CMC changes" throughout the document, for clarification. **Proposed change:** Reporting Categorisation of Post-Approval CMC Changes
103-105	7	**Comment:** The term "supportive information" must be clearly defined with examples. **Proposed Change:** Add a definition of supportive information to the Glossary and a referenceto this definition in the following sentence. This guideline describes how ECs are identified as well as what informationcan be designated as supportive information**(see Glossary)**that wouldnot require a regulatory submission, if changed.
104-106	6	**Comment:** The term "supportive information" must be clearly defined with examples. This is also applicable to line 213. Additional clarification for the term supportive information is provided in the proposed revised Figure 1. **Proposed change:** This guideline describes how ECs are identified as well as what information can be designated as supportive information (See Glossary and Figure 1)
105-106	7	**Comment:** Suggest to add clarification that the EC principle can also be applied for

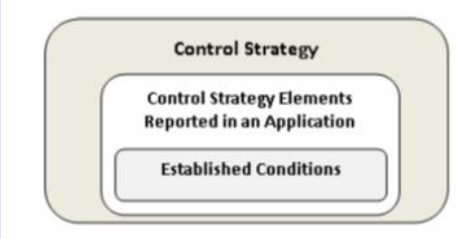
Line no.	Stakeholder no.	Comment and rationale; proposed changes
		already approved products on a voluntary basis or only applies to MAAs. **Proposed change:** In addition, guidance is included for managing revisions of the ECs over a product's lifecycle **and for implementing ECs for already approved products**.
108-161	2	**Comment:** This section on categorization of post-approval CMC changes will have much greater impact if additional detail is added. Even among regulatory bodies that have "prior-approval" or "notification" categories, the specific details about how these are managed varies greatly. This variation leads to great complexity in implementing changes globally. The encouragement for harmonization should be strengthened with much more specific expectations for each category of change. **Proposed change:** Please define specific expectations for the timing of submission and implementation of changes for both the prior-approval and notification categories. To accomplish this specificity it might be useful to incorporate the "notification moderate" and "notification low" categories used in the Annex. In addition, the Annual Report mechanism is a valuable tool for reporting of low risk changes. This tool should be incorporated to these recommendations to encourage global adoption.
112-116	7	**Comment:** Please clarify whether the PLCM can also be introduced for already approved products, or only applies to MAAs.
132-133	6	**Comment:** Clarify that ECs are just one component of the control strategy. In-process controls and design space could also be considered components of the control strategy.
132-133	7	**Comment:** Clarify that ECs are just one component of the control strategy. Also, suggest adding "CMC" to provide clarity and align with Section 2, which suggests that changes made to the product or other CMC aspects are managed by the PQS. **Proposed Change:** Pharmaceutical development activities result in an appropriate control strategy, elements of which are considered to be Established Conditions. ~~All~~**Process controls and design space could also be considered components of the control strategy. All CMC** changes to an approved product are managed through a firm's Pharmaceutical Quality System; changes to ECs must also be reported to the regulatory authority.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
133	6	**Comment:** Add "CMC" to provide clarity and align with Section 2. **Proposed change:** All CMC changes to an approved product are managed through a firm's Pharmaceutical Quality System
150	4	**Comment:** CMC changes vary from low to high potential risk with respect to product quality A definition of product quality would be helpful to avoid misinterpretation. **Proposed change:** A3P proposes: …. with respect to product quality (i.e. safety, efficacy and purity).
154-155	4	**Comment:** In such a regulatory system, the types of changes in the drug substance, drug product, production process, quality controls, equipment, and facility A3P suggests to add "container closures systems" in the list **Proposed change:** In such a regulatory system, the types of changes in the drug substance, drug product, container closures systems, production process, quality controls, equipment and facility
156-157	1	**Comment:** A typographical correction is proposed. The statement "are classified with regard to the potential to have an adverse effect on ~~product~~ quality of the drug product" needs to be rephrased by deleting 'product' as depicted here. **Proposed change:** Revised statement shall be – "are classified with regard to the potential to have an adverse effect on quality of the drug product"
159	4	**Comment:** Regulatory authorities are encouraged to utilise It seems that there is a mistake in the wording. **Proposed change:** ~~Regulatory authorities~~ MAH are encouraged to utilise
159	6	**Comment:** Both regulatory authorities and MAH must be aligned on the use of risk-based

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		regulatory processes. **Proposed change:** Regulatory authorities and MAH are encouraged to utilise a system that incorporates risk-based regulatory processes…
166	8	**Comment:** In Ch 2 (para 3-4, line 166) , it is stated that "an inspection may be associated with such changes". Further clarification on the inspection time point, whether the inspection takes place before or after the implementation of CMC changes, may be necessary. Examples may be helpful. As discussed in ch 6.1 (line 488-490), it is important to stress that Q12 does not anticipate any increase in inspections. **Proposed change:** If required by regional regulatory requirements, an inspection may be associated with such changes before (or after) the implementation (e.g, site changes).
167	6	**Comment:** Revised this paragraph for clarity and to aligned with lines 173-174, as well as proposed revised Figure 1. **Proposed change:** ~~Certain~~ ~~m~~Moderate ~~to low~~ risk changes are judged to not require prior approval….
167-172	4	**Comment:** Notification: Certain moderate- to low-risk changes are judged to not require prior approval and generally require less information to support the change. These changes are communicated to the regulatory authority as a formal notification that takes place within a defined period of time before or after implementation, according to regional requirements. A mechanism for immediate notification is useful when prior approval is not required, but timely awareness of the change by the regulator is considered necessary. It would be helpful to list the different reporting categories in the text or in appendix (instead of annex which is a specific document) and define the acronyms . "PAS, type II, PCA" PAS: Prior Approval Supplement, …..PCA: Partial Change Application . "CBE, type IB, MCN" CBE : Change Being Effected, …. MCN: Minor Change Notification . "AR, Type IA, MCN etc": AR = Annual Report…..MCN: Minor Change Notification

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: A3P would prefer that this paragraph "notification" is split in 2 parts: - moderate risk changes - low risk changes
173-174	4	**Comment:** In addition, the lowest risk changes are only managed and documented within the PQS and not reported to regulators,but may be verified on routine inspection. see proposed change **Proposed change:** Add a category "not reported" (paragraph with a bullet point as · Notification)
173-174	9	**Comment:** *Since lowest risk changes are not reported, according to "Figure 1. Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters" (page 8, lines 245-247), they would not be associated with a CPP or KPP. For consistency with the figure, Shire recommends that the text be aligned with Figure 1.* **Proposed change:** Shire recommends that lines 127-128 be presented in bullet-point format, similar to "prior approval" and "notification" in lines 121-126, in order to provide clarity and ensure alignment with Figure 1. We also recommend that the text in lines 127-128 be edited to clarify that lowest risk changes are unrelated to established conditions (ECs) and do not require any reporting to regulatory authorities (i.e. "not reported" category").
175	4	**Comment:** Harmonisation or convergence toward a system of risk-based categorisation of post approval changes is encouraged…. Fully agreed by the group. A3P supports the needs of harmonization and convergence
175-176	10	**Comment:** • Add "with defined timelines" corresponding and re-emphasizing "timeframes for decision" from line 162. **Proposed change:** • Sentence should read: "Harmonisation or convergence toward a system of risk-based categorisation of post-approval changes *<u>with defined timelines</u>* is encouraged as an important step toward achieving

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		the objectives of this guideline.”
183-184	5	**Comment:** “the need for regulatory inspection of the change may preclude the ability to use a lower category” Indivior request that conditions of change requiring inspection are made clear in this guideline or in an associated Annex.
186-188	4	**Comment:** Options for possible regulatory convergence regarding the association of a certain type of change with a particular category when reasons for being different from other regulatory authorities are not clearly established. A3P suggests to clarify the meaning of this sentence / rephrase to facilitate the understanding. (Possible/certain/particular do not lead to fully understand the meaning). Regulatory convergence is essential. A3P suggests that the regulatory convergence could be enabled by the following prerequisites: 1. PLCM approved by all authorities 2. Reporting categorisation (pre approval, notification, PQS) agreed by the authorities through PLCM submission and approval by all authorities **Proposed change:** ~~Options for possible~~ Regulatory convergence regarding the association of a certain type of change with a particular category (pre-approval, notification, PQS) should be enabled by PLCM approval by all authorities. ~~when reasons for being different from other regulatory authorities are not clearly established.~~
188	2	**Comment:** Clear guidance on what are considered implicit ECs is not provided. **Proposed change:** Provide clear guidance and examples describing what implicit ECs are (for example, are the data and information contained in white sections of table in Appendix 1 considered implicit ECs)?
191	4	**Comment:** For examples of risk-based categorisation systems, refer to existing regulations and guidance of ICH members, and WHO guidelines and guidance on changes to approved products. It would be helpful to integrate the examples of WHO in annexe of ICHQ12, or reference the text. This will facilitate the integration in the different regional regulations.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Add examples in annex or reference the WHO guideline
194-200	4	**Comment:** Chapter 3. Established Conditions A3P proposes to make a clear link with the control strategy. Control strategy contains established conditions and non established conditions (see drawing from FDA draft guidance)"Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products - Guidance for Industry") **Proposed change:** Control strategy contains established conditions and non established conditions 
194 to all chapter 3	4	**Comment:** Chapter 3. Established Conditions A3P suggests to review the order of the chapters inside the Chapter 3. Established Conditions. It would be preferable to define Ecs (currently in 3.2.3) before the ECs in regulatory submission (currently 3.2.2) and reverse the 2 chapters. **Proposed change:** see comment
201-202	2	**Comment:** The terminology for reporting categories varies significantly from region to region. If this information is described directly in the Module 3 sections this inconsistency will require extensive adjustment of the Module 3 documents for each region and will result in more complex lifecycle maintenance. Similar complexity will result if regulatory authorities do not come to similar conclusions during MAA review for EC and reporting category designation. **Proposed change:** The justification of ECs and the associated reporting categories should be located in the PLCM document to have a central location in the application to

