ICH Q12: Implementation Considerations for FDA-Regulated Products

Guidance for Industry

DRAFT GUIDANCE

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Office of Combination Products (OCP)

May 2021
Pharmaceutical Quality/CMC

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ICH Q12: Implementation Considerations for FDA-Regulated Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The International Council for Harmonisation (ICH) guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* and its *Annexes* (ICH Q12, May 2021) provide a framework to facilitate the management of postapproval chemistry, manufacturing, and controls (CMC) changes in a more predictable and efficient manner.[2] ICH Q12 includes regulatory tools and enablers with associated guiding principles that should enhance industry's ability to manage postapproval changes and increase transparency between industry and regulatory authorities, supporting innovation and continual improvement.

This guidance should be read in conjunction with ICH Q12, which this guidance complements by clarifying how the ICH Q12 tools and enablers can be implemented within the U.S. regulatory system. These guidances apply to drug substances and drug products[3] that are the subject of new drug applications (NDAs), biologics license applications (BLAs), abbreviated new drug applications (ANDAs), and supplements to these applications regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). They also apply to combination products[4] with device constituent parts that are the subject of NDAs, BLAs, ANDAs, and supplements to these applications regulated by CDER and CBER.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, and Office of Combination Products at the Food and Drug Administration.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] For the purposes of this guidance, *drug substance* and *drug product* include biological drug substances and drug products.

[4] See 21 CFR 3.2(e).

only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. CONSIDERATIONS FOR IMPLEMENTATION

The considerations below follow the order of the sections in ICH Q12 and are specific to FDA's implementation.

A. Introduction

As stated above, ICH Q12 and this guidance apply to drug substances and drug products that are the subject of NDAs, BLAs, ANDAs, and supplements to these applications regulated by CDER and CBER. They also apply to combination products with device constituent parts that are the subject of NDAs, BLAs, ANDAs, and supplements to these applications regulated by CDER and CBER.

B. Categorization of Postapproval CMC Changes

ICH Q12 describes two categories for regulatory communications: prior approval and notification. In the U.S. regulatory system, *prior approval* means a prior approval supplement (PAS), *notification moderate* means a changes being effected-30 (CBE-30) supplement, and *notification low* means a CBE-0 supplement or annual report.[5] As indicated in ICH Q12, the lowest risk changes are managed and documented within the pharmaceutical quality system (PQS) and do not need to be reported, but they may be verified during a surveillance or other inspection.

C. Established Conditions

ICH Q12 defines established conditions (ECs) as legally binding information considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority. This is consistent with FDA's regulations at 21 CFR 314.70(a)(1)(i), 314.97(a), and 601.12(a)(1). Although these regulations do not explicitly specify what constitutes an EC, they do set forth a risk-based paradigm for reporting changes. In addition, existing FDA guidance documents describe a broad set of postapproval changes and make recommendations for how they should be reported.[6] The risk-based paradigm set forth in the regulations and the recommendations in these associated guidance documents can help

[5] See 21 CFR 314.70, 314.97, and 601.12.

[6] See, e.g., FDA's Scale-Up and Postapproval Changes (SUPAC) guidances and the guidances for industry *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997), *Changes to an Approved NDA or ANDA* (April 2004), and *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports* (March 2014). Insofar as a guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 314.70 and 601.12, these adjustments do establish legally enforceable responsibilities and are not only recommendations.

applicants determine which elements of an application that FDA would typically consider to be ECs. ICH Q12 further helps applicants gain clarity around which elements of the product, manufacturing process, facilities and equipment, and control strategy in their applications are considered to be ECs and therefore require reporting if changed.

Proposing elements to be considered ECs that may differ from those FDA typically considers to be ECs based on the risk-based paradigm set forth in the regulations and the recommendations contained in guidance is voluntary. Applicants may propose ECs in their original applications or in a PAS.[7] If specific ECs are not proposed, ECs would be those that FDA typically considers to be ECs based on the risk-based paradigm set forth in the regulations and the recommendations contained in guidance regarding postapproval changes.

Applicants may also propose reporting categories for changes to ECs. The reporting categories proposed may be consistent with the risk-based paradigm set forth in the regulations and the recommendations contained in guidance. Alternatively, an increased understanding of the risk to product quality posed by a change to an EC may support a proposal for reduced reporting categories.

