

PHARMACEUTICAL CHANGE CONTROL: RISK BASED ASSESSMENT, REGULATORY IMPACT, AND PRODUCT LIFECYCLE MANAGEMENT

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ABSTRACT

Post-approval changes are an integral part of the lifecycle of pharmaceutical products because active pharmaceutical ingredient suppliers, manufacturing sites, analytical methods and formulations are often changed after approval. Such a change may have a negative impact on product quality, patient safety, regulatory status and/or supply if it is not properly identified, evaluated, and controlled. This narrative review article summarises the relevant scientific and regulatory literature and discusses post-approval changes with a particular focus on the following four areas: fundamentals and classification of post-approval changes; regulatory framework in the United States, Europe, the World Health Organization, and India; risk-based evaluation and underlying tools such as failure mode and effects analysis; and control of post-approval changes within the framework of a quality management system and ICH Q12. A running worked example, Product X, illustrates how a single API supplier change is risk assessed, classified, submitted and monitored across the product lifecycle. Two additional worked examples, a manufacturing-site/equipment change and an analytical-method change are compared to Product X in a case table. The review concludes with a discussion of areas of harmonisation, the slow global adoption of ICH Q12 tools such as Post-Approval Change Management Protocols, and the role of digital and artificial intelligence-enabled quality systems. The evidence suggests that thorough change control, informed by scientific risk analyses, an appropriate regulatory strategy and lifecycle quality management, contribute to consistent product quality, patient safety, regulatory compliance and medicine supply.

Keywords: change control; post-approval changes; ICH Q9; ICH Q12; quality risk management; pharmaceutical lifecycle management; regulatory affairs; FMEA.

1.INTRODUCTION

1.1 Concept of pharmaceutical change control

Change control is a documented formal process used by a pharmaceutical manufacturer to identify, assess, approve, implement, and verify changes to a marketed drug product that may affect its quality, safety or efficacy (1). This definition reflects the ICH Q10 standard, adopted by the FDA in its own change control regulations (2). Within the framework of a pharmaceutical quality system (PQS), change control is a control element encompassing the lifecycle management of changes proposed to the product and connecting these to their impact on critical product and process attributes (CPA), validated states,

and regulatory commitments (1). In other words, change control is not about preventing changes, as a modern manufacturer is not supposed to stagnate (ICH Q9(R1) views risk management as a tool to make smart changes, not the other way around (3)), but rather ensuring that every change, once implemented, has been properly assessed and, if necessary for regulatory or quality reasons, communicated to the pertinent authority. This includes following the FDA's 21 CFR 314.70 guidelines or the EU's variation regulations (5) depending on the jurisdiction.

1.2 Need for changes after marketing authorization

A marketing authorization is a set of specifications about a product's manufacturing processes, controls, and quality attributes that are established and validated at the moment of submission. It is, by definition, a snapshot of a product's manufacturing processes at a given moment in time (4). In practice, however, this moment seldom lasts forever – a product's life cycle often spans multiple years, and sometimes even decades, and manufacturers must make changes during this period in order to adapt to new realities. These include global supply chain disruptions (6), equipment obsolescence, the need to scale up production to meet demand (6), analytical method updates (6), and other factors affecting the manufacturing process or the product itself. Post-approval changes (PAC) are therefore made to a product on a deliberate and ongoing basis in order to maintain its robustness (6). This, in turn, helps to ensure patient access to the product (7).

1.3 Common drivers of post-approval changes

- Raw materials and suppliers: Qualification of a new API or excipient supplier or a change to a supplier's process. This is one of the most common types of changes according to the 2024 global industry benchmarking study (6).
- Manufacturing process and equipment: Process or equipment scale-up or -down, or substitution with an alternative device using a different design principle. This type of change is further discussed in the FDA's SUPAC guidelines (8).
- Manufacturing site: Moving the production to a different site within the same group or to a CMO. In the EU, this type of change falls under the "site" variation category (5).
- Analytical methods: Introduction of new analytical tests or test procedures, including method transfers between labs. ICH Q14, finalized in 2021, now provides guidance on this subject (9).
- Formulation and packaging: Changes to excipients, packaging, or packaging components (container closure systems). This type of change is also discussed in the SUPAC guidance, along with the others listed above (8).

1.4 Impact of poorly-managed changes

Implementation of a change without adequate assessment can have repercussions across a number of areas simultaneously, which ICH Q9(R1) specifically reminds manufacturers to consider before implementing change [3].

- Product quality - change that has not been properly assessed can lead to critical quality attribute going out of specification causing either out-of-specification results or reduced shelf life [3].
- Patient safety - change in dissolution, impurities or in vivo performance can directly impact the efficacy of the drug or lead to emergence of new safety concerns, exemplified by extensive comparability testing required for a change in cell-line in biosimilars [10].
- Regulatory compliance - improper change control can lead to warning letters, import alert or even withdrawal of marketing authorization due to non-submission or wrong submission as per requirements in 21 CFR 314.70 [4] and EU variation regulation [5].
- Product availability - on the flip side excessively rigorous change control can impact the product availability as a manufacturer might not be able to rapidly respond to changes in supply chain or quality issues at a given site, a concern highlighted in the 2023 revision of ICH Q9 [3], with supporting examples in the literature [7].

1.5 Aim and scope of the review, including introduction of the Product X running example

The aim of this review is to synthesis, critically rather than descriptively, the scientific and regulatory literature on pharmaceutical change control published predominantly between 2023 and 2026, organized around the classification of changes as defined in ICH Q12 [11]; the comparative global regulatory environment spanning FDA requirements [8], the EU variation system [5], WHO guidance [12], and CDSCO requirements [13]; risk-based assessment methodology based on ICH Q9(R1) [3]; workflow and documentation practice in line with ICH Q10 [1]; regulatory submission strategy; scientific comparability assessment; and lifecycle integration based on recent industry survey evidence on global change-management performance [6]. To ground these abstract principles, the review introduces a running worked example, Product X, a hypothetical oral solid-dosage generic product for which the manufacturer proposes to qualify a second API supplier. Product X is developed progressively, respectively, how a change is risk-assessed, how a regulatory pathway is selected and implemented, and how the change is monitored throughout the remaining product lifecycle.

2.FUNDAMENTALS AND CLASSIFICATION OF PHARMACEUTICAL CHANGES

2.1 Definition and scope of change control

Change control, as defined in ICH Q10, is one of four key elements of a pharmaceutical quality system: the other three being process performance/product quality monitoring, a corrective and preventive action (CAPA) system, and management review [1]. This structure is reflected in the FDA's own guidance adopting ICH Q10 [2]. Its scope runs from product development through commercial manufacturing to product discontinuation [1]. It is designed to interface with quality risk management under ICH Q9(R1): each proposed change is expected to be evaluated via formal or informal risk-assessment tools appropriate to the complexity and risk of the change [3], a link repeated by EMA's adoption of the revised guideline [14].

2.2 Planned, unplanned and emergency changes; temporary versus permanent changes; minor, moderate and major changes

Changes can be classified at least in three different ways. First, changes should be categorized based on the source of the need for change, including planned versus unplanned changes and emergency changes. Planned changes are “initiated as part of the continuous improvement or supply-strategy initiatives” [6], while unplanned changes are made “in response to an identified opportunity, a supplier notification or a process failure of some type” [6]. Emergency changes “are made immediately to avoid a supply interruption or safety concern and documented formally and retrospectively” [3] (p. 8), in accordance with the product-availability risk management framework in ICH Q9(R1) [3]. Furthermore, a change can be classified based on its nature or term, such as temporary versus permanent changes. Whereas temporary changes are “implemented on a temporary basis, such as use of an alternate analytical laboratory, while the primary laboratory is out of service” [1], permanent changes are integral part of product's manufacturing master plan and are reflected in PQS change-management element of ICH Q10 [1]. Finally, the changes can be divided on the basis of risk they pose to the product quality and require different evaluation: major, moderate and minor. The same grouping (but with different terminology) is used in FDA's regulations, specifically, in the context of Annual Report, CBE-30 and Prior Approval Supplement [8] and in the EU's Type IA, Type IB, Type II variations [5], and CDSCO's Category 1, 2, 3 [13].