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		manage this information.
203-204	8	**Comment:** Ch 3.2.1 (lines 203-204) The definition for ECs text currently states: *"ECs are legally binding information (or approved matters) considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority."* It is important to state that only ECs are reported, and that for any editorial change to ECs, a submission to the regulatory authority shouldn't be necessary **Proposed change:** Add: " *As a consequence, only ~~any~~ change to ECs (except editorial changes) necessitates a submission to the regulatory authority."*
210-214	4	**Comment:** ECs should not be confused with CMC regulatory commitments (e.g., stability and other commitments) made by a MAH to provide data or information to the regulatory agency in a marketing authorisation application (MAA). Such information, in the context of this guideline, is considered supportive information. Changes to CMC regulatory commitments are not addressed in this guideline, but are managed according to existing regional regulations and guidance. **Proposed change:** ECs should not be confused with CMC regulatory commitments (e.g., stability and other commitments) made by a MAH to provide data or information to the regulatory agency in a marketing authorisation application (MAA) or linked to current MA. Regulatory commitments are not in scope of this guideline. Such information, in the context of this guideline, is considered supportive information. Changes to CMC regulatory commitments are not addressed in this guideline, but are managed according to existing regional regulations and guidance.
212-221	2	**Comment:** The concept of Critical Process Parameter (CPP) is suitably introduced in ICH Q8(R2). The concept of Key Process Parameter (KPP), on the other hand, is not described in Q8(R2). Similarly to a CPP, designation and evaluation of a potential KPP is a development matter and should be introduced in Q8(R2). It is appropriate to reinforce its significance in Q12 but not sufficient to introduce it for the first time in this document. **Proposed change:** Add the concept of KPP to the next revision of ICH Q8(R2). As is provided in

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		the case of a CPP, additional guidance on the definition and use of a KPP and its presentation in the MAA should be included in Q8(R2).
215-224	4	**Comment:** ECs in a submission are either implicit or explicit:…. A3P considers that the terms implicit and explicit can be confusing. **Proposed change:** The removal of these terms throughout the guideline would be preferable. Otherwise, A3P considers that a clarification is needed for this concept. Proposals for alternative words are: implied (implicit); clearly stated (explicit)
215-224	7	**Comment:** As stated in General Comment #3, this current draft introduced new concepts such as Implicit ECs and Explicit ECs. Implicit ECs are not well defined. The current definition enables a wide scope of elements to be categorized as Implicit ECs. It does not seem necessary to create this category of ECs or make the distinctions between the approaches to define ECs. We suggest removing the distinction between Implicit/Explicit ECs and maintain a single category of ECs within the guideline, e.g. CPPs are ECs. However, if the concept of Implicit ECs is maintained in the guideline, then specific examples of Implicit ECs and Explicit EC should be included within the document. **Proposed change:** ~~ECs in a submission are either implicit or explicit:~~ ~~• Implicit Ecs are elements that are not specifically proposed by the MAH but are derived from and revised according to regional regulation or guidance related to post-approval changes.~~ ~~• Explicit~~ Ecs are specifically identified and proposed by the MAH together with their proposed reporting category as part of a regulatory submission (see Chapter 3.2.3). This guideline provides the opportunity to identify ~~explicit~~ Ecs and associated reporting categories. Unless otherwise specified by regional requirement, identifying ~~explicit~~ Ecs for a given product is not mandatory. ~~An MAH may use one or both approaches as described above to define Ecs and their associated reporting categories.~~ If the MAH wishes to propose a different reporting category than provided in regional regulation and guidance ~~for an implicit EC~~, the ~~explicit~~ EC approach should be used.
216	3	**Comment:** The definition of implicit versus explicit Ecs is not clear and how this is then applied when different regions have different regulatory requirements. Ultimately, Ecs should be negotiated based on the MAHs product and process knowledge based on scientific justification and rationale. Defining them as

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		either implicit or explicit is considered not necessary. **Proposed change:** ~~ECs in a submission are either implicit or explicit:~~ ~~Implicit ECs are elements that are not specifically proposed by the MAH but are derived from and revised according to regional regulation or guidance related to post-approval changes.~~ ~~Explicit~~ ECs are specifically identified and proposed by the MAH together with their proposed reporting category as part of a regulatory submission (see Chapter 3.2.3). This guideline provides the opportunity to identify ~~explicit~~ ECs and associated reporting categories. Unless otherwise specified by regional requirement, identifying explicit ECs for a given product is not mandatory.
216-221	6	**Comment:** Implicit Ecs should be removed from this document. Ecs should be proposed in the dossier by the MAH. Pharmacopeial requirements that are relevant should be explicitly listed as Ecs but the actual methods and criteria can be incorporated by reference. If during the review the HA determined that something implied by a regulation to be an EC is not identified, then the regulatory authority can propose that it be added. **Proposed change:** ECs in a submission can come from various sources and should be specifically listed to ensure clear understanding, between the MAH and the regulatory authority, what are the agreed upon ECs for the product. ~~Ecs are either implicit or explicit: Are either implicit or explicit:~~ • ~~Implicit Ecs are elements that are not specifically proposed by the MAH but are derived from a nd revised according to regional regulation or guidance related to post-approval changes.~~ ~~Explicit Ecs are specifically identified and proposed reporting category as part of a regulatory submission (see Chapter 3.2.3). This guideline provided the opportunity to identify explicit Ecs and associated reporting categories. Unless otherwise specified by regional requirements, identifying explicit Ecs for a given product is mandatory.~~
218–221	2	**Comment:** The definition of the "key process parameter" is problematic and is likely to lead to variation in interpretation between regulators and industry. Without a precise definition the interpretation could evolve over time resulting in expansion of regulatory oversight. The phrase "tightly controlled to assure process consistency as it relates to product quality" is ambiguous. The interpretation of "tightly" would likely be context dependent and difficult to apply consistently. Also, if a parameter does not impact a critical quality attribute, it is not clear why variation would be a concern leading to designation of an established condition. Established conditions should be focused solely on maintenance of the critical quality attributes of the product

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		to ensure efficient use of regulatory resources. **Proposed change:** Remove the definition and designation of KPPs from the guideline to ensure the focus of regulatory review remains on critical quality attributes of the product.
221	1	**Comment:** Kinapse understands that ICHQ12 tools (especially Ecs) would be optional. Upon implementation of this guidance, please clarify that the Agency will continue to accept new applications as per the current established process.
222	4	**Comment:** An MAH may use one or both approaches as described above to define ECs and their associated reporting categories. If the MAH wishes to propose a different reporting category than provided in regional regulation and guidance for an implicit EC, the explicit EC approach should be used. **Proposed change:** A3P requests to remove the paragraphs implicit / explicit ~~An MAH may use one or both approaches as described above to define ECs and their associated reporting categories. If the MAH wishes to propose a different reporting category than provided in regional regulation and guidance for an implicit EC, the explicit EC approach should be used.~~ An MAH may use either ECs definition and associated approved PLCM or follow requirements defined in the local regulatory framework.
222-224	6	**Comment:** Remove this section, to align with above comment, to remove concept of implicit Ecs. In addition, the PACMP approach already outlined in this guidance, serves as an approach to propose a different reporting category than provided in ICH member's regional regulation and guidance. **Proposed change:** ~~An MAH may use one or both approaches as described above to define Ecs and their associated reporting categories. If the MAH wishes to propose a different reporting category than provided in regional regulation and guidance for an implicit EC, the explicit EC approach should be used.~~
225-226	4	**Comment:** The MAH should provide rationales for the ECs and associated reporting categories in the appropriate CTD sections in Module 3. Inconsistent with chapter 5.4 remove "associated reporting categories"

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: The MAH should provide rationales for the ECs and associated reporting categories in the appropriate CTD sections in Module 3.
225-226	10	**Comment:** • "The MAH should provide rationales for the ECs and associated reporting categories in the appropriate CTD sections in Module 3." It remains unclear to which extend these rationales have to be adapted in case a proposed EC/reporting category is not accepted during regulatory review, and whether updating of a rationale during product lifecycle w/o changing the EC itself will require a regulatory submission. • Clearly declare such rationales as "supportive information". • To avoid divergent Modules 3, advise that reporting categories for ECs should be proposed in the framework of an overall risk-based categorization system as outlined in chapter 2 of the guideline (prior approval, notification), whereas region-/country-specific details as e.g. the region-/country-specific variation types (CBE30, Type II…) do not belong there. **Proposed change:** see below (lines 339 – 341)
225- 226	11	**Comment:** ICH Q12: It is proposed that MAH should provide rationales for the ECs and associated reporting categories in the appropriate CTD sections in Module 3. Appendix 1 gives information to which Module 3 sections may contain ECs and supportive information. LEO proposes to describe in more details if the rationales or justifications for ECs are supportive or regulatory binding during life cycle management.
229-234	7	**Comment:** Please provide reference to Appendix 1 for additional examples. **Proposed change:** This chapter outlines approaches to define ECs for manufacturing processes and analytical methods. A similar approach can be used to define other types of ECs (e.g., performance of the container closure system) and should be justified by the applicant and approved by the regulatory agency. **See Appendix 1 for additional examples.**
231	2	**Comment:** Consider to align approach title with the table in Appendix 1 of ICHQ8(R2). **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Change title to "Minimal approach".
233-234	4	**Comment:** The extent of ECs may vary based on the firm's development approach and potential risk to product quality. A3P suggests to refer to lines 223-229 or remove.
236-242	4	**Comment:** In addition to the unit operation and the sequence of steps, and in considering the overall control strategy, ECs proposed and justified in a manufacturing process description should be those inputs (e.g., process parameters, material attributes) and outputs (that may include in-process controls) that are necessary to assure product quality. These should include critical process parameters (CPPs, as defined in ICH Q8(R2)), as well as key process parameters (KPPs), which are parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency as it relates to product quality. A3P suggests to rephrase the paragraph (see proposed change). **Proposed change:** In addition to the unit operation and the sequence of steps (see Annex I: ECs illustrative examples), and in considering the overall control strategy, ECs proposed and justified in a manufacturing process should be: • Inputs like Process parameters and their ranges, material attributes, equipment and operating conditions • Outputs like in process controls that are necessary to assure product quality.
236-242	7	**Comment:** As stated in General Comment #2, this current draft introduced new concepts that that will need further clarification before this guideline can be adopted by industry. The term "KPP (Key Process Parameter)" is not a defined term or concept within ICH Q8 or ICH Q11, while Critical Process Parameters (CPP) and non-CPP have been well defined and broadly adopted by industry and regulators. The KPP definition in this draft is not very distinctive with that of CPP and make it difficult to differentiate CPP, KPP and Non-CPP on the criticality spectrum. The introduction of this new KPP concept will increase the complexity and variability for categorization of CMC changes, which could cause confusion to both sponsors and regulators. **Proposed change:** In addition to the unit operation and the sequence of steps, and in considering the overall control strategy, ECs proposed and justified in a manufacturing process description should be those inputs (e.g., process parameters, material

