Appendix: Summary of key content changes from ICH Q12 Step 2 draft to Step 4 final version.

Topic	Chapter	Step 2: Draft	Step 4: Final Version	Analysis/Comments
1	1	"In certain ICH regions, the current ICH Q12 guideline is not fully compatible with the established legal framework regarding the use of explicit EC referred to in Chapter 3 and with the 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."	"Regulatory Members of ICH are encouraged to provide publicly available information, preferably on their website, about the implementation of ICH Q12 in their region, especially with regard to regulatory considerations."	Final version removed the controversial "opt-out" provision to enable truly global applicability of the guideline across all ICH members and regions. Regional implementation strategy is delegated to individual ICH members.
2	3	"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 … 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."	"Regional legal frameworks, supplemented through regulation and guidance, may define ECs with their reporting categories and/or may allow the scientific risk-based approaches described in this chapter to be considered … All regulatory dossiers contain a combination of ECs and supportive information … An MAH should clearly identify the elements of CMC which they consider to be an EC and those which they consider to be supportive information. Similarly, the rationales for the associated reporting categories for changes to the ECs should be provided in the appropriate CTD modules."	Final version removed confusing definitions of implicit and explicit ECs, clarifying instead that some ECs with reporting categories may already be defined in the regional legal frameworks, and a MAH may use one or more approaches detailed in this chapter to propose their own product-specific ECs and reporting categories.

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3	3	"ECs proposed and justified… 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."	"CPPs and other process parameters where an impact on product quality cannot be reasonably excluded should be identified as ECs." "A suitably detailed description of the manufacturing process in Module 3 is expected to provide a clear understanding regardless of the approach used to identify ECs for manufacturing process parameters. Manufacturing process descriptions include supportive information as well as identified ECs."	Final version eliminated the term KPP, as "process consistency" is not a well-defined concept. It also emphasized that all ECs should be assessed and defined from the perspective of their impact on quality and added a clarification that manufacturing process descriptions in Module 3 are expected to remain suitably detailed, and to include both ECs and non-ECs (supportive information).
4	3	Three approaches detailed to identify ECs in the manufacturing process: • Parameter-based approach • Enhanced approach • Performance-based approach	Three approaches detailed to identify ECs in the manufacturing process: • Parameter-based approaches: - Minimal approach - Enhanced approach • Performance-based approach	Minimal and enhanced approaches were grouped together as parameter-based approaches. The description of performance-based approach was enhanced with some additional examples of its scope of applicability.
5	5	"The PLCM document outlines the specific plan for product lifecycle management that is proposed by the MAH, includes key elements of the control strategy, the ECs, proposed reporting categories for changes to ECs, PACMPs (if used) and any post-approval CMC commitments." "The PLCM document can be located in either the CTD Module 1, 2, or 3 based on regional recommendations."	"The PLCM document outlines the specific plan for product lifecycle management that includes the ECs, reporting categories for changes to ECs, PACMPs (if used) and any post-approval CMC commitments." "The PLCM document can be located in CTD Module 3.2.R … In some regions, PLCM may be included in Module 1."	The final version removed a summary of the product control strategy as one of the PLCM components and provided a more specific recommendation on PLCM CTD placement. These changes were made with the goal to simplify the PLCM document and make its implementation simple across all ICH regions.

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6	8–9	8. Post-approval changes for marketed products: • Structured approach to analytical procedure changes • Data requirements to support CMC changes (including stability)	8. Structured approaches for frequent CMC post-approval changes 9. Stability data approaches to support the evaluation of CMC changes	Chapter on post-approval changes to marketed products was generalized in the final version to describe key considerations for structured approaches for some of the more frequent CMC changes, such as analytical methods, scale, and packaging. The detailed example of an approach for analytical procedure changes was moved to Annex II. The discussion of the stability data approaches to support postapproval changes was separated into its own chapter.
7	Annexes	Annex I: ECs—Illustrative Examples • Annex IA: Chemical Product • Annex IB: Biological Product Annex II: PACMP—Illustrative Examples • Annex IIA: PACMP Example 1 • Annex IIB: PACMP Example 2 Annex III: Product Lifecycle Management Document—Illustrative Example	Annex I: Illustrative Examples • Annex IA: Identification of ECs for the Manufacturing Process—Chemical Medicinal Product • Annex IB: Identification of ECs for the Manufacturing Process Biological Medicinal Product • Annex IC: Identification of ECs for Analytical Procedures • Annex ID: PACMP Example 1 • Annex IE: PACMP Example 2 • Annex IF: PLCM—Illustrative Example Annex II: Structured Approach to Analytical Procedure Changes	Annex documents were revised and updated in the final version. The examples provided in Annexes IA and IB were reduced to focus on fewer individual process steps; however the provided examples of justification rationales were significantly expanded to facilitate deeper understanding and practical implementation. Annex IC was added to specifically illustrate how ECs can be identified for analytical procedures. The example of a PLCM document was moved to Annex IF, with a few additional critical clarifications based on public comments. Annex II contains the detailed example of a structured approach to analytical procedure changes.