2.3 Post-approval change categories

- Material or supplier changes - API or excipient source, grade, or specification changes, illustrated by the tiered comparability approach used for a biosimilar cell-line change [10].
- Process changes - modification of manufacturing steps, process parameters, or batch size, governed by the SUPAC decision trees [8].

- Equipment or facility changes - new equipment, new manufacturing site, or facility relocation, which are treated as major variations in the EU framework [5].
- Analytical-method changes - new, modified, or transferred test methods, guided by the science- and risk-based principles in ICH Q14 [9] and the revised ICH Q2(R2) [15].
- Formulation or specification changes - excipient substitution, strength changes, or specification tightening/widening, addressed within the SUPAC framework [8].
- Packaging changes - container-closure system or pack-size modifications, to be reported under 21 CFR 314.70 [4].

3.REGULATORY LANDSCAPE OF POST-APPROVAL CHANGES

3.1 ICH guidelines relevant to change management - Q9, Q10 and Q12

The three ICH quality guidelines that are integral to change management are ICH Q9(R1), ICH Q10 and ICH Q12. ICH Q9(R1), adopted by ICH Step 4 on 18 January 2023, contains the quality risk management (QRM) provisions for evaluating a change proposal [3]. The revision updated recommendations on formality, subjectivity, and risk-based decision-making, with the FDA's Federal Register notice of adoption of the guideline [16] specifically noting the inclusion of product-availability risk due to manufacturing and quality issues, which was also explicitly acknowledged in the EMA's adoption notice of the guideline [14]. ICH Q10 describes the pharmaceutical quality system wherein change management is one of the four pillars, alongside CAPA, process/product monitoring, and management review [1]. ICH Q12, finalized in November 2019, includes a suite of tools – Established Conditions (ECs), Post-Approval Change Management Protocols (PACMPs), and the Product Lifecycle Management (PLCM) document – for post-approval change management, with the intent “to provide science- and risk-based flexibility in reporting category, once an appropriately controlled PQS and adequate process understanding have been demonstrated” [11]. The ICH region has had varying levels of adoption of the three Q12 tools, with Health Canada adopting both ICH Q12 and Q14 as per a 2026 notice [17] and China's National Medical Products Administration adopting ICH Q12 in 2023 [18].

3.2 US FDA regulatory framework

Under 21 CFR 314.70, an applicant of an approved New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) is obligated to report changes to Center for Drug Evaluation and Research (CDER) via different mechanisms depending on the potential impact of the proposed change on the identity, strength, quality, purity, and potency of the drug product [4]. The Scale-Up and Post-Approval Changes (SUPAC) guidance, first issued in November 1995 for immediate-release solid oral dosage forms, provides the decision tree on the basis of which a change to a component, site, scale, process, or equipment is categorized as a particular “level” of change with corresponding documentation requirements for Chemistry, Manufacturing, and Controls (CMC), dissolution, and bioequivalence [8]. The guidance was supplemented in multiple occasions, including the most recent addition in 2014 describing recommendations for manufacturing equipment, published in the Federal Register [19].

- Prior Approval Supplement (PAS): submission for approval before implementation for changes with potential for significant impact on product quality [4].
- Changes Being Effected in 30 days (CBE-30): implementation can occur 30 days after submission, unless objected by FDA, for changes with moderate impact [4].
- Changes Being Effected in 0 days (CBE-0): implementation can occur immediately upon submission for limited set of changes with reduced potential for negative impact [4].
- Annual Report: for minor changes with limited potential for impact, reported as part of an annual update [4].

In addition to the aforementioned reporting mechanism, FDA's 2024 guidance on post approval manufacturing changes to biosimilar and interchangeable products describes additional comparability-protocol expectations for Biologics License Application (BLA) supplements under Biosimilar User Fee Act (BsUFA III) [20].

3.3 European regulatory framework

The EU's variation system, established by Commission Regulation (EC) No 1234/2008, as amended most recently by Commission Delegated Regulation (EU) 2024/1701 of 11 March 2024, classifies post-authorization changes to medicines as minor variations of Type IA and IB and major variations of Type II [5]. A revised Variations Guidelines (C/2025/5045), replacing the 2013 guideline, becomes effective from 15 January 2026 [21]. It describes procedural improvements, such as “super-grouping” of Type IA variations to multiple marketing authorizations, and EMA has issued separate implementation guidance for the transition to the revised guidelines [22].

- Type IA: minimal or no impact on quality, safety, or efficacy; a “do-and-tell” category wherein a post-implementation notification is submitted as an annual update [5].
- Type IB: minor variations not meeting the criteria for Type IA; default 30-day notification applies, unless waived by the competent authority [21].
- Type II: major variations with potential for significant impact on quality, safety, or efficacy requiring assessment and approval before implementation [5].

3.4 WHO requirements and regulatory approaches

WHO published general guidance on variations to multisource pharmaceutical products (Technical Report Series No. 996, Annex 10) [12] and, for WHO Prequalification Programmed assessed products, specific guidance on variations to a prequalified product (Technical Report Series No. 981, Annex 3) [23]. Both documents consider the marketing-authorization holder's responsibility to evaluate the impact of a proposed variation on the quality, safety, and efficacy (QSE) of the product using categorization approach similar to that of FDA and EU [12]. In particular, the guidance on multisource products acknowledges the resource limitations of national regulatory authorities (NRAs) and recommends flexibility in applying reporting requirements depending on the capability of the NRA [12].

3.5 CDSCO/India requirements

In India, post-approval changes to drugs are regulated under the Drugs and Cosmetics Act, 1940 and New Drugs and Clinical Trials Rules, 2019, with CDSCO providing product-class guidance [13]. For biological products, the 2024 guidance “Post Approval Changes in Biological Products: Quality, Safety and Efficacy” describes the CMC data requirements according to the stage of manufacturing – drug substance, drug product, comparability, stability, and labeling [13]. Post-approval changes to biologicals are triaged according to risk, with administrative changes requiring simple notification, whereas changes necessitating re-evaluation per the definition in Rule 122E would require new permission for a new drug as opposed to a post-approval change [13].

3.6 Comparative regulatory framework

Despite different terminologies, the FDA [4,8], EU [5], WHO [12,23], and CDSCO [13] regulatory frameworks for post-approval changes appear to follow a similar paradigm, wherein the type of documentation and review is determined on the basis of the potential impact of a proposed change on the quality, safety, and efficacy of a drug product, with higher levels of documentation and review required for higher risk.

Table 1: Comparative regulatory reporting categories for post-approval pharmaceutical changes.
Sources: FDA [4,8]; EU [5]; WHO [12,23]; CDSCO [13].

RISK TIER	US FDA	EU (EMA/NCA)	WHO	CDSCO (India)
Minor / Low Risk	Annual Report	Type IA	Notification	Category 1
Moderate Risk	CBE-30/ CBE-0	Type IB	Minor Variation	Category 2
Major / High Risk	Prior Approval Supplement (PAS)	Type II	Major Variation	Category 3 / New-drug filing

4.RISK-BASED ASSESSMENT OF PHARMACEUTICAL CHANGES-CORE SECTION

4.1 Principles of Quality Risk Management

Quality risk management (QRM) is grounded in two principles stated in ICH Q9(R1): namely, that risk evaluation should be science-based and patient-focused, and that the number of resources spent on QRM should be commensurate with the level of risk [3]. The 2023 revision was necessitated by industry practices of subjective risk analyses and by the lack of consensus on the level of “formality”, acknowledged by the FDA’s Federal Register notice upon adopting the revision [16]. The revision clarified the definitions of hazard, harm, and risk, and explicitly addressed the management of risks to product availability to meet patient needs, acknowledging the opportunity cost of overly conservative change-control strategies causing shortages [3].