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		attributes) and outputs (that may include in-process controls) that are necessary to assure product quality. These should include critical process parameters (CPPs, as defined in ICH Q8(R2)), as well as ~~key~~**any non-critical** process parameter~~s~~**(s)** ~~(KPPs), which are parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly~~ **determined by a science driven, risk-based assessment that require** control~~led~~ to assure ~~process consistency as it relates to~~ product quality.
238	6	**Comment:** Revise text for clarification. **Proposed change:** and outputs, quality attributes and ~~that~~ may include in-process controls)
239-242	3	**Comment:** As a process is developed and improved over commercialization what were originally identified as KPPs for having the potential to impact the manufacturing process may change or be seen not to impact the process. Further, the term KPP may not be universally used across industry. Instead, focus should be on the concepts already established in ICH Q8 and on product and process knowledge, scientific rationale, and the potential any parameter may have on product quality attributes. **Proposed change:** These should include critical process parameters (CPPs, and CQAs, as defined in ICH Q8(R2)), ~~, as well as key process parameters (KPPs)~~, as well as potentially other ~~which are~~ parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency as it relates to product quality. Noting that is knowledge and experience is accumulated regarding how product performance relates to material attributes and process parameters, some parameters may not ultimately remain ECs.
239-242	9	**Comment:** Key process parameters (KPPs), in lines 202-204 as well as in Chapter 9 "Glossary" (line 668, page 20), appear to be defined as: "*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*". From this definition, the relationship of a KPP to product quality is not sufficiently clear. Since process consistency itself is an indication of process control, which in turn is part of an overall quality paradigm, KPPs should simply be parameters that impact/link to process consistency as defined by a MAH. Furthermore, the definition of KPP should be in alignment with and context of ICH Q8.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Shire recommends that the KPP definition is expanded to clearly indicate alignment with and context to ICH Q8 as well as clarify the KPP relationship to process consistency and quality. As worded currently, the KPP definition may contribute to inconsistency between these two ICH guidelines.
239-242	11	**Comment:** ICH Q12: "For the manufacturing process the concept of Key Process Parameter (KPPs) is introduced as a parameter that may not directly be linked to the CQAs but need to be tightly controlled to assure process consistency as it relates to product quality". KPP is a new parameter besides the well-known mentioned parameters from ICH Q 8 CPP and QCP. LEO is of the position that the introduction of KPPs to assure process consistency is not aligned with neither the ICH Q 8 nor the EU variation guideline or the general approach in the ICH Q12 to introduce a risk-based assessment of the potential adverse effect on the drug product quality. In addition, it is not clear: • Why /when should a KPP be considered as an EC when, per definition, it does not have direct critical impact on the quality of the product and • how changes to the KPP should be managed during life cycle as these parameters may primarily assure process consistency. In the EU changes to the KPP might not fit to any of the predefined variations in the variation guideline and therefore the reporting categories for changes to KPP would have to be applied for as a type 1B per default; LEO finds that this is in contradiction to the objective of ICH Q12
240	1	**Comment:** Please include additional clarity (with an example) in the ICH Q12 guideline around how KPP is different from CPP and normal process parameters.
240	4	**Comment:** as well as key process parameters (KPPs), which are parameters of the attributes, but need to be tightly controlled to assure process consistency as it relates to product quality. The KPP defined as Established Conditions is not 37oherent and the definition is not clearly understood by the A3P working group. The definition of KPP should be clarified and examples provided. Please clarify what "as it relates to product quality" means. **Proposed change:** Rephrase / precise
240-243	2	**Comment:** "Performance based approach" as described seems to be a subset of the

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"enhanced approach" **Proposed change:** Consider updating the "Performance based approach" to a subset of the "enhanced approach".
249	7	**Comment:** "Parameter based" is inaccurate because the broad basis for ECs in the approach includes parameters, attributes, and outputs. **Proposed change:** • A parameter **broad** based approach, in which product development prior to regulatory submission provides a limited understanding of the relationship between inputs and resulting quality attributes, will include a large number of inputs (e.g., process parameters and material attributes) along with outputs (including in-process controls).
249-252	6	**Comment:** Is the parameter approach analogous to the "Traditional/Minimal" approach in ICH Q8(R2)?
254	2	**Comment:** Because the manufacturing process is only one aspect of a control strategy to assure product quality, a description of the manufacturing process alone may not provide sufficient detail. **Proposed change:** Consider updating "manufacturing process" to "process development".
255	6	**Comment:** Example of outputs is provided for clarification. **Proposed change:** ..the most important input parameters along with outputs (example IPCs), as appropriate.
257-258	9	**Comment:** In its current phrasing, the statement that control can be based on unit operation output rather than process input appears contradictory to the basic Quality by Design (QbD) paradigm outlined in ICH Q8, which indicates that control is achieved by controlling the inputs upon having process understanding. Shire believes that the intent of this statement was to convey that unit operation output enables better control which is still achieved by control of inputs.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Shire recommends that lines 221-223 be reworded to reflect the intent that unit operation output enables better control which is still achieved by control of inputs. In addition, as this clearly describes the concept of PAT, we recommend that the guideline explicitly mentions PAT and relates this bullet point to the PAT concept.
261–271	2	**Comment:** Specific examples of what is considered low, moderate, and high risk are not provided. Omission will likely lead to inconsistencies of risk categorization between different MAHs and regulatory agencies. **Proposed change:** Provide specific examples of what is considered low, moderate, and high risk from agency perspective.
		Comment: No mention of design space is provided in this section. Are changes within design space considered not to be an EC? **Proposed change:** Define relationship between decision tree and filing requirements for design space.
262	4	**Comment:** When considering this approach, it is important to ensure that all relevant… **Proposed change:** When considering this approach, it is still important to….
262-267	9	**Comment:** Shire agrees with the FDA version of the ICH draft guideline which clearly indicates that the content in lines 227-232 is part of the bullet point starting on line 221. This is not the case in the EMA version of the document. **Proposed change:** Shire recommends that the EMA version of the ICH guideline in lines 253-267 be aligned to the FDA version in lines 221-232, which clarifies that content in lines 227-232 is part of the entire bullet point.
271-278	7	**Comment:** Based on the decision tree, a change to an EC that is of high risk is assigned as a prior approval. This may vary from product to product (i.e., a high risk

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		change to an EC for one product may not be high risk for a different product). Most, if not all, current post approval change guidances that have been issued by HA's are not written this way and would need to be updated to align with Q12.
274	4	**Comment:** The corresponding reporting category is dependent on the potential risk to quality. **Proposed change:** The corresponding reporting category is dependent on the potential ~~risk to~~ impact on product quality.
275	6	**Comment:** Reference to risk control added for completeness. **Proposed change:** Risk assessment and associated risk control activities should follow approaches described in ICH Q9.
276-278	11	**Comment:** ICH Q12: MAH should consider the overall control strategy and any possible concurrent changes. Comment: LEO finds that including possible concurrent changes when assessing the reporting category does not seem feasible due to the following: • It is basically not possible to predict all possible concurrent changes • In many cases concurrent changes would increase the reporting category compared to the stand-alone changes. As a consequence, if the MAH is in the situation of applying for the stand-alone change without concurrent changes the agreed reporting category would be too high.
277	8	**Comment:** Justification of parameters that are not ECs seems like unnecessary burden on a Marketing Authorization Holder. **Proposed change:** Appropriate justification should be provided in support of the identification of ECs ~~and those aspects that are not ECs~~.
277-278	9	**Comment:** The guideline states: "*Appropriate justification should be provided in support of the identification of ECs and those aspects that are not ECs*". However, the guideline does not specify in which section of the regulatory file/submission this information should be provided.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Shire recommends that the guideline be expanded to indicate in which section of the regulatory file/submission information regarding classification and justification for a change should be provided (e.g. S.2.6 or P.2.3 or appropriate analytical sections).
279 Fig. 1	3	**Comment:** In line with comment above, some KPPs may not ultimately be ECs depending on knowledge and experience with the process. **Proposed change:** Is the process parameter either a CQA or CPP?
279	4	**Comment:** Fig 1 – Decision Tree for Identification of Ecs and associated reporting categories for manufacturing process parameters The decision tree only mentions Ecs as "process parameters". What about material attributes and IPC, as explained in 3.2.3.1 ? A more general title and decision tree would be more useful. **Proposed change:** it would be helpful to propose a more general decision tree, not focussed on process parameters only and not so prescriptive (why are KPP considered as mandatory Ecs?)
279	4	**Comment:** Fig 1 – Decision Tree for Identification of Ecs and associated reporting categories for manufacturing process parameters Need to clarify the decision tree: systematic classification of CPP and KPP into Established Conditions? Focusing on certain/specific KPP (based on justification) is preferred. Add "relevant" KPP **Proposed change:** ~~is the process parameter either a CPP or a KPP?~~ Does the control strategy element impact the product quality? What is the level of potential risk associated with the ~~proposed~~ change of the EC

Line no.	Stakeholder no.	Comment and rationale; proposed changes
279-281	9	**Comment:** Whereas the Q12 guideline Annex considers outputs to be established conditions (ECs), Figure 1. Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters, refers to ECs related to inputs only. The apparent discrepancy should be clarified. **Proposed change:** Shire recommends that, Figure 1. Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters, be amended to include outputs as ECs in order to align with the ICH Q12 Annex.
279-282	7	**Comment:** The Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters (Figure 1 in ICH Q12) needs to be updated to remove reference to KPPs and to reflect the "not enough knowledge to determine" scenario where things default to ECs when a parameter-based approach was used to develop the process. **Proposed change:** Replace Figure 1 with the following (see below attachment B). Figure 1. Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters1
281–282	8	**Comment:** Ch 3.2.3.1 (Figure 1). Footnote 1 indicates that the decision tree does not apply for performance-based approaches. Comparable information for performance-based approaches would be helpful to include. **Proposed change:** Please consider that Figure 1 can also be applicable for performance-based approaches and remove footnote 1, or include an explanation or separate decision tree for reporting categories for performance-based approaches so it is clear what is expected in those cases.
283	4	**Comment:** Information regarding product-specific post-approval change activities, such as post change monitoring, may be provided as supporting information to aid in the determination of ECs and associated reporting categories. **Proposed change:** To be included in 3.2.4 or remove this sentence because already referred to in

