

From Variation to Convergence: Evolution of Global Regulatory Pathways for Post-Approval CMC Changes and Their Impact on Pharmaceutical Lifecycle Management

Afra P¹, Hanna Asaraf², Fairoosa thaikkat³

^{1,2,3}M. Pharm Pharmaceutical Regulatory Affairs, Students of Al shifa College of Pharmacy, Kizhattur, Poonthavanam post, Perinthalmanna, Malappuram, Kerala - 69325

Abstract

Post-approval chemistry, manufacturing and controls (CMC) changes are an integral component of pharmaceutical product lifecycle management. Manufacturing sites, processes, analytical procedures, specifications, equipment, facilities and supply chains may require modification after marketing authorization to accommodate technological improvements, strengthen manufacturing robustness, respond to increased demand, address regulatory requirements, or maintain continuity of supply. However, the regulatory classification, documentation requirements, review procedures and implementation timelines for such changes remain heterogeneous across jurisdictions. This variability can increase regulatory workload and complicate simultaneous global implementation of manufacturing changes.

The International Council for Harmonisation (ICH) Q12 guideline introduced a structured framework intended to facilitate more predictable and efficient management of post-approval CMC changes. Its principal regulatory tools include risk-based categorization, Established Conditions (ECs), Post-Approval Change Management Protocols (PACMPs), the Product Lifecycle Management (PLCM) document and integration with the Pharmaceutical Quality System. Nevertheless, evidence from recent international surveys indicates that implementation of these tools remains uneven. Recent studies also demonstrate continuing differences in classification and review timelines among national regulatory authorities.

This review critically examines the evolution of post-approval CMC change management and compares regulatory approaches in the European Union, United States, Japan, United Kingdom, Canada and Australia, with additional consideration of World Health Organization (WHO) reliance principles. Particular attention is given to the revised European variations framework, implementation of ICH Q12, regulatory reliance, collaborative assessment and emerging digital approaches to CMC submissions. Published evidence indicates increasing adoption of risk-based approaches but incomplete global convergence. Recent reliance pilots demonstrate the potential to reduce duplicated assessment and improve predictability, while digital dossier initiatives suggest a possible transition toward common-core global submissions. The review proposes that future progress is more likely to result from practical convergence, reliance and structured information exchange than from complete uniformity of national regulatory systems.

Keywords: Post-approval changes; CMC; ICH Q12; regulatory convergence; regulatory reliance; lifecycle management; PACMP; Established Conditions; pharmaceutical regulation; variations.

1. Introduction

The approval of a medicinal product does not represent the end of its pharmaceutical development or manufacturing lifecycle. Following authorization, manufacturers routinely modify processes, analytical methods, manufacturing sites, equipment, facilities, specifications and other elements of the Chemistry, Manufacturing and Controls (CMC) information. Such changes may be introduced to improve process robustness, increase manufacturing capacity, incorporate technological advances, respond to supply requirements, improve analytical controls, comply with evolving regulatory expectations or maintain the continued availability of a product. Consequently, post-approval change (PAC) management represents a substantial component of pharmaceutical Regulatory Affairs and lifecycle management.

The regulatory challenge arises because a manufacturing change must be scientifically assessed while also being communicated to regulatory authorities according to the applicable national framework. Although the underlying scientific principles used to evaluate quality risk are broadly shared, national regulatory systems differ in terminology, classification categories, submission requirements, review procedures and implementation mechanisms. This creates additional complexity for products manufactured and marketed across multiple jurisdictions.

The development of risk-based post-approval change systems has therefore been closely associated with the broader evolution of pharmaceutical quality regulation. Earlier frameworks often relied on relatively prescriptive change categories and reporting requirements. Subsequent regulatory initiatives increasingly incorporated product and process knowledge, risk management and pharmaceutical quality systems. ICH Q8, Q9, Q10 and Q11 established important scientific and quality foundations, while ICH Q12 specifically addressed technical and regulatory considerations for pharmaceutical product lifecycle management. [1] ICH Q12 was adopted as an ICH Step 4 guideline in 2019 and provides a framework intended to facilitate more predictable and efficient management of post-approval CMC changes. The guideline introduces or formalizes several regulatory tools, including risk-based categorization, Established Conditions (ECs), Post-Approval Change Management Protocols (PACMPs), the Product Lifecycle Management (PLCM) document and structured approaches for frequent CMC changes. [1,2]

Despite this international framework, implementation has not been uniform. A 2023 global industry survey covering selected ICH members and observers found broader adoption of risk-based approaches but continuing gaps in implementation of Q12 tools, including PACMPs, Established Conditions and the PLCM document. The survey also identified long and unpredictable approval timelines as an important concern. [3]

The issue is particularly important in the context of global pharmaceutical supply chains. A single CMC change may require submissions to numerous national authorities. If jurisdictions classify the same change differently or require substantially different supporting information, the manufacturer may need to prepare multiple regulatory packages and manage sequential rather than coordinated approvals. Recent literature has associated such divergence with extended implementation timelines and potential supply-chain consequences. [3–6]

The European Union provides an important contemporary example of regulatory modernization. Commission Delegated Regulation (EU) 2024/1701 amended the EU variations framework, with the

revised regulation applying from 1 January 2025. The revised European Commission Variations Guidelines subsequently became applicable from 15 January 2026. [7,8]

At the same time, other jurisdictions are developing their own approaches. The US Food and Drug Administration (FDA) has long used risk-based reporting categories and has incorporated ICH Q12 into its regulatory framework. FDA guidance also provides for comparability protocols as prospective approaches for managing certain CMC changes. [9,10] Japan has incorporated PACMP mechanisms and continues to develop approaches associated with ICH Q12 implementation. [11] The UK maintains a variation system incorporating Type IA, Type IB and Type II categories, while also adapting its framework following changes in its relationship with the EU. [12,13] Canada and Australia likewise operate structured post-approval change systems, although their terminology and procedural categories differ. [14,15]

Against this background, the objective of this review is not simply to catalogue national requirements. Instead, it evaluates the extent to which international post-approval CMC systems are converging, identifies persistent areas of divergence and examines whether ICH Q12, reliance, collaborative assessment and digital regulatory approaches can provide practical mechanisms for reducing duplication while maintaining regulatory oversight.