1. Submission of ECs

To ensure clarity regarding ECs when submitting an original NDA, BLA, or ANDA, applicants should:

- Include **one** of the following statements in the cover letter:
  - Specific ECs are proposed.
  - Specific ECs are not proposed; postapproval changes will follow the regulations and the recommendations in guidance.[8]
- Include **one** of the following statements in eCTD section 3.2.R of the application[9]:
  - Specific ECs are proposed. Specific reporting categories for changes to those ECs are not proposed and therefore will follow the regulations and the recommendations in guidance.

[7] Plans to include specific ECs in an original application or PAS are an appropriate topic for presubmission meetings with FDA, if available.

[8] In this guidance, FDA recommends as an option that the applicant state that it intends to follow both the regulations and the recommendations in guidance. In most cases, an applicant could choose to follow the regulations while taking a different approach than recommended in guidance and explain how its deviations from the guidance would satisfy the applicable legal requirements. However, if a guidance adjusts reporting categories pursuant to section 506A of the FD&C Act and 21 CFR 314.70 and 601.12, these adjustments do establish legally enforceable responsibilities and are not only recommendations.

[9] eCTD=electronic common technical document, the standard format for submitting applications, supplements, and other information to FDA. For more information, see https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd.

- Specific ECs are proposed. Specific reporting categories for changes to those ECs are proposed.

- Specific ECs are not proposed; postapproval changes will follow the regulations and the recommendations in guidance.

When proposing ECs in a PAS, applicants should:

- State in the cover letter that ECs are proposed.

- Include **one** of the following statements in eCTD section 3.2.R:

  - Specific ECs are proposed. Specific reporting categories for changes to those ECs are not proposed and therefore will follow the regulations and the recommendations in guidance.

  - Specific ECs are proposed. Specific reporting categories for changes to those ECs are proposed.

If applicants choose to propose specific ECs, they can propose them for the entire CMC section of the application (module 3: Quality) or for a subset of information provided in module 3 (e.g., for eCTD section 3.2.S or for eCTD section 3.2.P.3.3). If a limited set of ECs is proposed, such as for an individual unit operation in the manufacturing process, the applicant should list for the applicable eCTD sections all of the ECs for that unit operation. Additionally, the applicant should include a statement that, for the appropriate eCTD sections, changes to those unit operations for which ECs are not proposed will be reported according to the regulations and the recommendations in guidance.

A complete list of proposed ECs, their reporting categories (if proposed), and the eCTD locations for their scientific justification should be included in the Product Lifecycle Management (PLCM) document in eCTD section 3.2.R. See section II.E in this guidance for more information about the PLCM document. See section II.C.2 for information about the justification for proposed ECs, including where such justifications should reside in the application.

2. Identification of ECs

When proposing specific ECs, applicants should include a scientific justification for their selection in the relevant parts of module 3 of the application. In this justification, applicants should address both the identification of particular parameters or attributes as ECs and the proposed reporting categories (if applicable).

a. Parameters and attributes identified as ECs

In the justification, applicants should explain how they identified the parameters or attributes that are proposed to be ECs and why others that might typically be considered to be ECs (considering

the regulations and the recommendations in guidance as described above) were not. For example, in a manufacturing unit operation for which three of five process parameters are proposed to be ECs (in a parameter-based approach), the applicant should explain how the three parameters were identified as being ECs and why the other two were not. A description of the applicant's risk assessment process (including tools) used to identify particular parameters or attributes as ECs, the criticality assessment conducted to determine the level of impact of each parameter on product quality, and the supporting information for each (e.g., fundamental knowledge, empirical investigation, prior knowledge from experience with other products, commercial experience) should be provided. See also sections 3.2.3.1 "Identification of ECs for Manufacturing Processes" and 3.2.3.2 "Identification of ECs for Analytical Procedures" in ICH Q12. Applicants should not propose to manage attributes as ECs if changes to those attributes would require submission of a new original application (e.g., change in dosage form for an NDA).

For parameters or attributes identified as ECs that have associated acceptable ranges, applicants should include a justification for the proposed ranges.

b. Reporting categories

For each proposed EC, the applicant may identify a proposed reporting category: PAS, CBE-30, CBE-0, or annual report. If this reporting category differs from that recommended in existing guidance, the applicant should provide a justification in the relevant section of module 3. This justification can be part of or complementary to the justification provided to support identification of the EC. If the applicant chooses not to propose reporting categories, the applicant should include a statement that reporting categories for changes to those ECs will follow the regulations and the recommendations in guidance.