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		the first bullet point of 3.2.4
283-284	7	**Comment:** Whether monitoring is performed post-change should not determine whether something is an EC. **Proposed change:** Information regarding product-specific post-approval change activities~~, such as post change monitoring,~~ may be provided as supporting information to aid in the determination of ECs and associated reporting categories.
286-287	4	**Comment:** Criticality and risk should be evaluated periodically during the lifecycle of the product and, using the decision tree, the ECs should be updated based on acquired knowledge. Criticality and risk should be evaluated periodically during the lifecycle of the product and, using the decision tree, the ECs should be updated based on acquired knowledge. **Proposed change:** To be included in 3.2.4
286-287	6	**Comment:** An example of this approach for evaluating criticality and risk may be needed (e.g., in an accompanying Annex document or appendix to Q12) to help visualize how this will be implemented in practice within the dossier
286-287	9	**Comment:** The guideline indicates: *"Criticality and risk should be evaluated periodically during the lifecycle of the product and, using the decision tree, the ECs should be updated based on acquired knowledge."* Shire believes that this statement is not in line with the regulatory flexibility principle and may be too prescriptive. Evaluation of risk and criticality should be based on the evolving process understanding and product lifecycle events rather than prescribing temporal triggers (i.e. periodic) to evaluation. For example, evaluation triggers could be defined as CPV and Change Control. **Proposed change:** Shire suggests the following edit to lines 252-253 (indicated by red strikethrough and blue underlined text): *"Criticality and risk should be evaluated periodically <u>based on the evolving process understanding and product lifecycle events, which may or may not include periodic triggers,</u> during the lifecycle of the product and, using the*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		decision tree, the ECs should be updated based on acquired knowledge."
289 Fig. 1	6	**Comment:** Figure 1 needs to be revised to better align with core concepts of the guidance, for example lines 159-174. In addition, Figure 1 revisions are needed for clarity and to take probability, detectability, and severity into account. **Proposed change:** See proposed revised Figure 1 in attachment A below.
290-304	6	**Comment:** An annex with examples of ECs for an analytical procedure should be added. This is due to differences in the level of details of ECs between regions. Without specific examples harmonized global ECs cannot be established.
290-304	7	**Comment:** The level of details of EC for analytical procedure can be different between regions without specific samples. Specific samples are required to establish harmonized EC globally. **Proposed change:** Add an Annex for the example of EC.
291-292	7	**Comment:** The following revision is suggested to help clarify. **Proposed change:** ECs related to analytical procedures should include **those** elements which assure performance of the procedure.
295-297	7	**Comment:** The following revision is suggested to align ICH Q12 with the EU Variations Guidance regarding changes in analytical methods. For example, for minor changes to an approved test procedure for active substance (B.I.b.2.a), a Type IA procedure is recommended if the same method of analysis is used, no changes to the total impurity limits are proposed and the procedure passes the appropriate validation. This approach is also consistent with Chapter 8 in the Step 2 draft of this guidance. **Proposed change:** • Where the relationship between method parameters and method performance has not been fully studied at the time of submission, ECs will incorporate the **method of analysis (e.g., chromatographic column chemistry) and the** details of **the** operational parameters including system suitability **elements necessary to perform the test, or a validation**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		protocol.
296-297	4	**Comment:** ECs will incorporate the details of operational parameters including system suitability system suitability should not be a mandatory Established Condition **Proposed change:** Remove including system suitability
298-301	7	**Comment:** It is suggested to add the method principle to the case wherein "there is an increased understanding" because it is unlikely that information obtained during an enhanced development of an analytical method would be relevant to an analytical method using a different principle. Accuracy and precision are considered the critical performance criteria while other performance criteria, such as selectivity, are only considered supportive. A third bullet is added for those cases, exemplified by dissolution, wherein the method parameters, as part of a compendial description, play such a critical role in the performance of the procedure that it is unlikely to be able to avoid considering them as ECs. A fourth bullet is added to allow for method performance characteristics to be considered the ECs when the method capability is high (low risk of a failure to the control strategy) or the method is well-established and simple (e.g., Karl Fischer). **Proposed change:** • When there is an increased understanding of the relationship between method parameters and method performance defined by ~~a systematic~~**an enhanced** development approach including robustness studies, ECs ~~are~~**should be** focused on ~~method specific~~**the critical** performance criteria ~~(e.g., specificity, accuracy, precision) rather than a detailed description of the analytical procedure~~**of accuracy and precision, and if necessary, specificity (which are linked to the requirements of the associated control strategy), and should include the method principle (e.g., chromatography, IR spectroscopy, etc.)**. **• When compendial apparatus and associated conditions (e.g., dissolution apparatus, agitation speed and medium) are intrinsic to the control strategy they may constitute ECs.** **• Method performance criteria on their own may be considered ECs when an assessment of the product quality and safety risks associated with method selection and change indicates them to be low and when future method changes will be addressed through appropriate systems and processes.**
304	7	**Comment:** The rationale is to provide a decision tree for changes to analytical procedures

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		depending on whether or not ECs have changed, in an analogous manner to Figure 1 for manufacturing changes. **Proposed change:** Add the following text and figure. 3.2.3.3 Reporting Categories for Changes to Analytical Procedures A decision tree to identify reporting categories for changes to analytical procedures, based on ECs, is shown in Figure 2. See attachment C below.
312-313	8	**Comment:** Ch 3.2.4 (para 2, lines 312-313) The 'Justification may include information such as validation data and batch data' need to clarify for conditions of information. This can be applied to analytical procedure and manufacturing process. For the analytical procedure, validation data and batch analyses can be collected and used. But for the manufacturing process, many parameters are revised based on manufacturing experience only. We suggest to add 'or' in sentence. **Proposed change:** Justification may include information such as validation data and/or batch analyses.
323	4	**Comment:** Maintenance of the marketing application… Refer to line 28 **Proposed change:** Maintenance of the marketing application ~~(including aspects that are not identified as ECs)~~ should follow regional expectations.
328-334	2	**Comment:** It is not clearly stated in which cases a PACMP is recommended. From the decision tree on page 7, it seems only suitable for high risk changes that require prior approval. **Proposed change:** Clearly state in which cases of the decision tree a PACMP is recommended.
333-439	9	**Comment:** There appears to be a significant amount of similarities between an FDA comparability protocol and the Post-approval change management protocol (PACMP); Chapter 4 would benefit from a discussion and clarification of the relationship between the two protocols, including addressing whether the PACMP could replace the FDA comparability protocol. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Shire suggests that Chapter 4 be expanded to include a discussion with regard the relationship of an FDA comparability protocol to a PACMP and, given apparent overlap, address whether the latter could replace an FDA comparability protocol.

339–341	10	**Comment:**
		• Post-approval Change Management Protocols (PACMPs)
		  • The PACMP should not include "the suggested reporting category in line with regional requirements, i.e. a lower reporting category and/or shortened review period as compared to similar change procedure without an approved PACMP.", as this would make the PACMP a region/country-specific document and necessitate several PACMPs for the same change in different countries/regions.
		  • Delete this part of the sentence.
		  • Alternatively, replace "the suggested reporting category in line with regional requirements" by "the suggested reporting category in line with chapter 2" to clarify that the PCAMP should provide a justification for downgrading the step 2 submission in the framework of an overall risk-based categorization system as outlined in chapter 2 of the guideline. Delete "and/or shortened review period".
		  • Clarify that being regional/country-specific information the suggested region-/country-specific variation type (CBE30, Type IB…) and/or shortened review period for the PACMP step 2 submission belong in Module1.
		Proposed change:
		see above

344	1	**Comment:** In Questions and answers on PACMP i.e. EMA/CHMP/CVMP/QWP/586330/2010, the Agency has clarified that protocol should be included in Module 3.2.R. To avoid any ambiguity, Kinapse would suggest to add to the ICH Q12 guideline information about the location of PACMP in Original MAA or subsequent submissions. **Proposed change:** The below information might be captured in section 4 of the ICH Q12 guideline. "The protocol should be included in the marketing authorisation application or subsequent submissions as part of the Regional Section 3.2.R of Module 3.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		The relevant section(s) of Module 3 should cross refer to the protocol."
347	5	**Comment:** "A PACMP should describe changes with a level of detail commensurate with the complexity of the change." It may be an improvement to the guidance to Append examples for a routine level change requiring a PACMP so that Industry has a better understanding of the level of information and expectation of the Agency. Its seems that both Industry and Regulators may not be aligned on this point unless it is made clearer, resulting in extensive time delays for changes to PACMPs etc. **Proposed change:** Include additional example-driven Appendices to help Industry be consistent with Agency requirements. A recommendation may be to publish a metrics assessment so that Industry can see how well these are being received in the harmonised agencies with respect to content, and time for overall assessment.
348-349	5	**Comment:** "Once approved, in cases where implementation (see "step 2" below) is pending, there is an assumption that the proposed approach is re-evaluated by the MAH on a regular basis and its validity reconfirmed prior to implementation of the change(s)." **Proposed change:** Include more detail of whether this re-evaluation needs to be documented formally (e.g. protocols, in risk assessments follow-ups, against data trending collected). Assume this level of information would be routinely reviewed during site inspections. May be good to clarify the expectation of this sentence.
363	4	**Comment:** Application of a PACMP A3P suggests to clarify the location of the PACMP in the CTD (step 1): a suggestion would be to include under 3.2.R
384	4	**Comment:** patient safety, product quality or efficacy. Harmonisation of Product Quality definition would be helpful
416	4	**Comment:** 4.4. Modification to an Approved PACMP Modification to an approved PACMP is described while submission of a PACP, proposal to amend section 4.4. or create a new specific section 4.3.b

