POLICY AND PROCEDURES

Office of Pharmaceutical Quality

Implementation of Established Conditions as Described in ICH Q12

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PURPOSE

This MAPP will help staff in the Office of Pharmaceutical Quality (OPQ) conduct assessments of proposed established conditions (ECs) and associated reporting categories, and reevaluate approved ECs, when appropriate, in collaboration with the Office of Compliance/Office of Manufacturing Quality (OC/OMQ).

BACKGROUND

The concept of ECs—legally binding information "considered necessary to assure product quality"—is outlined in the International Council for Harmonisation (ICH) guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (ICH Q12) and its *Annexes* (May 2021).[1] This MAPP works in concert with the draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* (ICH Q12 implementation guidance, May 2021),[2] which supports ICH Q12 implementation within the U.S. regulatory system, and the internal procedural document *ICH Q12 Implementation Plan,* which establishes OPQ's Q12 Established Conditions Coordinating Committee (ECCC) and the Q12 Assessment Implementation Team (Q12AIT).

[1] 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.

[2] When final, this guidance will represent FDA's current thinking on this topic.

ICH Q12 provides a framework to facilitate the management of postapproval chemistry, manufacturing, and controls (CMC) changes in a more predictable and efficient manner. 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, thus supporting innovation and continual improvement. The ICH Q12 implementation guidance complements ICH Q12 by clarifying how its tools and enablers can be implemented within the U.S. regulatory system.

ICH Q12 and the ICH Q12 implementation guidance apply to drug substances and drug products[3] that are the subject of NDAs, BLAs, 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 CDER- and CBER-regulated combination products[4] with device constituent parts that are the subject of NDAs, BLAs, ANDAs, and supplements to these applications.

All postapproval CMC changes must be managed in accordance with current good manufacturing practice (CGMP) requirements. Any change to an EC is managed under the PQS and requires a submission to FDA (PAS, CBE-30 or CBE-0 supplement, or annual report).[5] This is consistent with 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, FDA guidance documents provide recommendations for how to report a broad set of postapproval changes.[6] The risk-based paradigm in the regulations and the recommendations in these associated guidance documents have been the basis for applicants to determine which elements of an application would typically be considered ECs. Applying the ICH Q12 tools related to ECs provides an opportunity for applicants to 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.

All applications contain a combination of ECs and supportive information. Supportive information is not considered to be ECs but is provided to share information about drug development and manufacturing and to provide context and justification for proposed ECs and their reporting categories. Knowledge gained throughout the product lifecycle (including pharmaceutical development and characterization of, and platform knowledge for, drug substances and drug products) is the basis for identifying the elements that are ECs and those elements that are supportive information.

Proposing ECs and reporting categories per ICH Q12 is entirely voluntary. If specific ECs are not proposed, no assessment specific to ECs is necessary; the ECs for that application would be those that FDA typically considers to be ECs based on the risk-based paradigm for

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

[4] See 21 CFR 3.2(e).

[5] PAS=prior approval supplement, CBE=changes being effected.

[6] See the References section of this MAPP for guidance documents that cover postapproval changes.

reporting changes set forth in 21 CFR 314.70, 314.97, and 601.12 and the recommendations contained in guidance regarding postapproval changes (see, e.g., the postapproval change guidances, including those related to Scale-Up and Postapproval Changes (SUPAC), in the References section).[7] If an applicant proposes specific ECs but does not specify reporting categories for postapproval changes to those ECs, the reporting categories are considered to be those indicated by regulation and as recommended in guidance.[8]

Applicants may:

- Specify elements to be considered ECs in an original application or in a supplement.[9] These elements may differ from those typically considered to be ECs as indicated by regulations and as recommended in guidance.

- Propose reporting categories for changes to ECs that are consistent with regulations and guidance.

- Propose reporting categories for changes to ECs that differ from the categories indicated by regulations and as recommended in guidance.

POLICY

- OPQ assessment teams will operationalize the scientific and regulatory concepts in ICH Q12 and the ICH Q12 implementation guidance, once finalized, when conducting assessments of original applications and supplements that contain proposals for ECs.

- Assessors will evaluate ECs in the context of a specific application (e.g., the process parameters that are considered ECs may differ among applications for the same drug).

- ECs must not be in conflict with CGMP requirements (e.g., an applicant's proposal to forgo laboratory activities necessary to determine the drug product's conformance to

[7] Because guidance documents are not mandatory, an applicant could in each case 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.