4.2 Application of ICH Q9 to change control

In the context of change control, QRM is manifested at two points: establishing the potential impact of a proposed change on product quality, which informs the need for additional studies [3], and defining the regulatory category for the change based on its overall risk profile [3]. ICH Q10 specifically requires that the risk-management principles be applied to a proposed change to a pharmaceutical product prior to its approval, effectively linking change-management and QRM processes within the pharmaceutical quality system [1].

4.3 Identification of Critical Quality Attributes (CQAs)

A critical quality attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that must be controlled, directly or indirectly, to ensure a product’s quality [3], such as the assay, content uniformity, dissolution profile, and related substances/impurities of an oral solid dosage form [8]. As per FDA’s SUPAC decision-tree, these are all considered CQAs, and the potential impact of a proposed change must be evaluated in context of these CQAs [8]. Prior to initiating a change assessment, the CQAs impacted by a proposed change must be established explicitly, as the risk-assessment process itself is inherently focused on QCs [3].

4.4 Identification of Critical Process Parameters (CPPs)

A critical process parameter (CPP) is a process input variable that has a direct influence on a CQA [3], such as blending time or compression force in the case of an oral solid dosage form. If a proposed change, such as a switch to a new API supplier with a different particle-size distribution, has the potential to alter a CPP’s range, this must be explicitly stated within the context of the proposed change’s impact assessment [3]. Oftentimes, the risk-ranking of a change is determined by its impact on a CPP’s range relative to the previously established range for the same parameter, with changes to Established Conditions potentially being classified as significant depending on the context [11]. The identification of CPPs is a key step within ICH Q12’s change management approach [11].

4.5 Risk assessment methodology

A protocol for pharmaceutical change assessment typically involves five distinct steps as recommended by ICH Q9(R1): risk identification, analysis, evaluation, control, and review [3]. First, a cross-functional team of analysts evaluates the potential failure modes associated with the proposed change. Next, each failure mode is assessed in terms of severity, probability of occurrence, and possibility of detection. These three factors are then combined to calculate the overall risk posed by a failure mode and compared to a set of risk acceptance criteria. Based on the risk assessment findings, risk control measures are developed and implemented, including the design of studies to support the proposed change, if needed. Finally, the risk assessment results are reviewed at the stage of applying the change in accordance with the findings of the post-implementation review using the collected production and quality data [3]. A simplified depiction of this process is presented in Figure 4 for a quantitative FMEA-based approach using severity-occurrence-detection scoring, which has been adapted from a hospital-pharmacy FMEA study [24].

4.6 Risk assessment tools

- FMEA/FMECA (Failure Modes and Effects [Criticality] Analysis): a standardized prospective risk-assessment tool that uses a scoring system to evaluate the potential failure modes of a process or product and their effects, including the severity, occurrence, and detection. It is considered one of the most comprehensive hospital-pharmacy risk-assessment tools [24], with similar applications described in the context of oncology-pharmacy processes.
- Risk matrix: a simplified 2D visual risk-assessment tool that uses a qualitative severity x probability risk matrix to prioritize the failure modes, which is a less resource-intensive alternative to the FMEA tool, particularly in accordance with the proportionality principle described in ICH Q9(R1) [3].
- RPN (Risk Priority Number): a calculation derived from the S-O-D (Severity x Occurrence x Detection) scores in FMEA, used to indicate the priority of failure modes. An illustrative example comes from a hospital-pharmacy FMEA study, where the RPNs were used to identify the key failure modes driving overall risk [24], along with a similar application in the context of an oncology computerized prescribing FMEA study.
- Ishikawa (fishbone) analysis: a root-cause analysis tool used to identify the key factors contributing to a specific failure mode, typically organized in a cause-and-effect diagram, to prioritize the implementation of controls based on the factors influencing the potential failure modes. The tool supports the fulfillment of the root-cause analysis expectations described in ICH Q9(R1) [3].

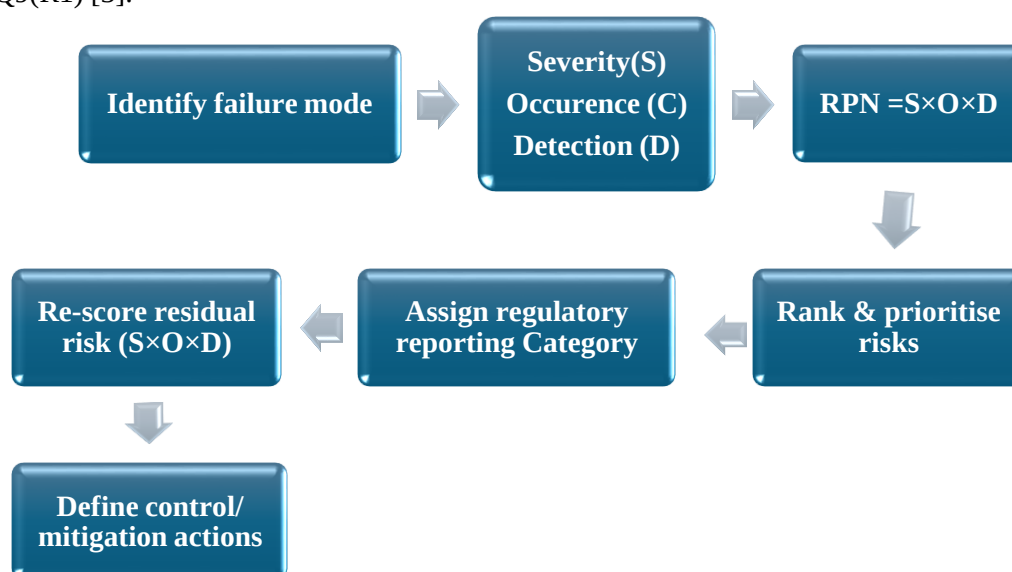


Figure1: FMEA-based quantitative risk assessment cycle applied to a pharmaceutical change.

4.7 Impact assessment domains

- Product quality - direct effect on CQAs such as assay, dissolution, impurities, and physical attributes [3].
- Validation status - whether existing process, cleaning, or method validation remains representative after the change [1].
- Regulatory status - whether the change falls within, or outside, previously approved Established Conditions [11].
- Manufacturing process - downstream effects on other unit operations or in-process controls, the focus of the SUPAC decision trees [8].
- Analytical methods - need for method revalidation, transfer, or bridging studies under ICH Q14 [9] and ICH Q2(R2) [15].
- Stability - need for accelerated or long-term stability data to support the revised process or material [8].
- Supply chain - effect on lead times, dual sourcing strategy, and continuity of supply, a driver repeatedly identified in the change-management literature [6].

4.8 Determination of supporting studies

The impact assessment findings drive the requirements for supporting comparative studies. Changes that are unlikely to affect a non-critical quality attribute may only require a rationale statement, according to [3]. For changes that may affect a CQA, a comparative study such as three-batch comparability would be required, per the example of cell-line comparability for biosimilars given in [10]. For changes to validated process parameters, re-validation of the process, including accelerated and possibly real-time stability studies, may be required before the change can be implemented at commercial scale, according to [8].

4.9 Risk-based decision making

ICH Q9(R1) clearly states that decisions are made based on risk throughout all phases of QRM, and not as a final step [3]. In addition, the guidance emphasizes that decisions are documented with rationale for the selected risk estimation and control strategy and regulatory reporting category, so that the decisions are clear to internal quality reviewers and external inspectors [3].

4.10 Worked example: Product X API supplier change

Product X is a commercial, immediate-release oral solid-dosage generic product. It is proposed by the manufacturer to qualify a second, geographically separate API supplier to reduce the risk of single-source supply, consistent with the dual-sourcing rationale reported in industry surveys of post-approval change drivers [6].