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: 4,4 Submission and modification to a PACMP "PACMP may be included in an initial application or may be submitted subsequently as a stand alone post approval change as per regional dispositions. A modification to an already approved …"
423	4	**Comment:** 4.5 Types of PACMP How to obtain convergence on PACMP strategy for products submitted through regional procedures across all regions?
425	6	**Comment:** Updated wording to reflect that CMC changes may be to the product, process, methods and/or materials. **Proposed change:** One or more change(s) ~~to~~ associated with a single product…
425	7	**Comment:** Suggestion to incorporate the proposed change below to reflect that CMC changes may be to the product, process, methods, and/or materials. **Proposed change:** • One or more change(s) ~~to~~**associated with** a single product – see above and Annex IIA, for content and implementation. A PACMP can also be designed to be used repeatedly to make a specified type of CMC change over the lifecycle of a product, applying the same principles.
440	4	**Comment:** 5. Product lifecyle management document general comments on this chapter A3P suggests that to guarantee the implementation of ICH Q12 and allow the benefits of this approach, the PLCM and risk based categorisation should be common / recognised for all regions of ICH. A recommendation on the expected location in the CTD would be helpful. module 1 (global overview in Module 1) or module 3 (for scientific analysis, technical justifications) are suggested. ICH position would be appreciated on the possibility for coexistence of the new approach PLCM/Q12 vs classical change management and variations, or possible combination of both.
440-445	6	**Comment:** This statement seems to be similar to the type of information provided in a US

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		comparability protocol/ EU PACMP (e.g., for a given change, it includes the tests to be performed along with acceptance criteria). The text in rows 272-274 should be clarified further on what is meant here. **Proposed change:** …"or impact on the process consistency (i.e. yield) as it relates to product.
440-445		**Comment:** Suggestion to remove PLCM and/or further clarify its location, contents and value. The PLCM is just a compilation of items that can be found elsewhere: Summary of Product Control Strategy • ECs • Reporting category for making changes to approved ECs • PACMPs • Post-approval CMC commitments This information is or can also be captured in M3 or M2. The Post-approval change management protocol (PACMP) is already an additional document to M2 and 3, but adds value and has a specific purpose: get agreement on post-approval change management between MAH and regulatory authority. The PLCM is just a compilation of data available elsewhere and in itself does not add value, just additional work and yet another document. At a minimum, more clarity around the PLCM is needed, including its CTD placement and more detailed examples.
440-445	7	**Comment:** The PCLM is a compilation of items that can be found elsewhere (e.g., Summary of Product Control Strategy ECs, Reporting category for making changes to approved ECs, PACMPs Post-approval CMC commitments, etc.). This information is or can also be captured in M3 or M2. The Post-approval change management protocol (PACMP) is an additional document to M2 and M3 and has a specific purpose, which is to build consensus on post-approval change management between MAH and CA. **Proposed change:** More clarity around the PLCM is needed, including its CTD placement and more detailed examples.
442-443	4	**Comment:** proposed reporting categories for changes to ECs, PACMPs (if used) and any post approval CMC commitments. A3P recommends to avoid integrating post approval CMC commitments in the PLCM document, to avoid that this document becomes regional specific.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		The commitments will still be managed through regional commitments. **Proposed change:** Proposed reporting categories for changes to ECs, PACMPs (if used) and any post approval CMC commitments.
446	8	**Comment:** Ch 5.1 Product Lifecycle Management is currently performed by drug substance manufacturers but not communicated to Health Authorities by ASMF/DMF holders. It is unclear if the PLCM document would be applicable to ASMF/DMF holders. In most cases an ASMF/DMF is applicable to more than one MAH, and consequently there may be differences in the control strategy and ECs requirements for different customer applications, and this would need consideration if PLCM concept is applied to ASMF/DMFs. **Proposed change:** Please clarify the scope/applicability of the PLCM concept to ASMF/DMF holders.
449-450	1	**Comment:** Is it mandatory to submit PLCM document if explicit ECs are being proposed?
450	4	**Proposed change:** Remove explicit / implicit
452	6	**Comment:** Proposed rewording of section title to align with ICH Q10. **Proposed change:** Summary of ~~Product~~ Control Strategy.
452-454	7	**Comment:** This concept of "Product Control Strategy" as described in this guideline was initially defined in ICH Q10, where is it referred to simply as "Control Strategy". The nomenclature should be consistent throughout ICH documents. Recommend rewording to align with the ICH Q10 definition of this concept. **Proposed change:** Recommend rewording the following lines to align with the ICH Q10 definition of this concept. Summary of ~~Product~~ Control Strategy: A high level summary of the ~~product~~ control strategy should be included in the PLCM document to clarify and highlight which elements of the control strategy should be considered ECs.
457	4	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Reporting category for making changes to approved ECs (refer to Chapter 3): please, precise how to manage the PLCM document for the changes managed through PQS : internal PLCM document gathering all the changes (changes submitted to the authorities with variations and changes managed through PQS).
458	4	**Comment:** The detailed justification of the reporting categories is located in the relevant sections of the CTD If PLCM is not submitted, how should we deal with the justifications of reporting categories?
459-460	4	**Comment:** The reporting category may be based on regional regulations or guidance, or MAH justification. A common document for all regions is preferable, harmonisation of Regional regulations is a prerequisite
466	4	**Comment:** Post-approval CMC commitments: As Post-approval CMC commitments are country specific, A3P suggests to remove the paragraph **Proposed change:** ~~Post-approval CMC commitments: CMC commitments (e.g., specific process monitoring, revisions to ECs) that will be implemented during the commercial phase should be listed in the PLCM document.~~
470-473	11	**Comment:** In our opinion it is not clearly described if the submission of the PLCM is a variation in itself, in case it was not included in the original MAA. This should be clarified.
475-478	11	**Comment:** ICH Q 12: It is proposed that the MAH should follow regional expectations for maintaining a revision history for the PLCM document. Comment: LEO finds that it is not clear what is meant by "regional expectations for maintaining a revision history"- does it refer to regulatory documents/regulations or practices and how should it be managed in case of no regional expectations. LEO suggests that ICH Q12 includes a proposal for how to maintain a revision history that can be used by both MAH and Authorities (assessors and inspectors).

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Additionally, it is unclear whether an updated PLCM document should be included in all post-approval submissions independent on an EC being affected by the actual change or not
476	4	**Comment:** A3P suggests to remove the link with commitments to avoid regional specificities **Proposed change:** The updated PLCM document will capture the change in ECs and other associated elements (reporting category, commitments, PACMP).
477-478	5	**Comment:** "The MAH should follow regional expectations for maintaining a revision history for the PLCM document." **Proposed change:** The MAH should follow regional expectations for maintaining a revision history for the PLCM document. Refer to Annex X for further information on regional expectations. Please include more clarity on what the regional expectations may be with respect to location and maintenance of the PLCM document either in an Annex or elsewhere.
482-483	7	**Comment:** Please provide a single recommendation for the location of the PLCM document in the CTD Module in order to facilitate a harmonized approach globally.
482-483	10	**Comment:** • Location of the PLCM document in the CTD is basically left completely open ("either in CTD Module 1, 2, or 3 based on regional recommendations.") More definite guidance should be provided to avoid divergent national/regional requirements. • To reflect the character of the document as an overall summary, proposed location in the CTD is Module 2.3, preferably as an appendix to enable an independent revision history. Proposed reporting categories for ECs should be left on the level outlined in chapter 2 of the guideline. No region-/country-specific information (e.g. variation type) should be mentioned in the PLCM document. • If required, this could be complemented by a region-/country-specific document in Module 1, which refers to Module 2.3 and lists ECs + variation types only. • Clarification should be added as to which extent implicit ECs

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		(as defined by regional/national regulation or guidance) have to be listed in the PLCM document. Specific guidance is also required in case regional/national legislation does not define certain ECs, but basically the whole dossier content has to be considered regulatory relevant. • Proposal: The MAH has to define per CTD section which of the following approaches has been chosen: Full set of explicit ECs proposed (= implicit ECs do not apply for this section), or nothing proposed (= implicit ECs fully apply for this section) or mixed approach (explain). **Proposed change:** see above
487-495	7	**Comment:** Reference is made to ICH Q10 and the basic requirements contained therein for a Change Management System. ICH Q12, and Appendix 2 in particular, goes well-beyond the broad description of a Change Management System described in ICH Q10 and provides a significant level of detail describing the principles of change management. One of the key elements of the Change Management System described in ICH Q10 is the recognition that "There is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission, where changes to the regulatory filing might be required under regional requirements." In Table III, ICH Q10 describes four separate applications of a Change Management System throughout the Product Lifecycle. In particular, ICH Q10 recognizes that "Change is an inherent part of the development process and should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development." As ICH Q12 is a lifecycle guidance document, it is important that the recognition in ICH Q10 that "the formality of the change management process should be consistent with the stage of pharmaceutical development" be maintained in this document, particularly given the increased description of a Change Management System described in Appendix 2. **Proposed change:** ~~An effective PQS as established in ICH Q10 and in compliance with regional GMPs is the responsibility of a firm (manufacturing sites and MAH where relevant) and it is not the intent of this guideline to ICH guideline to require a specific inspection assessing the state of the PQS before the firm can use the principles in this guideline. The conduct of routine inspections in connection with submitted marketing applications and surveillance will nevertheless continue as foreseen by regional regulatory requirements.~~ ~~In the event that the PQS is found not to be compliant, it may result in restrictions on the ability to utilise flexibility in this guideline.~~ Consistent with the basic requirements of ICH Q10, an effective change management system