[8] Throughout this MAPP, when we use the phrase "indicated by regulation and as recommended in guidance" (and similar phrasing), we are referring to the specific regulations and guidance documents discussed in the Background section.

[9] ECs may be proposed in a prior approval manufacturing or efficacy supplement as those submission types are defined in the Prescription Drug User Fee Act (PDUFA) and Biosimilar User Fee Act (BsUFA) commitment letters or in a PAS as defined in the Generic Drug User Fee Amendments (GDUFA) commitment letter. For ease of reference, this MAPP uses *PAS* to refer to these supplements. PDUFA, BsUFA, and GDUFA commitment letters are available via the FDA User Fee Programs website at https://www.fda.gov/industry/fda-user-fee-programs.

final specifications, including the identity and strength of each active ingredient, before its release).

- If ECs are proposed in an amendment to an application, FDA may consider the amendment to be a major amendment (Prescription Drug User Fee Act (PDUFA) or Biosimilar User Fee Act (BsUFA))[10] or an unsolicited amendment (Generic Drug User Fee Amendments (GDUFA)).[11]

- Assessors will evaluate the inclusion or exclusion of elements as proposed ECs and reporting categories for postapproval changes to those elements (where proposed). Proposed ECs could apply to the entire CMC section of the application (module 3: Quality) or to a specific subset of information provided in module 3 (e.g., for electronic common technical document (eCTD) section 3.2.S, or for eCTD section 3.2.P.3.3).

- Assessors will follow this MAPP for matters related to:

    - Location of ECs and reporting categories.

    - Specific assessment considerations for ECs: EC identification and justification and ECs related to drug substances in drug master files (DMFs), device constituent parts of combination products, manufacturing processes, and analytical procedures.

    - Assessment of proposed reporting categories.

    - Requests for additional information or modifications from applicants.

    - Considerations regarding the facility and PQS assessment in support of EC and reporting category assessment.

[10] FDA's decision to review an amendment, and whether the amendment should extend the review clock, is based on identifying the most efficient path to completing a comprehensive review that addresses application deficiencies and, when possible, leads toward a first-cycle approval. See the draft guidance for industry *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications* (September 2018). When final, this guidance will represent FDA's current thinking on this topic.

[11] An unsolicited amendment is an amendment with information not requested by FDA, except for routine or administrative amendments that do not require scientific assessment. The unsolicited amendment will be classified as either major or minor based on its content. FDA will generally accept an unsolicited amendment submitted during the review cycle and adjust the goal date for the application. However, FDA may defer assessment if the discipline assessments are almost complete and either (1) the submitted amendment contains a significant amount of new information to be assessed, or (2) the amendment is submitted after the relevant assessments are complete and while an information request, discipline review letter, or complete response letter is being prepared because amendment submissions at these times cause inefficiencies in assessments. See the guidance for industry *ANDA Submissions—Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018).

- Considerations regarding PAIs and PLIs for original applications and supplements with proposed ECs and reporting categories.
- Application actions.
- Postapproval activities related to approved ECs following an OAI facility classification.[12]

RESPONSIBILITIES

- Regulatory business project managers (RBPMs) from the Office of Program and Regulatory Operations (OPRO) will:
  - Check the submission for proposed ECs (i.e., cover letter and section 3.2.R of the eCTD), or changes to approved ECs.
  - Request additional OPQ members (Office of Quality Surveillance (OQS) assessor and additional assessment team members from the ECCC and Q12AIT[13]) to join the OPQ assessment team.
  - Schedule team meetings related to EC assessment, as needed.
  - Manage communications to applicants regarding ECs.[14]
- Assessors from the Offices of Product Quality Assessment (OPQA) I, II, or III (depending on the application type) and the Office of Pharmaceutical Manufacturing Assessment (OPMA) will:
  - Check the submission for proposed ECs (i.e., cover letter and section 3.2.R of the eCTD).
  - Assess ECs and reporting categories (where proposed) in determining whether to approve the application.

[12] An inspection conducted under compliance program 7356.002 *Drug Manufacturing Inspections* or compliance program 7356.843 *Postapproval Inspections* that is classified OAI may warrant postapproval activities related to approved ECs described in this MAPP.

[13] See OPQ- SOP-0046 for instructions. See also the *ICH Q12 Implementation Plan,* which describes the roles and responsibilities of ECCC and Q12AIT members in facilitating assessment of applications with proposed ECs.

[14] Throughout this MAPP, when the assessment team requests information or changes from the applicant, the communication goes through the OPRO RBPM.

- Following the concepts of four-part harmony,[15] draft language for information requests and complete response (CR) letters related to requests for revisions or additional information and deficiencies.