Change

Introduction of a second, qualified API supplier producing the same polymorphic form and particle-size specification as the incumbent supplier, intended to run in parallel rather than replace the original source.

Risk identification

The cross-functional team (Quality Assurance, Quality Control, Production, Regulatory Affairs) identifies candidate failure modes following the risk-identification stage of ICH Q9(R1) [3]: (i) subtle differences in impurity profile between suppliers; (ii) differences in particle-size distribution affecting blend uniformity and dissolution; (iii) differences in residual-solvent profile; (iv) potential downstream effect on tablet hardness and disintegration, a failure-mode structure consistent with published hospital-pharmacy FMEA practice [24].

FMEA

Each failure mode is scored for severity (impact on a CQA if it occurs), occurrence (likelihood given the two suppliers' qualification data), and detection (probability that existing in-process and release testing would catch the failure before release), following the severity-occurrence-detection scoring convention reported in a published hospital-pharmacy FMEA application [24].

Risk score

The particle-size/dissolution failure mode returns the highest Risk Priority Number, owing to a moderate severity score (dissolution is a CQA), a low-to-moderate occurrence score (the new supplier's particle-size distribution overlaps but is not identical to the incumbent's), and a moderate detection score (routine release testing would detect an out-of-specification result, but only after batch manufacture), a scoring pattern consistent with the RPN ranking reported in an oncology-pharmacy FMEA application .

Controls

The team defines control measures: tightening the incoming particle-size specification for the new supplier's material, running three confirmatory process-performance qualification batches, and commissioning comparative dissolution profiling across both supplier sources, an approach consistent with the tiered comparability strategy reported for a post-approval material change in a biosimilar product [10].

Regulatory classification

Because the change affects a CQA (dissolution) but is supported by robust comparability data and does not alter the qualitative or quantitative formulation, manufacturing process, or specifications, it is provisionally classified as a moderate-risk change, illustrated in the central branch and consistent with the Established-Conditions logic of ICH Q12 [11], pending confirmation of the applicable regulatory pathway.

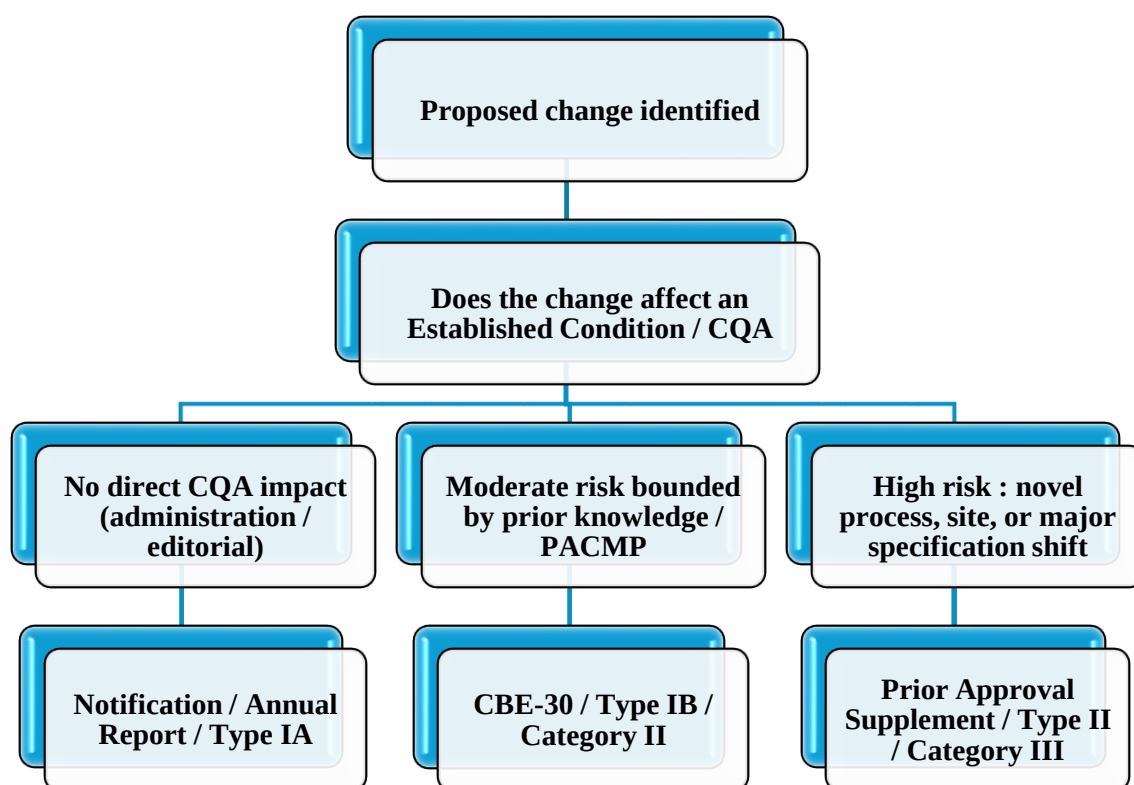


Figure 2: Risk-based decision logic for post-approval change classification, applied to the Product X API supplier change.

4.11 Risk-based change classification decision tree

The logic for classifying changes to Product X to a decision tree is introduced: the key first distinction is whether the change under review affects an Established Condition or CQA, the umbrella concept introduced by ICH Q12 [11]. From there, changes, which have no direct CQA impact, are steered towards a notification-type reporting process, similar to the FDA's Annual Report [8] and the EU's Type IA variation [5]. Changes, which are implemented within the limits of prior process knowledge or a pre-agreed PACMP, are directed towards a lower risk stream, reflecting the efficiency benefits of using a PACMP identified in industry analyses [7]. Finally, changes, which involve a new process, site or significant specification shifts are channeled towards a prior-approval pathway, corresponding to the FDA's Prior Approval Supplement [4] and the EU's Type II variation [5].

5. CHANGE CONTROL WORKFLOW AND DOCUMENTATION

A change is formally initiated when a change request is opened in the quality-management system, describing the change and its context and scope, meeting the requirements for change-management documentation in ICH Q10 [1]. Upon issue, the change request is given a reference number for tracking and is sent to the appropriate cross-functional reviewers for initial assessment [1].

5.2 Preliminary impact assessment

Prior to a formal risk assessment, each proposed change is run through a screening gate to triage and prioritize proposed changes in terms of resource allocation, identifying those that are clearly non-impactful (e.g., clerical corrections) or that can be formally risk-assessed [3]. This represents the proportional assessment guidance in ICH Q9(R1), which aims to avoid resource investment in low-impact changes, while ensuring that no high-impact change is missed [3].

5.3 Risk evaluation

For changes passing the preliminary screening, the structured risk-assessment approach is used as described in Section 4 and incorporated into a formal risk-assessment report in the ICH Q9(R1) logical sequence [3]. For certain changes in the moderate-to-high risk category, an FMEA-scoring approach, similar to that proposed in a hospital-pharmacy publication [24], can be used to derive a formal risk score, rationale, and control strategy.

5.4 Cross-functional review and approval

The change request, including the risk-assessment report, is then reviewed by Quality Assurance, Quality Control, Production, R&D, Engineering, and Regulatory Affairs functional leads, who evaluate the change from their discipline perspective before the change can be formally approved by the quality unit, in line with ICH Q10 recommendations for cross-functional change-review governance [1].

5.5 Implementation of the change

The approved change is then implemented in accordance with an implementation plan, which may involve equipment qualification, process-performance qualification batches, method validation or transfer, and specification or SOP updates, with reference to SUPAC documentation practices for implemented changes [8].

5.6 Effectiveness verification

Post-implementation, the change is evaluated for control effectiveness in accordance with the verification protocol established during risk assessment. For instance, for a change impacting dissolution, assay, and impurity profiling, this would involve verifying that post-change lots meet specification and are comparable to historical controls, using the analytical data as evidence of control effectiveness in line with the principles of comparability testing for a post-approval change to a biosimilar [10].