3. Identification of ECs for a Drug Substance or Drug Product in a Drug Master File

If information about the drug substance or drug product is incorporated in an application by reference to a Type II drug master file (DMF),[10] ECs associated with that drug substance or drug product can be proposed, but they should only be proposed as part of the application.[11] In such cases, the DMF holder will need to share sufficient information with the applicant[12] so that proposed ECs and their associated reporting categories can be specified in and approved as part of the application. The justification in support of the identification of ECs can be located in the DMF, as long as the application refers to the specific location of the justification in the DMF. The applicant should provide a justification for proposed reporting categories in the application because the justification will generally be specific to the final drug product and its conditions of approval (e.g., dosing, route of administration) rather than generalizable across different products

[10] FDA has proposed rulemaking to codify the expectation that BLA applicants submit drug substance, drug substance intermediate, and drug product information directly to the BLA rather than incorporating it by reference to a master file. See 84 FR 30968.

[11] The same approach applies to information incorporated by reference from other types of DMFs (e.g., Types III, IV, or V, where applicable).

[12] See guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (November 2016).

incorporating the same drug substance or drug product. When ECs are approved for an application that incorporates by reference information from a DMF, the applicant maintains responsibility for reporting changes to ECs; however, the applicant should share the relevant approved ECs with the DMF holder to ensure that the DMF holder is aware of how changes to the referenced drug substance or drug product will be managed by the applicant.

4. Identification of ECs for Device Constituent Parts of Combination Products

Applicants may propose ECs for the device constituent part of a combination product in an NDA, BLA, or ANDA. The combination product as a whole, including the roles and interactions of the constituent parts, should be considered in proposing ECs and reporting categories for the product, including in relation to each constituent part. The focus of this section is identifying ECs for device constituent parts in particular. One approach is to assess the "characteristics of the product that are essential for its safe and proper use"[13] (primary characteristics) relating to the device constituent part and to identify the associated ECs. The primary characteristics for the device constituent part of a combination product generally include:

- Functions essential for safe use based on risk management principles (see, e.g., ICH guidance for industry *Q9 Quality Risk Management* (June 2006); ISO 14971:2019, Medical devices—Application of risk management to medical devices).

- Design features essential to achieve delivery of the labeled dose to a specific body site (e.g., for a device constituent part that provides drug delivery).

- Characteristics that impact the drug constituent part's critical quality attributes.

Applicants should consider the following as potential ECs:

- Design features that are primary characteristics.

- Manufacturing process elements for the device constituent part that need to be controlled to ensure a primary characteristic.

- Other control strategy elements for the device constituent part that ensure a primary characteristic.

See appendix A for a description of elements that are generally considered to be ECs for device constituent parts. As with identifying ECs for drug constituent parts, whether it may be appropriate to propose ECs for device constituent parts or a lesser reporting category for them will vary based on extent of product and process understanding, knowledge gained from design and development to manage the risks, and evidence to support designation and justification of the primary characteristics. Similarly, the level of risk associated with a change to an EC will

[13] See ISO 13485:2016, Medical devices—Quality management systems—Requirements for regulatory purposes, Section 7.3.4 Product realization—Design and development—Design and development outputs. ISO=International Organization for Standardization.

determine the appropriate reporting category for that change. See appendix B for an approach that can be followed for device constituent parts when identifying ECs and their associated reporting categories.

5. Changes to Approved ECs

As indicated in ICH Q12, applicants may propose to add, eliminate, or make changes to approved ECs or revisions to their associated reporting categories through:

- Submission of a supplement.
  - Addition of an EC that provides increased assurance of the quality of the drug substance or product with a reporting category provided for in the regulations or recommended in guidance should be submitted as a CBE-0 (see § 314.70(c)(6)).
  - All other changes should be submitted as a PAS.
- Submission of a postapproval change management protocol (PACMP; see section II.D in this guidance).
- Fulfillment of a previously approved postapproval commitment submitted in a supplement or annual report. For example, this may be done if an EC was approved with an allowance for a modification pending the availability—and submission, where specified—of certain information.

6. Postapproval Submissions in Accordance With Approved ECs

When submitting postapproval supplements and annual reports to report CMC changes in accordance with approved ECs, applicants should state in the cover letter that the submission contains changes made in accordance with previously approved ECs. These submissions should also include an updated PLCM (see section II.E in this guidance).