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		is necessary for implementation of this guideline**. Change is an inherent part of the lifecycle of a product and should be documented. However, there is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission, where changes to the regulatory filing might be required under regional requirements. The formality of the change management process should be consistent with the stage of pharmaceutical development and product lifecycle. Consistent with the basic requirements of ICH Q10, an effective commercial change management system supports the principles of this guideline** and is summarised in Appendix 2.
494-495 and Annex II	6	**Comment:** Replace current Annex 2 with reference to Annex 1 in ICH Q10. **Proposed change:** Consistent with the basic requirements, in Annex 1 of ICH Q10, an effective change management system is necessary for implementation of the guideline~~, and is summarised in Appendix 2.~~
507-513	4	**Proposed change:** Merge the paragraphs from lines 537-543 and lines 544-545.
512	8	**Comment:** Ch 6.2 (final bullet, line 512) Communication mechanisms are typically defined in quality agreements. Contracts deal with commercial matters and requirements for a quality agreement. **Proposed change:** The communication mechanisms regarding MAA changes and GMP issues should be defined in relevant documentation, including quality agreements and/or contracts with CMOs.
521-524	1	**Comment:** Kinapse understands that the implementation of ICH Q12 will require increased communication and coordination between inspectors and assessors. Please clarify if MA holder has any role and responsibilities in facilitating this communication or establishing the communication mechanism.
525	4	**Comment:** General comment on chapter 8. 8. POST-APPROVAL CHANGES FOR MARKETED PRODUCTS A3P proposes to place this chapter before chapter 7.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		This guideline can be useful for marketed products beyond analytical procedures and stability (site change, transfer to CMO). We propose to complete this chapter with other examples not focused on analytical methods and stability) Details are appreciated for analytical procedures and stability. Other examples would be appreciated for the product /process. Why is there a specific chapter focused on marketed products whereas the interpretation is that the ICHQ12 can be implemented both for new products and marketed products? Title of this chapter is confusing.
525-531	3	**Comment:** Suggest changes in introductory paragraph and title of this section in order to clarify the intent of this section. Also to clarify that this is an example of a structured approach for some changes, but not to imply that a similar structured approach could be leveraged for other types of changes. **Proposed change:** 8. Some Common Post-Approval Changes for Marketed Products It is recognized that in addition to leveraging ECs and PACMP, some product or process changes could also benefit from additional approaches. As such, this chapter describes an example strategy for a structured approach for more common CMC changes (e.g., analytical methods) and data requirements for CMC changes (e.g., stability).
528-529	6	**Comment:** To provide clarification on the purpose of this section, proposed wording is provided. **Proposed change:** In addition, such products would also benefit from additional approaches to facilitate changes. To provide some guidance on how these concepts could be applied. ŧThis chapter describes a strategy for a structured approach…
529	4	**Comment:** This chapter describes a strategy for a structured approach for frequent CMC changes (e.g., analytical methods) and data requirements for CMC changes (e.g., stability). A3P supports that it would be useful to integrate ICHQ12 principles for analytical methods management (lifecycle). A suggestion for better readability is to transfer analytical examples in appendix and add the same kind of examples for process, primary packaging in appendix.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
533-536	7	**Comment:** The following changes are suggested to clarify that for marketed products the procedure described in section 3.2.3.2 may be used in lieu of Section 8.1. **Proposed change:** Marketed products have existing analytical procedures that may benefit from advances made in analytical sciences. The intent of this chapter is to incentivize structured implementation of equivalent analytical procedures that are fit for purpose. **For products for which ECs for analytical procedures have been defined, the path for changes outlined in Section 3.2.3.3 should be followed.** An approach wherein specific criteria are defined for changes to analytical procedures used to test marketed products **for which ECs have not already been defined** is described below.
540-545	7	**Comment:** The examples given are "assay for identity by peptide map" and "assay for complex drug substances". It is not clear what these examples convey and why they would be out of scope. How complex does a DS have to be to be excluded? Monoclonal antibodies? ID by peptide map is an excellent example of a method that should be included in the scope since peptide map methods frequently need small changes to improve robustness but specification will not be impacted. These changes should be "Do and Tell" since filings would not add any value and the principles included in section 8.1.1 can be applied. **Proposed change:** Clarify or delete lines 540-545.
546-548	7	**Comment:** More complex method types should be in scope of this aspect of the guidance and should not be fundamentally different than other method types. These methods would still be required to meet the provisions of 8.1.1. This appears to be consistent with the definition of ECs described in section 3.2.3.2. **Proposed change:** Delete the following lines. ~~• Change(s) to a test method based on a biological/immunological/immunochemical principle or a method using a~~ ~~biological reagent (e.g., bioassay, binding assay, ELISA, testing for viral adventitious agents).~~
546- 557	2	**Comment:** Discussion of the relationship between regulatory assessment of an application and GMP inspection is a helpful topic. This section should be expanded to clarify the purpose of each activity.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: The regulatory review of an application should focus on the development of the product and the quality control strategy. GMP inspection should focus on implementation of GMP defined in ICH Q7. Items that are defined elements of GMP should not be the subject of application review and should not be required in regulatory filings. An example of this is designation of starting material suppliers. Section 13.11 of ICH Q7 requires manufacturers to have written procedures for approval of changes in raw materials, and this can be verified during a GMP inspection. As such this should not be an established condition in a marketing application, and should not be subject to post-approval change management.
549	7	**Comment:** Updates to predictive models may be considered analogous to other analytical method modifications within the same principle and should be within scope of Chapter 8. **Proposed change:** • **Significant** ~~C~~**c**hanges to predictive models**, such a new algorithm,** used with multivariate methods **would be out of scope of this chapter; minor changes, such as an update to the existing predictive model should be within scope**.
552-555	4	**Comment:** Making use of Chapter 8.1 is dependent on the regional implementation of ICH guidelines (e.g., ICH Q2, Q9 and Q10) and routine application of these guidelines by industry. The flexibility provided in Chapter 8.1 may not be available in all regions and in all situations; some specific changes may require prior approval as defined in regional guidance. A3P reinforces the need for global harmonization for efficient implementation of the guideline. **Proposed change:** Proposed change: remove the paragraph ~~Making use of Chapter 8.1 is dependent on the regional implementation of ICH guidelines (e.g., ICH Q2, Q9 and Q10) and routine application of these guidelines by industry. The flexibility provided in Chapter 8.1 may not be available in all regions and in all situations; some specific changes may require prior approval as defined in regional guidance~~
552-555	6	**Comment:** Delete paragraph. This chapter should be applied to all the regions for alignment of change control strategies and their implementations between regions, which is essential for enabling efficient global implementation of changes. Science and risk-based assessments by regulatory authorities for

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		adopting this approach should not be different between regions. **Proposed change:** ~~Making use of Chapter 8.1 is dependent on the regional implementation of ICH guidelines (e.g. ICH Q2, q9 and Q10) and routine application of these guidelines by industry. The flexibility provided in Chapter 8.1 may not be available in all regions and in all situations; some specific changes may require prior approval as defined in regional guidance.~~
552-555	7	**Comment:** This chapter should be applied to all the regions for alignment of change control strategies and their implementations between regions, which is essential for enabling efficient global implementation of changes. Science and risk-based assessments by HAs for adopting this approach should not differ between regions. **Proposed change:** Delete the following lines. ~~Making use of Chapter 8.1 is dependent on the regional implementation of ICH guidelines (e.g., ICH Q2, Q9 and Q10) and routine application of these guidelines by industry. The flexibility provided in Chapter 8.1 may not be available in all regions and in all situations; some specific changes may require prior approval as defined in regional guidance.~~
558-559	7	**Comment:** Methods of detection should be outside the scope of changes that would benefit from a regulatory review prior to implementation. Irrespective of the method of detection, a robust validation package held in the sponsor's PQS should account for this type of change. **Proposed change:** The high-level description of the original method and the revised method should be the same (e.g., chromatography ~~with spectroscopic detection~~).
562	8	**Comment:** Ch 8.1.1 (para 1, line 562) While in general it is understandable that results should be equivalent – particularly in terms of equivalent outcome, method changes may be made to improve performance (e.g. improved precision, accuracy, resolution for control of impurities) that may not lead to "equivalent results" (particularly when comparing results of two methods), but still support equivalent outcomes. We strongly advocate that the criteria for assessment of method change should be either fully revalidate or perform equivalence testing. It is unnecessary to stipulate both. Where methods are very old comparison of

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		methods would be unnecessarily burdensome. (see also lines 607-608) **Proposed change:** Test results obtained using the original method and revised method should be equivalent to each other or offer improvements (e.g. precision, accuracy). ~~This~~ Equivalency can ~~should~~ be assessed in two ways: • ~~First,~~ ~~t~~The revised method should give an equivalent outcome, i.e., the same quality decision will be made regardless of whether the data was obtained by the original or the revised method. or • ~~Second,~~ ~~t~~The validation protocol should contain explicit criteria that compare results obtained using the new and revised method. See step 2 below for further details.
590-591	7	**Comment:** Methods of detection should be outside the scope of changes that would benefit from a regulatory review prior to implementation. Irrespective of the method of detection, a robust validation package held in the sponsor's PQS should account for this type of change. Thus, when two techniques are coupled together, it is recommended that only the method principle be considered since specifying the detection method does not change the high-level description of the method. For instance, column chromatography with UV detection is considered to have the same high-level description as column chromatography with electrochemical or spectroscopic detection. **Proposed change:** When two techniques are ~~used~~ **coupled** together (e.g., HPLC with UV detection), ~~both would~~**only the method principle, and not the detection method, would be considered to** be part of the method description (i.e., column chromatography ~~with spectroscopic detection~~).
648-649	4	**Comment:** The data needed for submission to the regulatory authority in support of a post approval change is established by regional regulations and guidance. Remove the sentence (regional regulations) **Proposed change:** The data needed for submission to the regulatory authority in support of a post approval change is established by regional regulations and guidance.
672	9	**Comment:** In the glossary on page 20, the guideline defines KPPs as: "*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*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		assure process consistency as it relates to product quality". The current KPP definition may cause confusion because it states that a KPP is still related to Quality, albeit in an indirect way. **Proposed change:** The guideline should be edited to clearly indicate that KPPs are related to process consistency only.
675	4	**Comment:** Glossary Add a definition for EC, state / clarify the definition of KPP (What does "as it relates to product quality" mean) **Proposed change:** PQR : Product ~~Periodic~~ Quality Review
675	7	**Comment:** If the ICH keeps the concept of KPPs, more clarification is needed on the meaning of "process consistency".
690	7	**Comment:** Appendix 1 of ICH Q12 defines CTD Sections 3.2.S.7.2 and 3.2.P.8.2 (post-approval stability protocol and stability commitment) as supporting information. These protocols govern post-approval testing of batches and are understood to be used for stability testing of batches that incorporate a CMC change to assure that the approved retest period/shelf-life period continue to be applicable to the post-change drug substance/drug product. As such, these protocols should be considered Established Conditions, not supportive information.
690	7	**Comment:** In Appendix 1, suggestion to add PACMP as EC in 3.2.R (Regional Information).
690-698	6	**Comment:** PACMP should be included as an EC in 3.2.R.
Appendix 1	8	**Comment:** Appendix 1 (Line 698) Table Error in CTD numbering. **Proposed change:** Correct 3.3.P.4.3 to 3.2.P.4.3 Correct 3.3.P.4.4 to 3.2.P.4.4