5.7 Change closure

After verification, the change is formally closed, with the supporting documentation filed and, if relevant, the regulatory submission updated to capture the implemented change in accordance with PQS requirements in ICH Q10 [1].

5.8 Roles and responsibilities

- The Quality Assurance function owns the change-control process, facilitates the cross-functional change-review meeting, and approves the change for implementation, in line with the governance recommendations in ICH Q10 [1].
- The Quality Control function is responsible for designing and implementing the necessary comparative testing and analytical studies in support of the change, similar to the testing and study design responsibilities for a post-approval change to a biosimilar [10].
- The Production function is responsible for assessing the change's impact on manufacturing operations and for implementing the change at the production site [1].
- The R&D function provides formulation and process-development expertise and support, particularly in the context of comparability assessment, consistent with the biosimilar reference-product analytical-filing guidance [10].
- The Engineering function is responsible for equipment qualification in support of the change and for addressing any other built-environment aspects [1].
- The Regulatory Affairs function identifies the appropriate regulatory category for the change, in accordance with FDA [4], EU [5], CDSCO [13], or other relevant regulatory guidelines, and manages the corresponding filing or notification.

5.9 Electronic change-control systems

Change-control processes are increasingly managed using electronic quality management system (eQMS) tools that employ digitized change records to drive the required approvals and to manage the connection between the change record, deviations, corrective and preventive actions, and training records, in line with the digital-quality trends identified in an AI-enabled quality-control publication [25]. This supports the traceability and audit evidence requirements in 21 CFR Part 11 and the EU's Annex 11, with regards electronic records and signatures.

5.10 Documentation and data-integrity requirements

The documentation practices should be aligned with ALCOA+ data-integrity principles, including attributable, legible, contemporaneous, original, and accurate data, with documentation that is complete, consistent, enduring, and available, in accordance with ICH Q10 documentation requirements [1]. From a regulatory inspection point of view, the change record is the key documentation demonstrating that a change was formally assessed and approved prior to implementation in line with FDA requirements at 21 CFR 314.70 [4] and the relevant EU variation regulation [5].

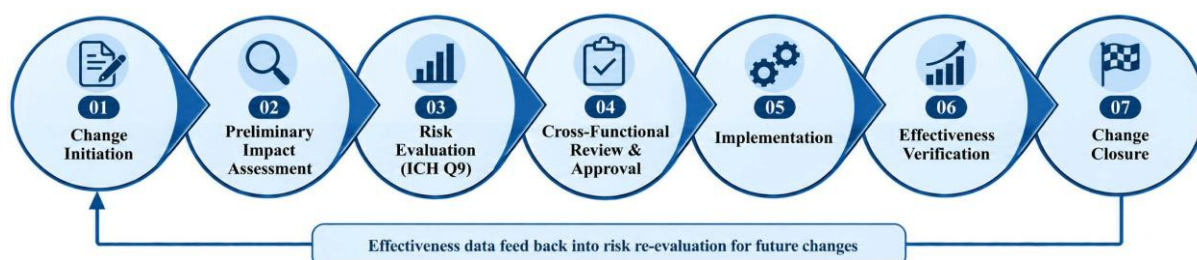


Figure 3: Generic pharmaceutical change control workflow from initiation through closure.

6.REGULATORY IMPACT AND SUBMISSION PATHWAYS

6.1 Need for regulatory-impact assessment

Once the scientific risk assessment is complete, a distinct but closely related question must be answered: which regulatory submission pathway(s), in each market where the product is registered, equates to the assessed level of risk. In the US this is defined by 21 CFR 314.70 [4]; in the EU by the variation classification framework [5]; and in India by CDSCO's category system [13]. This regulatory-impact assessment is essential because reporting-category thresholds are not perfectly aligned across jurisdictions and a change classified as moderate risk in one market may be treated as major in another, particularly where local Established Conditions differ, a divergence ICH Q12 was designed to reduce [11].

6.2 Assessment of approved CMC information

The regulatory-impact assessment begins with a line-by-line comparison of the proposed change against the currently approved Chemistry, Manufacturing, and Controls (CMC) dossier-specifically the Established Conditions defined under ICH Q12 [11] and the approved specifications recorded under 21 CFR 314.70 [4] - to determine precisely which sections of the dossier the change will impact.

6.3 Prior approval versus notification-based changes

Depending on this assessment, a change will be routed either to a prior-approval pathway-in which implementation must wait for explicit regulatory authorization, consistent with the FDA's Prior Approval Supplement category [4] - or to a notification-based pathway - in which the change may be implemented before, or shortly after, submission, with the health authority retaining a right to object within a defined review window, as under the EU's Type IB procedure [21].

6.4 FDA submission pathways

For the US market, the pathway options are the Annual Report, CBE-0, CBE-30, and the Prior Approval Supplement, selected according to the SUPAC-derived "level of change" [8] and the 21 CFR 314.70 risk criteria [4].

6.5 EU variation pathways

For the EU the pathway options are Type IA, Type IB and Type II variations, under the revised Variations Regulation [5] with the specific classification determined by matching the change against the detailed change list in the Classification Guideline annex [21]. Changes not explicitly listed default to Type II unless the applicant can justify a lower category [21].

6.6 CDSCO submission requirements

For India the pathway is determined against CDSCO's risk-tiered categories with API and drug-substance related changes for biological products following the CMC data-package structure set out in the 2024 CDSCO guidance [13]. Any change which meets the Rule 122E definition of a "new drug" requires a full new-drug application, rather than a standard post-approval-change filing [13].

6.7 Regulatory timelines

Reported approval timelines vary substantially across markets and change type. Published industry survey data covering more than 145,000 post-approval changes across 156 countries found only a single national regulatory authority accepted all submitted changes within six months [6]. Typical approval timelines for changes requiring prior authorisation commonly extend to several years in some jurisdictions, according to analysis of the same global dataset [7].

6.8 Regional differences in post-approval change classification

A recurring theme in the regulatory literature is that identical technical changes are frequently classified differently across regions due to the absence of harmonised Established Conditions and reference specifications, a gap which is explicitly documented by industry survey respondents [6]. This is precisely the gap that ICH Q12 was designed to narrow [11], though survey evidence indicates that formal Q12 implementation remains limited among ICH member regulators several years after adoption [6].

6.9 Common regulatory pitfalls and causes of delays

- Submitting a change to only some of the markets where the product is registered leading to divergent manufacturing baselines across regions, a pitfall which is identified directly by industry survey respondents [6].
- Underestimating the classification in a given market leading to rejection or delay upon regulatory review [6].
- Incomplete comparability data packages, particularly for biological products where cell-line or process changes require extensive analytical bridging [10].
- Failure to update all affected dossier sections consistently - specifications, stability commitments, labelling - in a single coordinated submission, a requirement under both 21 CFR 314.70 [4] and the EU variation regulation [5].

6.10 Strategies for reducing regulatory uncertainty

- Early engagement with regulatory authorities through scientific-advice or pre-submission meetings for complex or novel changes, a strategy which is recommended in industry survey analysis [6].
- Use of Post-Approval Change Management Protocols (PACMPs) to pre-agree the study design and acceptance criteria for a defined future change reducing review time at point of implementation, a tool which is defined under ICH Q12 [11] and whose efficiency gains are quantified in industry analysis [7].
- Participation in regulatory reliance and work-sharing pilots which allow multiple national regulatory authorities to leverage a single reference assessment shortening global approval timelines for supply-critical changes [26].
- Maintaining a harmonised global regulatory strategy which submits the same change package (adapting only where legally required) across all markets simultaneously, an approach which is supported by survey evidence on reliance mechanisms [6].