7. Maintenance of the Application

As indicated in ICH Q12, maintenance of the application is subject to regional requirements. To ensure that FDA has access to up-to-date analytical procedures, applicants should include in the annual report a copy of all analytical procedures that have been appropriately modified during the reporting period without a submission (i.e., managed only through the PQS as changes did not relate to ECs). This information is intended to be for information only and typically is not subject to review unless it is determined that changes to ECs for the procedure were in fact made. Applicants should include this information in eCTD section 1.13.5 or 1.13.7 with a statement such as “For information only: Changes made to analytical methods, including those not requiring submission.”

D. Postapproval Change Management Protocol

In the U.S. regulatory system, PACMPs are referred to as comparability protocols and are voluntary. These protocols differ from the use of ECs in one important respect. Both comparability protocols and the use of ECs address the element to be reported if changed and the reporting mechanism, but a comparability protocol requires the tests and studies to support a future change to an EC to be specified at the time of the protocol submission (21 CFR 314.70(e)).

FDA recommends that comparability protocols be submitted in eCTD section 3.2.R. For a comparability protocol that includes one or more changes that apply to more than one product, see draft guidance for industry *Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information* (April 2016)[14] for information on the appropriate content and format of the submission and the circumstances in which a comparability protocol might be useful.

E. Product Lifecycle Management Document

As described in ICH Q12, the PLCM document should include proposed ECs, reporting categories for making changes to approved ECs, a list of comparability protocols (if submitted), and postapproval CMC commitments, if applicable. FDA recommends that the PLCM document be provided in tabular format in eCTD section 3.2.R, with specific references to the submission sequence, eCTD section number, and page number where each EC's scientific justification can be found. FDA further recommends that the PLCM indicate the manufacturing sites (preferably by facility establishment identifier (FEI) number) where an EC will be implemented.[15] For example, if there are two drug product manufacturing sites named in the application, but the manufacturing process-related ECs will only be associated with the manufacturing at one of those two sites, the FEI number of this site should be specified in the PLCM for those process-related ECs. It is then assumed that ECs for operations at the other facility will follow the regulations and the recommendations in guidance. If the ECs will be implemented at both sites, both FEI numbers should be listed. Applicants should attribute FEIs to ECs in the PLCM at the most inclusive level (e.g., one FEI listed at the beginning of 3.2.P if all subsequent ECs in the section are associated with one drug product facility). See appendix C in this guidance for an example of a PLCM document.

Applicants should provide an updated PLCM document with each supplement or annual report that reports changes to approved ECs. If no specific ECs are proposed, submission of a PLCM document is not necessary.

[14] More specifically, see the appendix, section A, question 6. When final, this guidance will represent FDA's current thinking on this topic.

[15] Such facilities may include facilities responsible for design control for a combination product. See guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017).

F. Pharmaceutical Quality System and Change Management

As indicated in ICH Q12, in addition to compliance with current good manufacturing practice (CGMP) requirements,[16] an effective PQS is necessary to support the use of the tools in that guidance. However, also as noted in that guidance, FDA will not require a specific inspection before an applicant can make use of the principles in the guidance. FDA's assessment of the effectiveness of the PQS will generally be informed by routine inspections conducted by FDA and capable foreign regulators[17] and other available information. Management should employ the principles of ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009) to ensure the continued capability of the PQS to support the management of ECs.

Because of the importance of the PQS in supporting the use of ICH Q12 tools, when an applicant proposes to introduce a new manufacturing site after approval, the applicant should not assume that the initially approved ECs will apply. Instead, if ECs are proposed, applicants should include the following in supplements that propose a new site:

- Reassessment of the relevant ECs.
- Justification for proposed changes to ECs as a result of this reassessment in the relevant parts of module 3 of the application.

FDA will also consider information included in a supplement that supports a determination that the new site deserves the same level of regulatory flexibility regarding postapproval changes as the site included in the original application. The determination of PQS capability will consider factors such as whether the new site is operated under the same PQS as the original; the state of regulatory compliance determined by FDA and other national drug regulatory authorities; conformance with ICH Q10, especially as concerns change management practices; and conformance with other applicable change management regulations and policies.

As indicated in ICH Q12, inspection observations that raise concern regarding the effectiveness of the PQS, and change management in particular, may lead to a need to modify previously approved ECs, reporting categories, or comparability protocols until such time as the PQS effectiveness has returned to an acceptable state. In these cases, FDA intends to communicate the impact of such findings on previously approved ECs, reporting categories, and comparability protocols with facilities and applicants, as appropriate.