- No later than midcycle, inform the OQS assessor of the facilities where ECs or reporting categories would provide more postapproval regulatory flexibility than that indicated by regulation and recommended in guidance. Use the input from the OQS assessor regarding the PQS at the facilities where the ECs are to be implemented when assessing the approvability of ECs and reporting categories.

- OPMA assessors will additionally:

  - Inform the Office of Inspections and Investigations (OII) that a facility being evaluated is proposed to implement ECs when OPMA is assessing an original application or supplement.[16]

  - Consult OC/OMQ regarding facility compliance status and remediations, when indicated (e.g., OAI).

- OQS assessors will:

  - Confirm that the submission identifies the facilities where ECs will be implemented by FDA establishment identifier (FEI) number and coordinate with the RBPMs from OPRO to issue information requests for any necessary clarification to the Product Lifecycle Management (PLCM) document regarding facility identification.

  - Conduct a PQS and facility[17] assessment by assessing information from completed inspections related to PQS effectiveness, including change management operations at the facility.

  - Provide feedback to OPQA I, II, or III and OPMA assessors, as applicable, on the effectiveness of the PQS and whether it is likely to be capable of managing the proposed ECs and associated reporting categories.

  - Consult OC/OMQ regarding facility compliance status and remediations, when indicated (e.g., the facility compliance status is OAI).

[15] See MAPP 5016.8 Rev. 1 *Using Four-Part Harmony in Quality-Related Assessment Communications* (September 2023).

[16] OPMA assessors should follow internal MAPP 4151.11 *OPQ Facility Evaluation Management for NDA/ANDA Postapproval Submissions* (February 2023) when evaluating manufacturing facilities named in NDA/ANDA postapproval submissions.

[17] For those supplements where OPMA is not assigned to perform the facility assessment.

- Document the assessment and conclusions of whether to support the application action and the use of regulatory flexibility/tools in ICH Q12 and the ICH Q12 implementation guidance.

- OC/OMQ staff will:

  - Respond to consults from OQS or OPMA, as applicable, regarding OAI classifications for a facility, associated remediations, and the ability of the facility to effectively manage changes.

  - Collaborate with OPQ on postapproval activities related to approved ECs following an OAI facility classification.

PROCEDURES

Location of ECs and Reporting Categories

Relevant OPQ offices: OPRO; OPQA I, II, or III; OPMA; OQS

1. OPRO RBPMs and assessors identify when an applicant has proposed specific ECs by the presence of (1) a statement in the submission cover letter, and (2) a statement in eCTD section 3.2.R of the submission or the inclusion of a PLCM document (see section II.C.1 of the ICH Q12 implementation guidance).

2. When ECs are proposed, OPRO RBPMs request members from the ECCC, Q12AIT, and OQS to join the OPQ assessment team, and then schedule team meetings.

3. Assessors check the PLCM document, which should be located in eCTD section 3.2.R, for a list of the specific ECs proposed by the applicant, their associated reporting categories, the eCTD locations for their scientific justification, and the manufacturing facilities (by FEI number) where the ECs will be implemented. Assessors consult the ECCC when PACMPs are used to establish ECs or revise approved ECs.

4. If an applicant proposes a limited set of ECs (e.g., for an individual unit operation in the manufacturing process), assessors consider whether the applicant listed all of the ECs in the applicable eCTD sections (e.g., for that individual unit operation). If the applicant did not include a statement in the appropriate eCTD sections acknowledging that changes to those unit operations for which ECs are not proposed will be reported according to regulations and as recommended in guidance,[18] the assessment team requests that the applicant confirm the statement's accuracy and to update the PLCM document for clarity.

[18] See footnote 7.

5. If the applicant proposes a general reporting category in the PLCM document, such as "notification," the assessment team requests a revised PLCM document that provides sufficient information to indicate specific submission types consistent with 21 CFR 314.70 or 21 CFR 601.12 (i.e., PAS, CBE-30, CBE-0, or annual report).

6. If an applicant proposes specific ECs without proposing specific reporting categories and does not specify that postapproval changes to the identified ECs will be reported according to regulations and as recommended in guidance,[19] the assessment team requests this information from the applicant.

7. If the PLCM document does not clearly identify the facilities that will implement specific ECs by FEI number, the assessment team requests this information from the applicant.