Continuing the Product X thread: regulatory pathway for the supplier change

Returning to Product X, the API supplier change assessed in Section 4.10 is evaluated against the CMC dossier and is found to impact an approved Established Condition - the identity of the qualified API source - under the ICH Q12 framework [11], but not the qualitative or quantitative composition, manufacturing process or approved specifications of the finished product. In the United States, this profile equates to a CBE-30 supplement allowing implementation 30 days after FDA receipt of the comparative dissolution and three-batch process-performance qualification data, unless FDA raises an objection [4]. In the European Union, the equivalent change -addition of an alternative approved API

manufacturer - supported by comparability data is classified as a Type IB variation under the current Classification Guideline, following the default 30-day notification procedure [21]. In India, the change is filed with CDSCO as a Category 2 post-approval change [13], accompanied by the comparative dissolution and impurity-profile data generated during the FMEA-driven control strategy [24]. Because Product X is registered in all three jurisdictions the manufacturer submits a harmonized comparability package simultaneously to each authority, reducing the risk of a divergent approved manufacturing baseline across markets, an outcome consistent with the reliance-based efficiency gains reported in recent industry case studies [27].

7. SCIENTIFIC ASSESSMENT AND COMPARABILITY OF CHANGES

7.1 Comparability assessment

Comparability assessment is the data-supported demonstration that a product made after a change is essentially equivalent within specific acceptance criteria compared to the product made prior to the change [10]. For small molecules this commonly relies on side-by-side analytical and dissolution comparison consistent with SUPAC testing framework [8], whereas comparability for biologicals is far more involved due to the potential for changes that don't show up analytically at the point of the change to impact immunogenicity or clinical performance [10]. This is exemplified in a 2023 case study of a post-approval production-cell-line change in a bevacizumab biosimilar, where an extensive quality-attribute comparability exercise was required following a tiered risk-ranking approach in the absence of a specific cell-line change regulatory guideline [10].

7.2 Process validation and revalidation

When a change impacts a process parameter that has already been validated, either full or partial process revalidation is required as would be expected according to PQS lifecycle expectations of ICH Q10 [1], thereby generating fresh process-performance qualification data that demonstrate the process remains capable of consistently producing product fulfilling its predefined quality attributes in line with changed conditions, in accordance with SUPAC-derived revalidation expectations [8].

7.3 Continued Process Verification (CPV)

Continued process verification, the third step in the FDA process-validation lifecycle, enables ongoing statistical monitoring of a validated process during routine commercial manufacture [1]. It is particularly valuable after post-approval change because it provides the manufacturer with the opportunity to spot any subtler shifts in process-performance using trending of process and quality data that might have been masked by traditional batch-release testing, a capability also increasingly harnessed by digital process-monitoring approaches described in recent literature [27].

7.4 Analytical testing

Analytical testing required to support a change commonly includes assay, related substances/impurities, dissolution, and any change-specific tests, for example residual solvents for a new API supplier, performed on a statistically justified number of comparative batches, consistent with both SUPAC testing framework [8] and the comparability-batch approach reported for a biosimilar post-approval change [10].

7.5 Analytical method validation

When the change required involves a new or modified analytical method, ICH Q14, finalized at ICH Step 4 in November 2023 and adopted by EMA in mid-2024, provides harmonized science and risk principles for analytical procedure development [9]. The revised ICH Q2(R2) adopted on the same timeline provides the associated validation principles [15]. Together they are explicitly designed to support more efficient post-approval change management for analytical methods via an "enhanced" development approach that pre-defines the method's operable design region [9].

7.6 Stability studies

Depending on the nature of the change it can be sufficient to support initial implementation of the change using accelerated stability data, typically three to six months, according to SUPAC stability expectations [8]. Long-term, real-time stability data are generated in parallel in the post-approval stability commitment in order to confirm the product's approved shelf life is still valid in line with the changed conditions [8].

7.7 Dissolution and performance testing

For oral solid-dosage products dissolution profiling, typically comparing multiple pH media which reflect the physiological range, is one of the most common indicators of whether a manufacturing, formulation or supplier change has modified in vivo product performance, as the central premise of SUPAC dissolution-testing requirements [8].

7.8 Assessment of Critical Quality Attributes

All comparability data generated are ultimately synthesized against the CQAs identified during the initial risk assessment [3], closing the loop between the prospective risk assessment and the retrospective scientific evidence generated to support the change, mirroring the comparability logic applied to the biosimilar cell-line case study [10].

7.9 Impact on product quality, safety and efficacy

The overall conclusion of the scientific assessment - whether the change has, or has not, materially altered product quality, safety, or efficacy - is the single determinant that ultimately justifies the chosen regulatory pathway under frameworks such as 21 CFR 314.70 [4], and the decision to release post-change product to patients [3].

8. CHANGE CONTROL WITHIN PRODUCT LIFECYCLE MANAGEMENT

8.1 Change control as a continuous lifecycle activity

Change control is not a single, one-time gate but rather a continuous activity that recurs, in some form, throughout the commercial life of a pharmaceutical product - from initial technology transfer through routine manufacturing to eventual discontinuation, the lifecycle view embedded in ICH Q12 [11] and reflected in the ongoing PQS obligations of ICH Q10 [1].

8.2 Integration with Pharmaceutical Quality System (PQS)

As established, change management is one of four core PQS elements defined in ICH Q10, functioning alongside process/product monitoring, CAPA, and management review as an integrated whole rather than as discrete procedures [1].

8.3 Relationship between change control, deviations and CAPA

Change control and CAPA are very closely related, yet distinct: a CAPA addresses an unplanned deviation or non-conformance that has already occurred, whereas change control governs a planned change, a distinction drawn directly from the PQS structure of ICH Q10 [1]. In practice, however, a CAPA investigation often concludes that a permanent process or specification change is required in order to prevent recurrence, at which point the CAPA output becomes the formal trigger for a new change-control record, illustrating the intended feedback loop between the two systems described in ICH Q10 [1].

8.4 Link with Annual Product Review/Product Quality Review

The Annual Product Review (APR) or Product Quality Review (PQR) in EU terminology provides a structured annual retrospective on a product's quality performance including a summary of all changes implemented during the review period and their outcomes, a review mechanism specified under ICH Q10 [1]. This creates a natural checkpoint at which the cumulative impact of multiple smaller changes

can be assessed collectively, which individual change-control assessments, considered individually under the ICH Q9(R1) framework, may not fully capture [3].

8.5 ICH Q12 and Established Conditions

Established Conditions, as defined in ICH Q12, are the legally binding elements of the approved dossier - specific process parameters, specifications, or analytical procedures - which require regulatory notification or approval prior to any changes [11]. Identifying which elements of the dossier are Established Conditions, and which represent supporting information that a robust PQS can internally manage, is the core analytical step that unlocks the reduced-reporting flexibilities ICH Q12 is designed to offer [11].

8.6 Post-Approval Change Management Protocols (PACMPs)

A PACMP is a regulatory tool that allows a manufacturer to get pre-approval agreement from a health authority on the specific tests, studies, and acceptance criteria that will be used in order to demonstrate the acceptability of a defined future change, prior to that change being implemented [11]. Industry analysis suggests that PACMP use can significantly shorten approval timelines -by around six months in some estimates -as the supporting evidence package has essentially already been pre-reviewed and agreed [7]. Despite this benefit, published survey evidence indicates that PACMP uptake, and ICH Q12 implementation more broadly, remains limited across ICH member and observer regulatory authorities several years after the guideline's adoption [6].

8.7 Continued Process Verification and lifecycle monitoring

CPV, functions as the primary lifecycle-monitoring mechanism after a change has been implemented, generating the ongoing statistical evidence needed to confirm sustained process control [1] and detect any drift that might warrant a further change or CAPA, a capability increasingly enhanced by digital process-monitoring tools [27].