G. Relationship Between Regulatory Assessment and Inspection

The use of ICH Q12 tools, such as ECs, is not expected to change FDA's processes for how information is assessed as part of the application or from a facility inspection. Similarly, it does

[16] See section 510(a)(2)(B) of the FD&C Act; 21 CFR parts 4, 210, 211, and 600; and guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products*.

[17] Capability determinations are made in accordance with section 809 of the FD&C Act; see also https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra.

not change the expectations regarding the type of information to be submitted in an application or the information that is to be available for an inspection.

H. Structured Approaches for Frequent CMC Postapproval Changes and Stability Data Approaches To Support the Evaluation of CMC Changes

Sections VIII and IX of ICH Q12 and section II of the ICH Q12 Annexes provide alternative approaches for certain CMC postapproval changes. FDA supports the use of such approaches. FDA also encourages applicants to gain its feedback before proposing or implementing novel approaches.

APPENDIX A. ESTABLISHED CONDITIONS FOR COMBINATION PRODUCTS WITH DEVICE CONSTITUENT PARTS

The combination product as a whole, including the roles and interactions of the constituent parts, should be considered in proposing established conditions (ECs) and reporting categories for the product, including in relation to each constituent part. This appendix provides general guidance about the elements that are generally considered ECs for the device constituent part of combination products.[1] It does not contain a complete list of ECs for a device constituent part; each application should include a justification for the identification of proposed ECs.

The following are generally considered ECs for the device constituent part of combination products:

- Identification of the device: If purchased from a third party, manufacturer identifiers for the device (e.g., brand name); references to device clearance or approval (if applicable).

- Description and design features: Device description; principle (e.g., mechanical, electrical) and mechanism (e.g., spray, mixing) of operation for delivery of the drug product; design features that are primary characteristics; materials of construction in direct or indirect contact with the drug product and patient.

- Manufacturers: Name, address, and responsibilities for sites that perform assembly, packaging, and testing of the device constituent part.

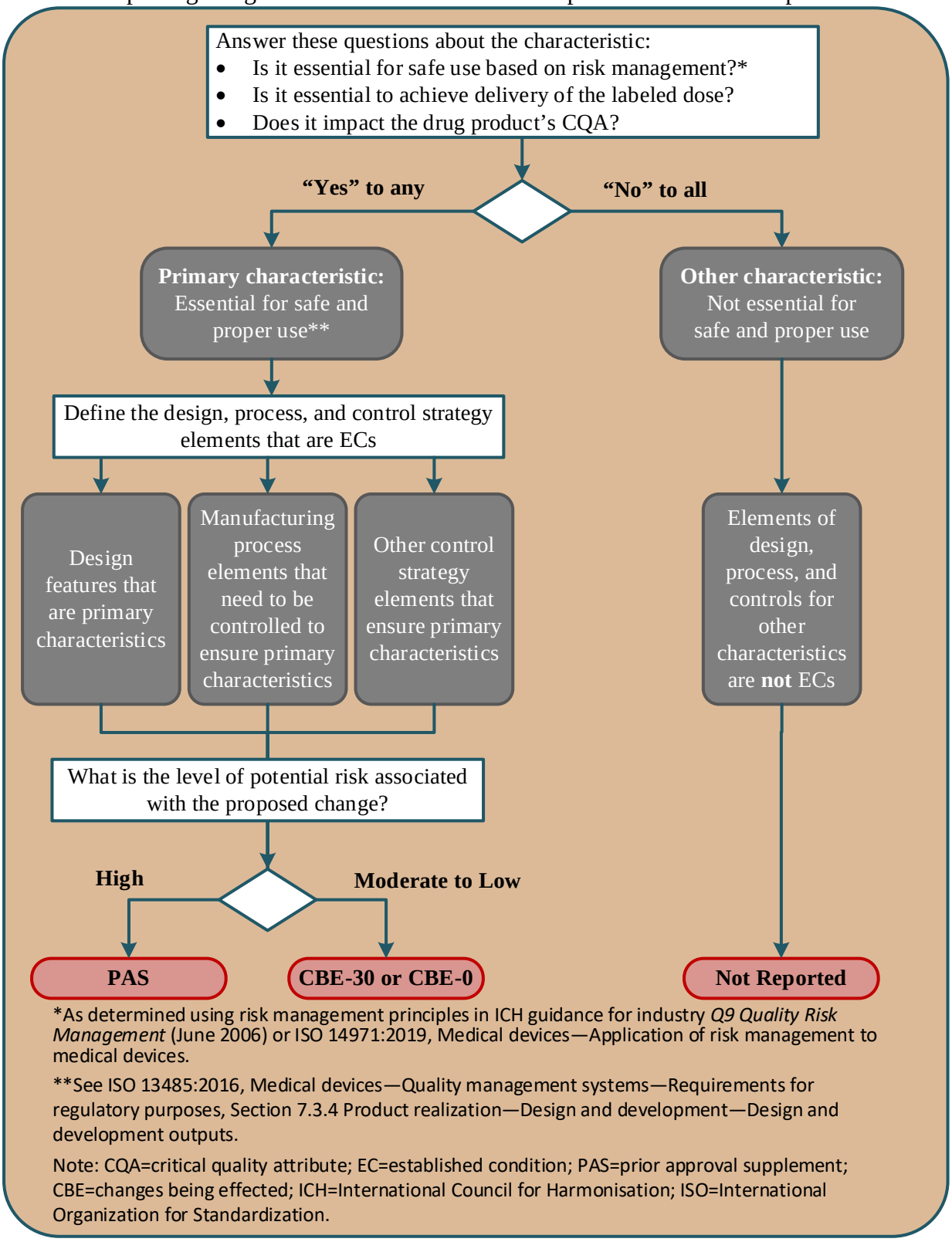
- Manufacturing (e.g., assembly): Unit operations and sequence in the manufacturing process; manufacturing process parameters, material attributes, and in-process controls, where variability impacts primary characteristics.