Line no.	Stakeholder no.	Comment and rationale; proposed changes
698 Appendix 1 (Sec 3.2.S.5)		**Comment:** Appendix 1 (Line 698) Table Section 3.2.S.2.4 and 3.2.P.3.4 states ECs would be: "Specifications (e.g., test, elements of analytical procedure and acceptance criteria) for critical steps and intermediates **including storage conditions of critical intermediates."** Specifying the storage conditions here is additional, product-specific detail, inconsistent with the general approach in this table. This detail should be removed. **Proposed change:** 'Specifications (e.g., test, elements of analytical procedure and acceptance criteria) for critical steps and intermediates ~~including storage conditions of critical intermediates~~ '
698 Appendix 1 (Sec 3.2.S.5)	1	**Comment:** Currently, there is no classification category covered in Variation guidelines *(as laid down as per Commission Regulation [EC] No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations)* for reference material however in this draft guidance; reference materials information is considered as an EC. Does the Agency plans to add a relevant category for a change in reference material information when the legal framework will be revised?
698 Appendix 1 (Sec 3.2.S.6)	1	**Comment:** Please clarify that information with respect to secondary packaging material will be considered as "Supportive information" only. **Proposed change:** Kinapse proposes to include specific details i.e. "*Material of construction and specifications of primary container closure system."*
698 Appendix 1 (Sec 3.2.S.5 and 3.2.S.6)	8	**Comment:** Appendix 1 (Line 698) Table Sections 3.2.S.5 and 3.2.P.6: Qualification Protocols are successfully used as a mechanism to manage changes to Reference Materials (3.2.S.5 and 3.2.P.6) in a number of regions, particularly for biological products including vaccines. Although the concept has similarities to PACMPs, upon approval of the protocol for certain changes such as the use of a new batch of reference material without changes to the specification, there is no need to report the data in a subsequent regulatory step. Thus the specification of the reference material should be considered as an EC and a Qualification Protocol could be recommended to manage changes to the Reference material that do not result in changes to the specification.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Reference Material specification ~~qualification~~ (e.g., test, elements of analytical procedure, where appropriate, and acceptance criteria) Add footnote: A Qualification Protocol is recommended to manage changes to Reference Material that do not result in changes to its specification.
698 Appendix 1 (Sec 3.2.P.4.1)	1	**Comment:** As per current variation guidelines *(as laid down as per Commission Regulation [EC] No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations)*, there is no need to notify the competent authorities about an updated monograph of the pharmacopoeia if reference is made to the '*current edition*' in the dossier. For such cases, we understand specifications of an excipient would not be an 'Established Condition' but just "Supporting Information". And, the applicant should be responsible to update these specifications within 6 months to remain compliant. Please confirm that the statement "*Or if applicable - Reference to pharmacopoeial monograph*" applies to cases where a version no. of pharmacopoeial monograph is specified in the dossier.
698 Appendix 1 (Sec 3.2.P.6)	1	**Comment:** Currently, there is no classification category covered in variation guidelines *(as laid down as per Commission Regulation [EC] No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations)* for reference material however in this draft guidance reference materials information is considered as an EC. Does the Agency plan to add a relevant category for change in the reference material information when legal framework will be revised?
698 Appendix 1 (Sec 3.2.P.7)	1	**Comment:** Please clarify that information with respect to secondary packaging material will be considered as "Supportive information" only. **Proposed change:** Kinapse proposes to include specific details i.e. "*Material of construction and specifications of primary container closure system"*
698 Appendix 1 (Sec 3.2.P.7)	1	**Comment:** Supplier information for container closures is considered to be a GMP issue; companies qualify new suppliers ensuring that quality/ approved pack specification is unchanged. However in this guidance, this information is considered as an EC which will

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		limit the regulatory flexibility i.e. *unlike to the aim of ICHQ12.* **Proposed change:** Kinapse proposes to remove "Supplier/manufacturer of container closure" from Established Conditions list.
698 Appendix 1 (Sec 3.2.P.7)	8	**Comment:** Appendix 1 (Line 698) Table Section 3.2.P.7 This section states that the supplier/manufacturer of a container-closure is an EC. However, this should not be an EC if equivalently sourced materials are appropriately qualified and controlled via the PQS. This requirement should be deleted as an EC. The container-closure is stated to be provided as "material of construction and specification" but it is considered that there are other ways to provide commitments to container closure than by providing materials statements, for example by providing the Moisture Vapour Transmission Rate (MVTR) which can be considered as a way of describing one aspect of the performance of the container closure system. **Proposed change:** ~~Supplier/manufacturer of container closure~~ Material of construction and specification (or suitable performance characteristics and acceptance criteria)
709	8	**Comment:** Appendix 2 Point 4 (line 709) Current statement Point 4 includes elements that are not required under the change management system. **Proposed change:** Requires a science and data based risk assessment ~~and risk categorization of the proposed change including the management of risk in the event the proposed change is not implemented~~
728	8	**Comment:** Appendix 2 Point 11 (line 728) Not all statements in Point 11 (a. to d.) are effectiveness checks – many are post implementation actions. An effectiveness check needs to be focused on whether the change met the desired outcome with no unintended consequences. Lessons learned activities focus on the business process/project aspect of doing the change, whereas effectiveness checks focus on the quality aspects. The management review, as outlined in ICHQ10, already includes evaluating

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		opportunities for improvement of the PQS. **Proposed change:** ~~10. Captures new product/process knowledge gained during implementation of the change~~; 10. Verifies, post-implementation, that relevant changes have been effective in achieving the desired outcome with no unintended consequences for product quality If deviations associated with post-approval changes are detected, ensures that the issue is managed via the firm's deviation management process and appropriate corrective and/or preventive actions are identified and undertaken via the firm's corrective and preventive action (CAPA) system 11. ~~Verifies,~~ ~~p~~Post-implementation~~, that changes have been effective in achieving the desired outcome with no unintended consequences;~~ a. Captures new product/process knowledge gained during implementation of the change ~~If deviations associated with post-approval changes are detected, ensures that the issue is managed via the firm's deviation management process and appropriate corrective and/or preventive actions are identified and undertaken via the firm's corrective and preventive action (CAPA) system~~ b. Where applicable, ensures that regulatory filings are updated and an assessment is made as to whether updates to the PLCM document are needed ~~c. Requires a post-implementation lessons-learned exercise to build on the product and process knowledge gained with a view to continual improvement, including improvement of the PQS~~ c. ~~d.~~ Where applicable ensures that the change is included and assessed as part of the Product Quality Review (PQR)
739-741	2	**Comment:** To support the efficiency of post-approval change implementation, confirmatory studies should be recommended only when the other approaches described do not provide confidence in the comparability in stability of the post-change material. If a regulator feels that confirmatory stability studies are warranted when reviewing a change, this should be added as a commitment and not a requirement for submission of data prior to implementation of the change.
Appendix 1 (Sec. 3.2.P.4.1)	4	**Proposed change:** Excipient Specification For each Quality Attribute on the specification · Test Method

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		· Acceptance Criteria ~~Or, if applicable, Reference to pharmacopoeial monograph~~
Appendix 1 (Sec. 3.2.P.7)	4	**Proposed change:** ~~Supplier/manufacturer~~ of container closure Material of construction and specification
Appendix 1 (Sec. 3.2.A.1)	4	**Comment:** Supportive information? if EC in facilities and equipment, are described in other sections **Proposed change:** In grey as supportive information
Appendix 1 (Sec. 3.2.A.1)	8	**Comment:** Appendix 1 (line 698) Table 'Facilities and Equipment' is listed as an EC per "regional regulation and guidance" but this information should not be considered as ECs because it is GMP-related and regulatory oversight provided through inspection. Additionally, this statement perpetuates regional diversity rather than harmonization. **Proposed change:** Remove statement and mark section as supportive information and a non-EC section.
702 Appendix 2	4	**Comment:** APPENDIX 2: PRINCIPLES OF CHANGE MANAGEMENT 1. Capture stimuli: please add a definition of stimuli **Proposed change:** 1. Capture stimuli (reason, triggering element....)
771-773 Appendix 2	8	**Comment:** Appendix 2 Use of Knowledge (para 4, line 771-773) The statement in Line 773 ("there is no added requirement for a formal knowledge management system") seems to contradict that line 771 ("use of knowledge … should be described in the PQS"). Q10 does not state "there is no added regulatory requirement for a formal knowledge management system" – this is in 'Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4)' **Proposed change:** Use of knowledge is the responsibility of the firm ~~and should be described in~~

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		~~the PQS~~ (for more detailed information reference is made to ICH Q8, Q9, Q10, Q11, Q/IWG Q&A). As described in ~~ICH Q10~~ ICH Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4), 'there is no added regulatory requirement for a formal knowledge management system. However it is expected that knowledge from different processe s and systems will be appropriately utilised.'
Annex I (page 5)	4	**Comment:** Change Reporting Categories: Prior Approval (PA) – PAS, Type II, PCA, etc. Notification Moderate (NM) – CBE 30, Type IB, MCN, etc. Notification Low (NL) –AR, Type IA, MCN etc. Not Reported (NR) Please add the definitions for abbreviations **Proposed change:** define the acronyms . "PAS, type II, PCA" PAS: Prior Approval Supplement, …..PCA: Partial Change Application . "CBE, type IB, MCN" CBE : Change Being Effected, …. MCN: Minor Change Notification . "AR, Type IA, MCN etc": AR = Annual Report…..MCN: Minor Change Notification
Annex I	6	**Comment:** Example for a small molecule drug substance should also be added. The chemical synthesis process of a drug substance can be more miscellaneous and difficult to classify in a consistent way. Examples should be shown so that the companies and the ICH member's regional regulatory authority will have consistent understanding.
Annex I 31-33	7	**Comment:** Please clarify that the example of explicit ECs provided in Annex 1 is not intended as a new document to be submitted with the process description, but is illustrative of how the explicit ECs and Reporting Categories would be presented in the Product Lifecycle Management Document (Annex 3).
Annex I 51-53	7	**Comment:** The rationale of the classification of the parameters is only explained for Enhanced Approach and Performance Based Approach in the "Comments/Justification" column (with the exception of the biological product example "Speed train" in line 70). The rationale for Parameter Based