8.8 Benefits of lifecycle-based change management

- Reduced regulatory burden for well-understood, low-risk changes managed within a demonstrated PQS, the intended outcome of the ICH Q12 Established Conditions framework [11].
- Faster implementation of supply-critical changes using pre-agreed PACMPs [11] and regulatory reliance mechanisms, both associated with measurable timeline reductions in industry analysis [26].
- Stronger linkage between prospective risk assessment and retrospective quality monitoring, closing the continuous-improvement loop described in ICH Q9(R1) [3].
- Improved resilience of the global supply chain through more predictable, harmonized change-approval timelines, as demonstrated by the reliance-pilot case study across 48 national regulatory authorities [26].

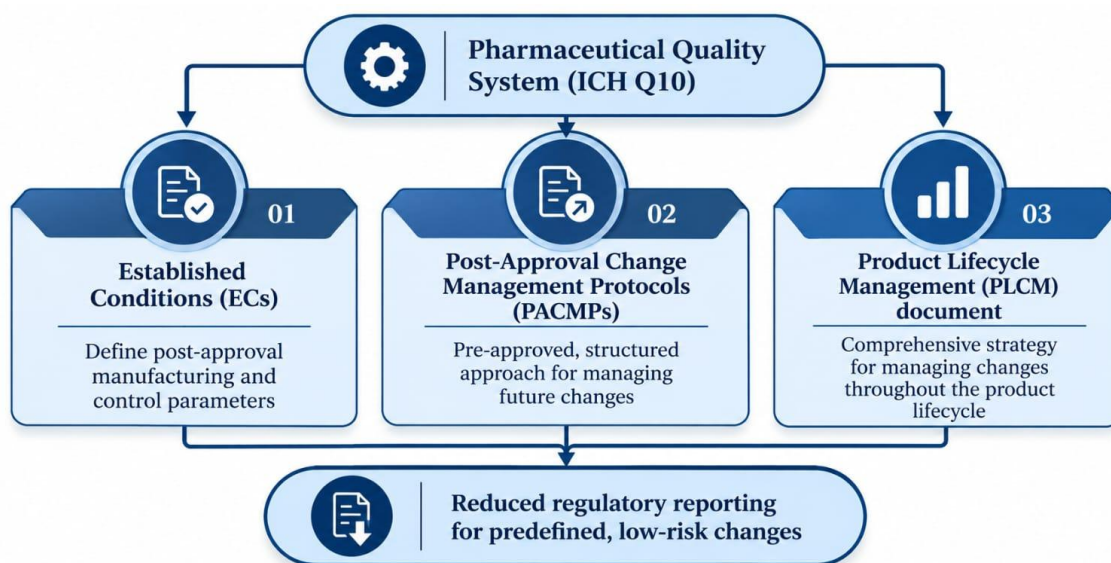


Figure 4: Relationship between the ICH Q12 lifecycle-management tools - Established Conditions, PACMPs, and the PLCM document -and the pharmaceutical quality system.

Key concept

Change Control → Risk Management → Regulatory Management → Continuous Monitoring → Product Lifecycle Improvement



Figure 5: Conceptual chain linking change control, through risk and regulatory management and continuous monitoring, to product lifecycle improvement.

Closing the Product X thread: lifecycle-monitoring outcome

After the approval and implementation of the API supplier change across all three markets, as described in Section 6, Product X enters the lifecycle-monitoring stage as per ICH Q12 lifecycle management framework [11]. At this stage, the continued process verification (CPV) is performed to ensure that the process capability comparable to the one demonstrated at the beginning of the process validation is still met. Assay, dissolution, and content-uniformity data from the first twelve commercial batches produced after the change are compared to the data obtained from the control group prior to the change using the process-control limits established during the original validation to assess the impact of the change on CQAs [1] as recommended by the CPV recommendations [1]. The change is reported to the APR as a successfully implemented dual-sourcing initiative within the allocated period of one year [1]. In addition, the comparability data package, risk-assessment report, and CPV trend data are kept for future reference. The information may become useful if there emerges a need for another API supplier and a corresponding change control investigation. By applying the lessons learned, the manufacturer can be prepared to implement a post-approval change management protocol (PACMP) in case the second API supplier becomes available in the future and would be introduced into the supply chain using the similar PACMP-based change control strategy [7].

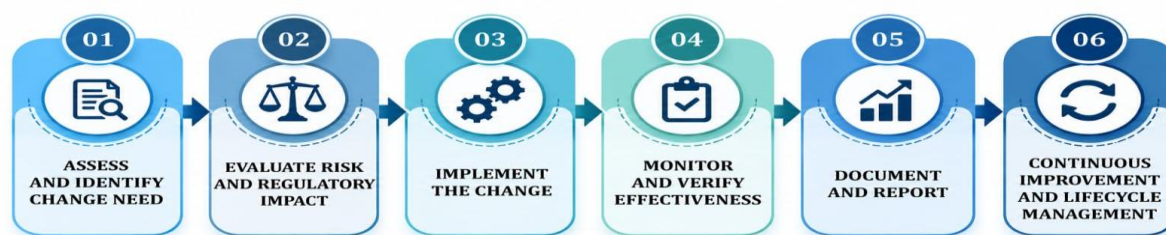


Figure 6: Product X worked example: progression of the API supplier changes from risk identification through lifecycle monitoring.

9. ILLUSTRATIVE CASE STUDIES

9.1 Manufacturing-site / equipment change

Trigger: A mid-sized generic manufacturer wishes to transfer commercial production of an established oral solid-dosage product from an ageing legacy facility to a newly qualified, larger-capacity site (governed by the FDA's SUPAC framework for site-related changes [8]) and replace existing high-shear granulation equipment with a continuous-manufacturing training during the course of the transfer.

Risk assessment: The cross-functional team identifies the site change as high risk in combination with the introduction of new continuous-manufacturing technology (a change in the established condition [11] under ICH Q12 in most jurisdictions), which represents a change from batch granulation to continuous processing that may affect blend uniformity, residence-time distribution, and downstream tablet compressibility (the CQAs identified per the ICH Q9(R1) risk-identification process [3]). FMEA scoring assigned high severity and moderate-to-high occurrence in the team's analysis of risk-related failure modes for the granulation-technology change (based on the fundamentally different process mechanism), consistent with the scoring convention reported in published hospital-pharmacy FMEA practice [24].

Validation / regulatory pathway: The change requires full process-performance qualification at the new site and revised Critical Process Parameter ranges per the continuous-manufacturing control strategy (a Prior Approval Supplement in the US due to the potential impact on product quality attributes [4], and Type II variation in the EU due to the change's nature as a manufacturing-site-plus-technology change [5]).

Outcome: Following successful process-performance qualification and three months of accelerated stability data demonstrating comparability, the change was approved under the Prior Approval Supplement pathway [4], and twelve months of continued process verification demonstrated higher overall process capability under the continuous-manufacturing control strategy compared with the historical batch process [28].

9.2 Analytical-method or formulation change

Trigger: A manufacturer wishes to replace a legacy high-performance liquid chromatography (HPLC) assay method for a drug substance with a new ultra-high-performance liquid chromatography (UHPLC) method offering shorter run times and improved resolution on a known degradation impurity (developed under the enhanced, science- and risk-based approach described in ICH Q14 [9]).

Risk assessment: Because the change involves an approved analytical procedure directly associated with a release specification (related substances), it was scored as moderate risk under the ICH Q9(R1) risk-evaluation framework [3]. The principal failure mode identified was a potential difference in impurity quantitation between the old and new methods (which could, in principle, mask or falsely flag

an out-of-specification result), a risk profile consistent with the FMEA failure-mode categories reported in published pharmacy practice [24].

Validation / regulatory pathway: The change requires full method validation under ICH Q2(R2) (specificity, accuracy, precision, and a formal method-comparison (bridging) study against the original HPLC method across a representative batch set [15]). Because the analytical-procedure change does not impact the finished-product specification, it was classified as a CBE-30 supplement in the US [4] and Type IB variation in the EU [21].