- Release/expiry specification and associated test methods for attributes that ensure primary characteristics.

[1] Similar to appendix 1 in International Council for Harmonisation guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021).

APPENDIX B. DECISION TREE FOR IDENTIFYING ESTABLISHED CONDITIONS AND REPORTING CATEGORIES FOR DEVICE CONSTITUENT PARTS

The decision tree below can be used to guide the identification of established conditions and associated reporting categories for the device constituent part of a combination product.



*As determined using risk management principles in ICH guidance for industry *Q9 Quality Risk Management* (June 2006) or ISO 14971:2019, Medical devices—Application of risk management to medical devices.

**See ISO 13485:2016, Medical devices—Quality management systems—Requirements for regulatory purposes, Section 7.3.4 Product realization—Design and development—Design and development outputs.

Note: CQA=critical quality attribute; EC=established condition; PAS=prior approval supplement; CBE=changes being effected; ICH=International Council for Harmonisation; ISO=International Organization for Standardization.

APPENDIX C. PRODUCT LIFECYCLE MANAGEMENT DOCUMENT EXAMPLE

In this example,[1] where the applicant proposes to follow FDA regulations and the recommendations in guidance for a change to a particular established condition, the reporting category has been left blank.

eCTD Section	Established Conditions ***(Note that identification and justification of each EC is presented in the relevant eCTD section)***	Reporting Category When Making a Change to the EC
	The ECs below are to be implemented at the following sites: FEI xxxxxx FEI yyyyyy	
Seq 0001, 3.2.P.3.3, p. 4	The manufacturing process consists of the following sequence of unit operations: 1. Powder blending 2. Roller compaction 3. Tablet compression 4. Film coating	PAS
Seq 0001, 3.2.P.3.3, p. 44	**1. Powder Blending** The active substance and three excipients are mixed together. The following process parameters are defined as ECs.	
Seq 0003, 3.2.P.3.3, p. 45	Operating principle: Diffusion mixing	PAS
Seq 0001, 3.2.P.3.3, pp. 45–47	Equipment type: V-blender	Change to equipment of same operating principle: AR
Seq 0001, 3.2.P.3.2, p. 8, and 3.2.P.3.3, pp. 48–49	Scale: 200 kg	Increase up to 10x: AR Increase beyond 10x: CBE-0
Seq 0004, 3.2.P.3.4, pp. 10–15	Design space for blending process parameters Blend speed: 10-20 rpm	CBE-30

[1] Adapted from annex IF in the International Council for Harmonisation guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management: Annexes* (May 2021).

	Blend time: 15-25 minutes	
	2. Roller Compaction	
	3. Tablet Compression	
	4. Film Coating	

Note: eCTD=electronic common technical document; EC=established condition; FEI=facility establishment identifier; PAS=prior approval supplement; AR=annual report; CBE=changes being effected.