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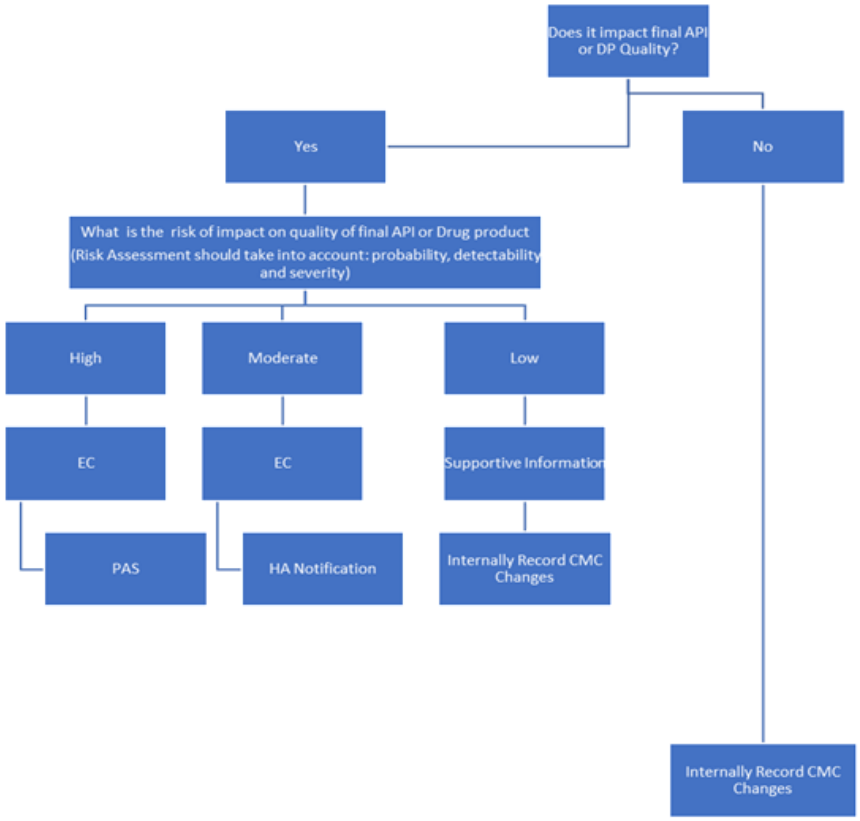
		Approach should also be explained throughout the Annex so that the basis of the parameter categorization, especially the rationale of CPPs with the reporting category of NM (e.g., Line 66, Blend Speed and Time, Line 68, Roll gap/Roller compaction force and speed) can be understood. Since these examples in the Annex will serve as the guide for the EC categorization, the rationale of categorization should be clearly illustrated. **Proposed change:** Add a description of the rationale for the classification of parameters for Parameter Based Approach.
Annex I 62	7	**Comment:** Chemical synthesis process of a drug substance is more miscellaneous and difficult to classify CPP/KPP and PA/NM/NL/NR in a consistent way. Examples should be shown so that the companies and the regional HAs will have consistent understanding. **Proposed change:** Add an example of a small molecule drug substance.
Annex IA 66	8	**Comment:** Annex IA (lines 66) Enhanced approach: If the PSD of the API demonstrated no impact on dissolution or absorption, why not consider it as "NR" or "NL"? It demonstrated no impact on quality, so it should fulfil criteria for low or no reporting required. **Proposed change:** Change the reporting category to "NR" or "NL"
Annex IA 66-70	8	**Comment:** Annex IA (lines 66-70) With regards to the reporting categories presented in the tables for the small molecule and biologic example, it is not clear how the reporting category relates to proposed changes in ranges (widening versus tightening). For instance, for homogeneity, NM is proposed for the specification <5% RSD (IPC). It is unclear how the reporting categories are defined when tightening or widening the specifications, and how they will differ (since the risk is different). Can you widen or delete an acceptance range post approval with a notification low (NL) reporting category based on a risk assessment? Shouldn't the reporting categories correspond to a lower regulatory risk for the performance based approach as more is known about the manufacturing process? **Proposed change:**

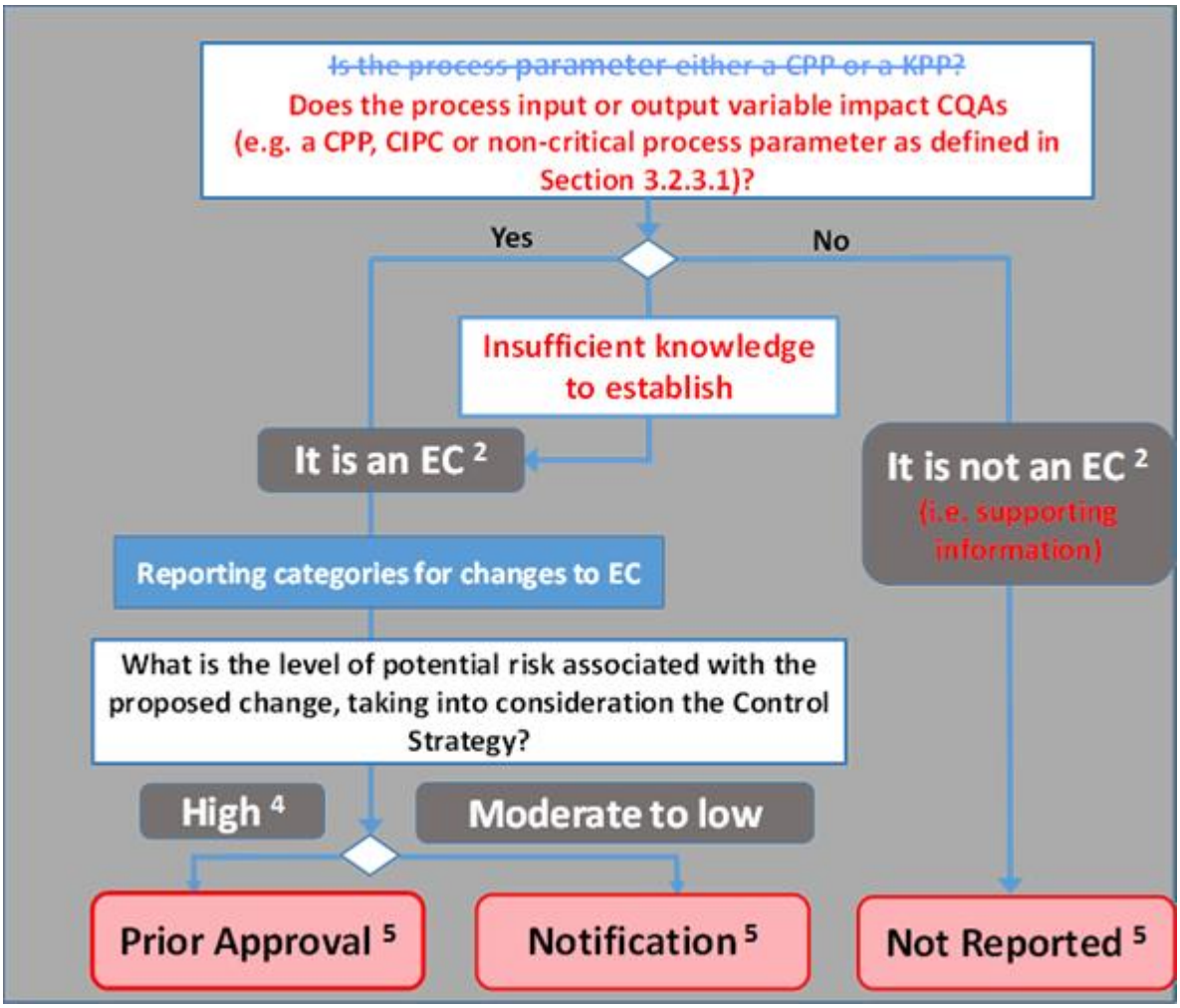
Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Clarify how reporting categories change when widening or tightening ranges.
Annex IIA 106-129	8	**Comment:** Annex IIA: PACMP Example 1 (lines 106-129) It would be helpful to: 1. Exemplify alternate approaches to facilitate assessment of change by MAH and regulators for a low risk change and/or one supported by prior knowledge and one that promotes innovation 2. Include an accommodation for continuous manufacture, (e.g. also add commentary around expectations for site change for continuous manufacture.) The requirements in the bulleted list seem to reflect requirements when a parameter-based approach has been taken even though there is an acknowledgement that these should reflect a lower submission category than provided for in existing guidance i.e. does not seem to take into consideration enhanced or performance-based approaches. **Proposed change:** • In a comparative batch analysis if the risk is low and/or there is prior knowledge, one batch of drug substance manufactured at the alternative manufacturing site should meet approved specification to demonstrate equivalence to batches manufactured at the currently • approved site. • Stability studies will be initiated immediately on one batch of drug substance manufactured at the alternate manufacturing site . Alternate approaches such as modelling could be used to demonstrate comparability of stability profiles of drug substance produced at both sites. Stability data are to be reported to the regulatory authority subsequent to implementation of the new site according to regional requirements. • specification and analytical methods for starting material or intermediates should be appropriate to control the materials and be equivalent or better • analytical methods or specification for release and stability testing for drug substance manufactured at the alternative site should be appropriate to control the drug substance and be equivalent or better
Annex IIA 113-114	8	**Comment:** Annex IIA (line 113-114) Why are DP stability studies needed if lines 124-125 state that there is no change in synthetic route, control strategy, impurity profile or physicochemical properties?

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Remove the requirement for DP stability
Annex III	4	**Comment:** example of PLCM In the full text of the guideline (figure 1 - decision tree), the reporting category is not only linked to the EC but also to the impact of the change (level of risk). In the PLCM example provided annex 3, it is less clear that the reporting category is linked to the risk assessment. A3P proposes to add a note to refer to the risk assessment described in the full text.

Attachment A: Stakeholder 6 - Proposed revision of Figure 1



Attachment B: Stakeholder 7 - Proposed revision of Figure 1



Attachment C: Stakeholder 7 - Figure 2 proposal – see comment on line 304