Specific Assessment Considerations for ECs

Assessment of EC Identification and Justification

Relevant OPQ offices: OPQA I, II, or III; OPMA; OQS

1. No later than midcycle, assessors inform the OQS assessor of the facilities when ECs or reporting categories would provide more postapproval regulatory flexibility than indicated by regulation and as recommended by guidance.

2. If ECs are proposed for a marketed product, assessors may identify certain aspects of the application submitted to date that do not meet current quality expectations (e.g., the product specification does not include a particular impurity that should be controlled). If current quality expectations are not met, the assessment team may request that that applicant update those aspects of the application *related to the proposed ECs*.

3. Assessors confirm that ECs are not in conflict with CGMP requirements.

4. When determining whether specific ECs and reporting categories proposed by the applicant are appropriate, assessors consider the applicant's scientific justification and information provided by OQS about the PQS at the facilities where the ECs will be implemented:

    a. The justification should describe how the applicant identified the parameters or attributes that are proposed to be ECs and why others that are typically considered ECs (considering regulations and recommendations in guidance) were not.

[19] Ibid.

b. The justification should address why the applicant determined that control of the parameters or attributes was necessary (or not) to ensure product quality.

c. The justification can be based on development studies, prior knowledge from development or manufacturing of similar products, commercial manufacturing experience (for an approved product), scientific principles, or a combination of these. For ECs associated with the manufacturing process, see additional considerations below.

d. The applicant may use information provided to FDA in a previous submission for the same application to support their justification for ECs. The PLCM document should include the submission sequence number and eCTD location where supporting justification for the EC is located.

e. The facility should have an effective PQS that should be able to manage changes (informed by principles in ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009)).

Assessment of ECs for a Drug Substance or Container Closure System in a DMF[20]
Relevant OPQ offices: OPQA III, OPMA

FDA may approve proposed ECs associated with a drug substance if they are proposed as part of the application when information about a drug substance is incorporated in an application by reference to a Type II DMF. Additionally, FDA may approve proposed ECs for a container closure system if they are proposed as part of the application when information about the container closure system is contained in a Type III DMF. In such cases, the applicant will need to have sufficient information from the DMF holder to justify the proposed ECs and their reporting categories in the application.

1. Assessors evaluate the justification for ECs and the reporting categories for the drug substance considering the final drug product and its conditions of use (e.g., dosing, route of administration).

2. Assessors access the DMF for relevant justification for ECs and reporting categories for the drug substance.

3. Assessors review each DMF and ensure appropriate justification is provided if multiple DMFs are referenced in support of proposed ECs for the drug substance.

[20] A similar approach would apply in the less common instance in which information regarding a drug product is incorporated by reference to a Type II DMF. Note that drug substance, drug substance intermediate, and drug product information for a biological product is not appropriate for inclusion in a Type II DMF; this information must be located in the application (see 21 CFR 601.2(g)).

Assessment of ECs for the Device Constituent Part of a Combination Product
Relevant OPQ offices: OPQA I, II, or III; OPMA

1. Assessors consider the drug-device combination product as a whole, including the roles and interactions of the constituent parts, when evaluating proposed ECs and reporting categories for the product.

2. Assessors follow normal procedures to initiate consults with the Center for Devices and Radiological Health (CDRH), as applicable, for CDRH assessment of ECs related to the device constituent part. See section II.C.4 and appendix A of the ICH Q12 implementation guidance for more information.

Assessment of ECs for the Manufacturing Process
Relevant OPQ offices: OPMA; OPQA I, II, or III

1. Assessors generally look for unit operations and their sequence to be proposed as ECs for the manufacturing process.

2. Assessors evaluate whether the ECs proposed for a manufacturing process are those inputs (e.g., process parameters, incoming material attributes) and outputs (e.g., in-process controls, attributes measurement) that are necessary to ensure product quality.

3. Assessors consider the applicant's development approach, product and process knowledge, and the relevant elements of the overall control strategy. Assessors ensure that proposed ECs are commensurate with the justification provided (e.g., in a performance-based approach, ECs could be primarily focused on control of process outputs rather than process inputs).

4. For process parameters,[21] assessors evaluate the following information in the application that explains how the applicant identified ECs (see also the decision tree in Figure 1 in ICH Q12):

    a. The applicant's initial risk assessment that is informed by the application of knowledge gained through executed studies and prior knowledge to identify which process parameters may impact product quality.

    b. The applicant's criticality assessment that determines the level of impact that a process parameter could have on product quality. The criticality assessment should account for severity of harm and whether the ranges studied sufficiently account for the meaningful and expected variability in the EC. Criticality should not be minimized solely due to tight control of parameters.