Outcome: The bridging study showed equivalent or improved impurity recognition with the UHPLC method (in line with the enhanced development approach described in ICH Q14 [9]) and the change had no negative impact on batch disposition; reduced analytical cycle times also contributed to improved overall batch-release turnaround.

Table 2: Comparative summary of the three illustrative change-control cases discussed in this review.

Case	Change	Main risk	Assessment	Regulatory pathway	Outcome
Case 1: Product X	API supplier addition	Dissolution / particle-size variability	FMEA (RPN-ranked)	CBE-30 (US) / Type IB (EU) / Category 2 (India)	Approved; no CQA shift on CPV monitoring
Case 2: Site/equipment	Site transfer + continuous granulation	Blend uniformity / process capability	FMEA + full PPQ	PAS (US) / Type II (EU)	Approved; improved process capability
Case 3: Analytical method	HPLC to UHPLC assay/impurity method	Impurity quantitation discrepancy	Bridging study (ICH Q2(R2)/Q14)	CBE-30 (US) / Type IB (EU)	Approved; equivalent/improved detection

10. CHALLENGES AND FUTURE DIRECTIONS

10.1 Global regulatory harmonization gaps

Despite nearly two decades of ICH quality-guideline development, published survey evidence indicates that formal ICH Q12 implementation is limited: a 2023 industry survey of nine ICH member and nineteen observer countries found that no responding regulatory authority considered ICH Q12 fully implemented, most of which described it as "in progress" or "not yet implemented" [6]. This lag between guideline publication and operational adoption arguably constitutes the single largest constraint on the efficiency gains the guideline itself was designed to deliver [11].

10.2 Differences in regulatory classification

Identical technical changes are being classified differently across jurisdictions because Established Conditions and the risk-tier thresholds aren't fully harmonized, a divergence directly documented in industry survey data [6]. This forces multinational manufacturers to have parallel, market-specific change-classification logic rather than a single global assessment, as the FDA [8], EU [5], and CDSCO [13] frameworks each apply their own thresholds.

10.3 Approval timelines and implementation delays

Industry-reported data analyzing more than 145,000 post-approval changes across 156 countries over a three-year period found approval timelines of three to five years were not uncommon for changes

requiring prior national regulatory approval [7]. These delays directly increase the risk of manufacturing-associated drug shortages, a risk ICH Q9(R1) explicitly asks manufacturers to weigh against the cost of the change itself [3].

10.4 Limited use of PACMPs

While PACMPs provide a mechanism to pre-agree study design and materially shorten review timelines, a benefit defined under ICH Q12 [11] and quantified in industry analysis [7], their uptake is moderate, reflecting both regulatory-authority capacity constraints and industry hesitancy to invest upfront effort in a protocol whose long-term regulatory acceptance across multiple markets may not always be guaranteed [6].

10.5 Digital change-control systems and AI-assisted risk assessment

Artificial intelligence and Internet-of-Things (IoT) sensor integration are proposed to enhance pharmaceutical manufacturing quality control, facilitating real-time analysis that could strengthen the occurrence and detection components of a change-related FMEA by replacing periodic sampling with continuous, sensor-based process data [28]. Machine-learning approaches have also been proposed to support quality-by-design frameworks by predicting critical quality attributes from critical process parameters [25], and natural-language-processing tools have been proposed to manage the substantial volume of regulatory documentation a change-control programme generates [29]. Applications of both remain largely at proof-of-concept or descriptive-review stage rather than validated regulatory practice [25].

10.6 Data-driven lifecycle management and Process Analytical Technology (PAT)

A shared industry-academic perspective published in 2025 on "Quality by Digital Design" (QbDD) describes an emerging framework that integrates digital twins, mechanistic and AI-based models, and Findable-Accessible-Interoperable-Reusable (FAIR) data practices across the CMC development lifecycle [27]. The authors argue that current challenges -- siloed data, limited predictive capability, and continued reliance on empirical, experience-based judgement -- can be addressed by model-driven experimental design and shared CMC ontologies [27]. This has implications for how future post-approval changes might be assessed using accumulated digital process knowledge rather than change-by-change empirical testing, an aspiration echoed in subsequent AI-focused manufacturing literature [25].

10.7 Advanced manufacturing technologies

Continuous manufacturing, and other advanced manufacturing technologies introduce opportunities and complexity for change control as they lie outside the discrete-batch decision trees of the original SUPAC guidance [8]. These technologies can reduce batch-to-batch variability and improve real-time release testing capability, beneficially described in the QbDD literature [27], but also require regulators and manufacturers to develop new risk-assessment paradigms suited to continuous rather than discrete-batch production, a gap ICH Q9(R1) leaves for product-specific risk assessment [3].

10.8 Regulatory reliance and convergence

Reliance pilots, in which one national regulatory authority's assessment is leveraged by others to accelerate their own review, have demonstrated meaningful timeline reductions in early

implementations [26]. A 2024 case study of a monoclonal-antibody post-approval variation piloted across 48 national regulatory authorities, using an EU assessment as a reference, targeted a 6.5-month global approval timeline for a supply-critical change, substantially faster than typical unilateral country-by-country review [26].

10.9 Outlook

- Predictive quality - increasing use of continued process verification [27] and AI-assisted trending [28] to anticipate, rather than just detect, the need for a future change.
- Greater international harmonization -- continued, if gradual, progress towards common Established Conditions and reporting-category definitions as ICH Q12 implementation matures across more regulatory authorities, an ambition survey data suggests is still years from being realized [6].
- Proactive change management -- a shift from change control as a reactive, compliance-driven gate towards change management as a proactive driver of continuous quality and supply-chain improvement, integrated with the broader digitalization agenda described across recent AI-in-manufacturing literature [25].

CONCLUSION

Post-approval changes represent, by their very nature, an inseparable and beneficial aspect of the pharmaceutical product life cycle, rather than a regulatory burden that should be minimized in any way. Thus, the review has covered in detail the basics of the change-control process, from the theoretical foundations of the change classification to the global regulatory considerations of the FDA, EU, and CDSCO. It has additionally explored the risk-based assessment of a proposed change within the ICH Q9(R1) framework, outlined the general workflow and multidisciplinary aspects of the change control process per ICH Q10, defined the key principles of the regulatory submission strategy for changes, discussed the scientific comparability assessment issue using the biosimilar cell-line example, and finally demonstrated how such changes could be incorporated into the framework of a lifecycle quality management system in accordance with ICH Q12. The Product X worked example demonstrated, concretely, how a single API supplier change moves from FMEA-based risk identification through jurisdiction-specific regulatory classification to sustained continued-process-verification monitoring, while the two additional case studies illustrated how the same underlying risk-based logic extends to a major manufacturing-site and equipment change and to an analytical-method change of narrower scope.

Together, the evidence synthesised in this review supports the conclusion that:

Effective Change Control + Scientific Risk Assessment + Appropriate Regulatory Strategy + Lifecycle Management

together support the four outcomes that ultimately justify the entire change-control discipline:

- Consistent pharmaceutical quality across the commercial life of a product, despite the many manufacturing and analytical changes that inevitably occur.
- Patient safety, ensured by ensuring that no modification reaches the market without documented evidence that critical quality attributes remain unaffected.
- Regulatory compliance, achieved by mapping the reporting pathway to the assessed risk in every jurisdiction where a product is registered.
- Uninterrupted product availability, supported by change-management systems that are efficient and predictable enough to prevent the change-approval process itself from becoming a source of drug shortage, the goal underlying recent reliance-based reforms piloted across 48 national regulatory authorities.

Persisting gaps in global harmonisation reflected in survey evidence that no responding regulatory authority has yet reported full ICH Q12 implementation together with the slow uptake of PACMPs and the still-evolving role of digital and AI-enabled quality systems represent the principal frontiers for further development of the discipline, and are likely to shape how pharmaceutical change control is practised over the upcoming decade.

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