[21] Per ICH Q12, critical process parameters and other process parameters where an impact on product quality cannot be *reasonably* excluded should be identified as ECs.

Assessment of ECs for Analytical Procedures
Relevant OPQ offices: OPQA I, II, or III; OPMA

1. Assessors determine whether ECs related to analytical procedures include elements that ensure performance of the procedure, and they ensure that proposed ECs are commensurate with the justification provided.

2. Assessors consider the applicant's understanding of the relationship between method parameters and method performance, the method complexity, and the control strategy in determining appropriateness of proposed ECs and their reporting categories.

Assessment of Proposed Reporting Categories

Relevant OPQ offices: OPQA I, II, or III; OPMA

1. Assessors confirm that proposed reporting categories have been identified based on level of risk justified by the risk assessment or they are commensurate with the reporting categories defined in 21 CFR 314.70 or 601.12. Applicants might propose different reporting categories for specific, unique changes to the EC, which should account for the outcome of the risk assessment. For example, an applicant could demonstrate that there is a higher risk to quality when changing one particular end of a process parameter range than the other, and as a result, reporting categories for changes to either end of the range might be different.

2. When reporting categories are not consistent with 21 CFR 314.70 or 601.12:

    a. Assessors evaluate the applicant's justification for the proposed reporting categories, taking into account the applicant's assessment of the potential risk to product quality associated with changing the EC and their understanding of the product, process, and overall control strategy (see ICH guidance for industry *Q9(R1) Quality Risk Management* (May 2023)).

    b. Assessors ensure that justifications for proposed reporting categories for changes to an EC address the risk of potential necessary concurrent changes to related ECs.

3. When proposed reporting categories are consistent with 21 CFR 314.70 or 601.12, assessors do not need to continue their assessment of the justification for reporting categories.

Requests for Additional Information or Modifications to Proposed ECs or Reporting Categories

Relevant OPQ offices: OPRO; OPQA I, II, or III; OPMA; OQS

1. If the applicant proposes ECs or reporting categories without sufficient justification, the assessment team issues an information request or deficiency (as applicable, considering the stage of the review process), following the concepts of four-part harmony, to the applicant requesting such justification.[22]

2. If the applicant's justification for specific ECs is unclear, the assessment team requests that the applicant provide further justification for certain parameters or attributes that were identified as ECs versus those that were not (considering the regulations and the recommendations in guidance).

3. If assessors do not agree with the absence of a parameter or attribute within the subset of proposed ECs, the assessment team requests that the applicant amend the PLCM document to include the missing ECs. In the request, the assessment team explains why the parameter or attribute should be an EC and why the applicant's justification for its exclusion is insufficient.

4. If assessors do not agree with the flexibility proposed within a proposed EC (e.g., the parameter range is too wide), the assessment team sends an information request to the applicant requesting the additional information that would be needed to support the proposed flexibility or requesting that the proposed EC be revised.

5. If the applicant defines supportive information as an EC, the assessment team may ask the applicant to remove such information from the proposed ECs.

6. If the reporting category has an appropriate scientific justification but the PQS assessment uncovers concerns with the facility's ability to manage changes, the assessment team issues an information request to the applicant requesting that the reporting category be modified to a level commensurate with regulations and recommendations in guidance. Unresolved PQS deficiencies that do not allow for implementation of more flexible reporting categories, or reporting categories that have not been appropriately revised by the applicant, may be considered a deficiency.

7. The assessment team must find the applicant's proposed ECs and reporting categories acceptable to recommend approval for the application.[23] If engagement with the applicant during the review cycle is unable to resolve outstanding issues with

[22] See the ICH Q12 implementation guidance, section II.C: Established Conditions.

[23] Under 21 CFR 314.125(b)(1), 314.127(a)(1), and 601.2(d), FDA may refuse to approve an application if appropriate controls to preserve quality (NDAs/ANDAs) or safety, purity, and potency (BLAs) are not in place. ECs or reporting categories that do not provide for appropriate controls to preserve quality or safety, purity, and potency are therefore a reason to issue a CR letter.

proposed ECs or reporting categories, the assessment team communicates its outstanding concerns to the applicant as deficiencies in a CR letter.[24]

Considerations Regarding the Facility and PQS Assessment in Support of EC and Reporting Category Assessment

Relevant OPQ offices: OQS, OPMA

1. OPQ assessors conduct a facility evaluation by assessing information from completed inspections related to CGMP compliance and they evaluate PQS[25] effectiveness for facilities that will implement and manage ECs and associated reporting categories listed in the PLCM document.

    a. For original applications and supplements where OPMA is assigned to perform the facility assessment:

        i. OPMA assessors conduct an initial facility evaluation for facilities listed in the PLCM document where ECs are to be implemented and inform the assessment team no later than the facility target date if:

            a) Any facility where ECs are to be implemented is not CGMP compliant.

            b) The compliance history shows a trend of CGMP noncompliance (e.g., OAI to Voluntary Action Indicated (VAI) in the last 5 years or a history of recommended OAI downgraded to VAI).

        ii. OQS assessors conduct a PQS assessment[26] for those facilities where ECs or reporting categories proposed by the applicant are more flexible than 21 CFR 314.70 or 601.12 and current postapproval change guidance.[27] OQS assessors inform the assessment team if they have concerns with the PQS that should be considered as the team assesses the appropriateness of ECs and reporting categories.

            a) One example of an issue that may raise concerns about the facility's ability to implement proposed flexibilities for ECs is a demonstrated lack of data integrity.

[24] Action letters sent to the applicant should contain template language specific to ECs.

[25] Though implementation of ICH Q10 is not a CGMP requirement, ICH Q12 states that an effective PQS as described in ICH Q10 is essential to support implementation of ICH Q12.

[26] This involves assessing information from completed facility inspections and assessments (such as remote regulatory assessments). Regarding ICH Q10 enablers and PQS elements, see appendix 2 of ICH Q12 for principles of change management and attachment B of compliance program 7356.002—*Drug Manufacturing Inspections* for examples of indicators of an advanced PQS.

[27] See footnote 6.

b) Examples of issues that may raise concerns about the facility's ability to implement proposed flexibilities for reporting categories include, but are not limited to, (i) identified hazards and their associated risks or postapproval changes for drugs manufactured at the facility that have not been evaluated through the facility's change management procedures, and (ii) failure to follow established change management procedures.

c) If there is uncertainty about a facility's PQS (e.g., incomplete information about certain aspects of a facility's PQS relevant to ICH Q10), this should not, on its own, limit the ability to establish ECs or grant requested flexibility with reporting categories that are scientifically supported.

b. For supplements where OPMA is not assigned to perform the facility assessment, OQS assessors conduct both the initial facility evaluation and a PQS assessment. When a new facility is proposed to be added to an application with previously approved ECs and OQS identifies concerns regarding the PQS at the new facility, the assessment team considers the impact of those concerns on the approvability of requested flexibility with reporting categories as applied to that facility.

2. When there are residual PQS risks or pending CGMP compliance remediation actions that may affect change management following an OAI-to-VAI classification of the facility, OPMA or OQS assessors should consult OC/OMQ for further information on these risks or remediations and incorporate this information into their assessment as needed.

3. OPMA and OQS assessors document assessments in their respective discipline templates.

Considerations Regarding PAIs and PLIs for Original Applications and Supplements With Proposed ECs and Reporting Categories

Relevant OPQ office: OPMA

1. OPMA assessors do not request or initiate a PAI or PLI solely because of uncertainty about the PQS's ability to support ICH Q12 implementation or because an applicant is proposing ECs or reporting categories that differ from regulations and as recommended in guidance.

2. If a PAI or PLI has been initiated per normal practices for a facility that will implement proposed ECs, OPMA assessors share knowledge of the proposed ECs with the inspection team. The inspection team follows compliance program 7346.832—*Preapproval Inspections*[28] to assess the following:

[28] Coverage of objective 4 helps FDA's decision-making related to the facility's effectiveness in developing new products and implementing changes within a facility. Objective 4 provides an opportunity for investigators

a. Integrity of development studies at the facility that support relevant ECs.
b. Ability of the facility to manage changes.[29]

3. OPMA assessors evaluate inspection findings and share relevant inspection information related to proposals for ECs and reporting categories in the application with the assessment team to be considered in the assessment of ECs and reporting categories.

4. If OPMA assessors note PAI or PLI observations that impact the effectiveness of the PQS in implementing and managing ECs, they notify the assessment team as soon as possible to inform its assessment[30] of ECs and reporting categories, as appropriate (e.g., the team may choose to send an information request, discipline review letter, or CR letter to highlight the need to revise ECs or reporting categories to conform with regulations).

   a. One example of an issue that may raise concerns about the facility's ability to implement proposed flexibilities for ECs is a demonstrated lack of data integrity.

   b. Examples of issues that may raise concerns about the facility's ability to implement proposed flexibilities for reporting categories include, but are not limited to, (i) identified hazards and their associated risks or postapproval changes for drugs manufactured at the facility that have not been evaluated through the facility's change management procedures, and (ii) failure to follow established change management procedures.

   c. If concerns related to the PQS are subsequently addressed through the facility's response to inspection findings, the assessment team should not revise their assessment of scientific justifications for ECs and reporting categories unless relevant supporting information has changed (e.g., data from previously undisclosed batches).

5. OPMA assessors, in conjunction with the assessment team, can recommend a postapproval inspection to assess residual concerns with the maintenance and oversight of ECs for applications that otherwise meet the standards for approval.

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to observe and document examples of mature quality practices that exceed CGMP requirements and are indicative of an advanced quality system.

[29] As detailed in compliance program 7346.832, this can include an assessment of change management effectiveness for already marketed products. For example, an assessment of complaints, deviations, failures, adverse drug experience reports, and the periodic product reviews or product quality reviews for related products can provide information about the facility's ability to effectively manage change relevant to the EC proposals for the application subject to the PAI or PLI.

[30] The assessment team should follow normal procedures for integrated quality assessment; initial assessments of the application are made by the assessment team while inspections are progressing, and may be modified further based on outcomes from the inspections.

Application Actions

Relevant OPQ offices: OPRO; OPQA I, II, or III

1. OPQ follows normal procedures when acting on applications and uses the appropriate action letter templates with language regarding ECs.

2. When an original application or supplement with ECs is approved, OPRO and OPQA I, II, or III ensure that the following language is included in the approval action letter:

> *It is your responsibility to monitor the compliance of facilities implementing established conditions (ECs) approved in this application. If a facility that implements ECs approved in this application is classified as Official Action Indicated (OAI), changes to ECs for this application relevant to operations managed by that facility should be submitted per [21 CFR 314.70 or 21 CFR 601.12], and not per the Product Lifecycle Management (PLCM) document, until FDA has communicated to the facility that these concerns have been satisfactorily resolved. You may monitor the current compliance status of the facility in the Agency's Inspection Classification Database at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database.*

Postapproval Activities Related to Approved ECs Following an OAI Facility Classification

Relevant OPQ offices: OPRO; OPQA I, II, or III; OPMA
Relevant OC office: OC/OMQ

1. If the initial classification for a surveillance inspection,[31] postapproval inspection[32] (e.g., an OII final determination that is referred to CDER), for-cause inspection, or remote regulatory assessment of a facility where approved ECs are implemented is OAI, OC/OMQ (surveillance inspection) or OPMA (postapproval inspection) considers whether these concerns impact the ability of that facility to effectively manage changes in its case evaluation.

2. When the inspection is finalized as OAI, OC/OMQ (surveillance inspection) or OPMA (postapproval inspection) enters and maintains a final OAI alert for the facility/FEI per normal procedures.

[31] As described in compliance program 7356.002, surveillance inspections are a type of CGMP inspection.

[32] See compliance program 7356.843–*Postapproval Inspections* for postapproval inspection procedures. In addition to actions described in this MAPP that ensure supplements are filed at the right category, FDA may request that an applicant submit a supplement to modify ECs named in the application.

3. OPMA requests that OPRO identify all applications with approved ECs managed by the facility.

4. OPRO identifies impacted applications through system reports that match the OAI alert to application projects designated with an EC identifier.

5. OPMA; OPRO; OPQA I, II, or III; and OC/OMQ coordinate on the relevant communications to facilities and applicants as described below to ensure that supplements are submitted using the correct reporting category[33]:

    a. Communication to the facility: When the facility is classified as OAI and there are concerns with its ability to effectively manage changes for approved ECs, OPMA (postapproval inspection) or OC/OMQ (surveillance inspection) includes the following language in the inspection decision letter to inform the facility of the impact of findings on managing ECs:

        Following review of inspection findings and your responses to deficiencies observed on the inspection, FDA has concerns regarding your facility's ability to effectively manage changes to approved products under your quality system. You should contact holders of approved applications for drugs manufactured at your facility and inform them of FDA's findings. Until FDA has communicated that these concerns have been satisfactorily resolved, changes to approved application products should be submitted per [21 CFR 314.70 or 21 CFR 601.12] and guidance, even if the Product Lifecycle Management (PLCM) document for an approved application identifies alternate reporting categories for established conditions (ECs).

    b. Communication to the applicant: While the facility is OAI, CDER ensures that CMC changes relevant to the OAI facility are submitted with reporting categories consistent with regulation and guidance. When a supplement is submitted per the PLCM document at a lower reporting category than required by regulation or recommended in guidance for an EC managed by the OAI facility, OPRO and OPQA I, II, or III reclassify the supplement category to one that is consistent with 21 CFR 314.70 or 21 CFR 601.12 (or as described in relevant postapproval change guidance) or inform the applicant to resubmit the supplement with the appropriate supplement category.[34]

        In addition to standard language sent to the applicant when a change in a supplement category is appropriate, OPRO ensures the following language is sent to the applicant in the communication regarding supplement reclassification/resubmission:

[33] FDA follows normal procedures to review CMC supplements per internal MAPP 4151.11.

[34] Ibid.

ANDA supplement:
Due to the current compliance status of [insert name and FEI] and concerns communicated by FDA to the facility regarding its ability to effectively manage changes, please resubmit this supplement with a filing category that complies with 21 CFR 314.70. Postapproval changes should be filed per 21 CFR 314.70, and not per the Product Lifecycle Management (PLCM) document, until FDA has communicated to the facility that these concerns have been satisfactorily resolved. You may monitor the current compliance status of the facility in the Agency's Inspection Classification Database at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database.

NDA/BLA supplement:
Due to the current compliance status of [insert name and FEI] and concerns communicated by FDA to the facility regarding its ability to effectively manage changes, FDA has recategorized the supplement to a [PAS or CBE30] to comply with [21 CFR 314.70 or 21 CFR 601.12]. Postapproval changes should be filed per [21 CFR 314.70 or 21 CFR 601.12], and not per the Product Lifecycle Management (PLCM) document, until FDA has communicated to the facility that these concerns have been satisfactorily resolved. You may monitor the current compliance status of the facility in the Agency's Inspection Classification Database at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database.

c. Follow-up communication to the facility: When FDA has confirmed that the facility has satisfactorily addressed deficiencies and has determined that the facility is in compliance with CGMP, OPMA (postapproval inspection) or OC/OMQ (surveillance inspection) includes the following language in the relevant inspection decision letter to inform the facility of the impact of its resolution of deficiencies in managing ECs:

FDA finds that previously communicated deficiencies regarding your facility's ability to effectively manage changes to approved products under the quality system have been satisfactorily addressed. You should contact holders of approved applications for drugs manufactured at your facility and inform them of FDA's findings. Postapproval changes to approved application products may now be appropriately submitted using alternate reporting categories for established conditions (ECs) identified in a Product Lifecycle Management (PLCM) document for those applications.

d. Once OPMA or OC/OMQ has sent the communication in step 5.c and the OAI alert has been removed, OPRO and OPQA I, II, or III may resume accepting

supplements for ECs for an approved application relevant to the subject facility according to the reporting categories in the approved PLCM document.

REFERENCES

- Compliance programs
  - 7346.832—*Preapproval Inspections*
  - 7356.002—*Drug Manufacturing Inspections*
  - 7356.843—*Postapproval Inspections*
- Guidances for Industry[35]
  - Postapproval Changes
    - *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997)
    - *Changes to an Approved NDA or ANDA* (April 2004)
    - *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports* (March 2014)
    - *CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports* (December 2021)
    - *Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA* (October 2022)
    - *Postapproval Manufacturing Changes to Biosimilar and Interchangeable Biosimilar Products: Questions and Answers* (July 2024); Draft
    - *SUPAC: Manufacturing Equipment Addendum* (December 2014)
    - *SUPAC-IR: Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995)

[35] When final, the guidances for industry marked "Draft" in this list will represent FDA's current thinking on these topics.

- *SUPAC-IR: Questions and Answers about SUPAC-IR Guidance* (February 1997)
- *SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (September 1997)
- *SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997)

o General

- *ANDA Submissions—Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018)
- *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications* (September 2018); Draft
- *ICH Q12: Implementation Considerations for FDA-Regulated Products* (May 2021); Draft

o ICH

- *Q9(R1) Quality Risk Management* (May 2023)
- *Q10 Pharmaceutical Quality System* (April 2009)
- *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* and its *Annexes* (May 2021)

- MAPPs
  - MAPP 5016.8 Rev. 1 *Using Four-Part Harmony in Quality-Related Assessment Communications* (September 2023)
  - Internal MAPP 4151.11 *OPQ Facility Evaluation Management for NDA/ANDA Postapproval Submissions* (February 2023)

EFFECTIVE DATE

- This MAPP is effective on November 29, 2024.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
11/29/2024	Initial	N/A
11/29/2024	N/A	Administrative update, reflects FDA reorganization