2. Objectives

The objectives of this review were to:

1. Describe the evolution of regulatory approaches to post-approval CMC changes.
2. Examine the contribution of ICH Q12 to pharmaceutical lifecycle management.
3. Compare selected international regulatory frameworks for CMC post-approval changes.
4. Examine differences in classification, submission requirements and regulatory procedures.
5. Evaluate the implementation of Established Conditions, PACMPs and PLCM concepts.
6. Examine the emergence of regulatory reliance and collaborative assessment for PACs.
7. Assess the relationship between regulatory convergence and supply continuity.
8. Examine emerging digital approaches to global CMC/PAC submissions.
9. Identify current gaps and future opportunities for greater regulatory convergence.

3. Methodology of Literature Review

3.1 Review design

A structured narrative review approach was adopted to integrate peer-reviewed literature with primary regulatory documents. Because post-approval change management is governed substantially by national legislation, regulatory guidelines and administrative procedures, official regulatory sources were considered essential alongside peer-reviewed scientific literature.

The review methodology and source hierarchy were designed according to the framework specified for this review, which prioritizes peer-reviewed literature indexed in major bibliographic databases and primary regulatory documents from competent authorities.

3.2 Literature databases and information sources

The literature search focused on:

- PubMed/MEDLINE
- Scopus
- Web of Science

- ScienceDirect
- SpringerLink
- Wiley Online Library
- Google Scholar as a supplementary discovery source

Primary regulatory sources were retrieved from:

- International Council for Harmonisation (ICH)
- European Commission
- European Medicines Agency (EMA)
- US Food and Drug Administration (FDA)
- Pharmaceuticals and Medical Devices Agency (PMDA)
- UK Medicines and Healthcare products Regulatory Agency (MHRA)
- Health Canada
- Therapeutic Goods Administration (TGA)
- World Health Organization (WHO)

3.3 Search strategy

Representative search terms included:

- “post-approval change” AND pharmaceutical
- “CMC post-approval changes” AND regulatory
- “ICH Q12” AND lifecycle management
- “post-approval change management protocol”
- “Established Conditions” AND pharmaceutical
- “regulatory reliance” AND post-approval changes
- “regulatory convergence” AND pharmaceutical
- “CMC change” AND EU AND US
- “variations” AND post-approval pharmaceutical
- “digital CMC dossier” AND regulatory

The search emphasized literature published between January 2019 and September 2026, while older publications were retained when necessary to describe historical development or foundational regulatory approaches.

3.4 Inclusion criteria

Sources were included when they:

- addressed pharmaceutical post-approval CMC changes;
- discussed regulatory classification or submission procedures;
- examined ICH Q12 or lifecycle management;
- evaluated regulatory reliance or convergence;
- reported empirical data on PAC review or approval;
- described regulatory implementation or case studies;
- were published by a recognized regulatory authority or peer-reviewed journal.

3.5 Exclusion criteria

Sources were excluded when they:

- addressed non-pharmaceutical regulatory topics;
- provided unsupported opinions without identifiable evidence;
- were duplicate publications;

- were commercial promotional material;
- could not be adequately verified;
- provided insufficient information to establish the regulatory claim being made.

3.6 Evidence synthesis

Evidence was synthesized thematically under five principal domains:

1. evolution of PAC regulation;
2. ICH Q12 lifecycle-management tools;
3. international regulatory comparison;
4. convergence, reliance and supply continuity;
5. digitalization and future regulatory models.

Regulatory requirements were preferentially interpreted from primary authority documents rather than secondary commentary.

4. Evolution of Post-Approval CMC Change Management

4.1 From prescriptive reporting to risk-based management

Post-approval regulatory systems have progressively moved from prescriptive reporting toward risk-based approaches. Earlier systems frequently differentiated changes according to predetermined categories and required specified levels of regulatory notification or approval.

The US experience provides an important example. FDA's SUPAC guidance framework established specific expectations for changes involving formulation, manufacturing process, manufacturing site and scale for selected dosage forms. [16,17] FDA subsequently developed broader approaches to CMC post-approval manufacturing changes and reporting categories. [9]

The scientific basis for risk-based management was strengthened by ICH quality guidelines. ICH Q8 introduced Quality by Design principles; ICH Q9 established quality risk-management principles; ICH Q10 provided a pharmaceutical quality-system framework; and ICH Q11 addressed development and manufacture of drug substances. ICH Q12 subsequently extended these concepts into the commercial lifecycle. [1,18–21]

The resulting regulatory philosophy can be represented as:

Product knowledge → risk assessment → defined controls → appropriate reporting category → efficient regulatory oversight

This represents an important conceptual change. The objective is not to eliminate regulatory oversight, but to focus regulatory interaction on changes that are relevant to product quality, safety and efficacy.

5. ICH Q12 and Pharmaceutical Product Lifecycle Management

5.1 Purpose and scope of ICH Q12

ICH Q12 was developed to facilitate management of post-approval CMC changes in a more predictable and efficient manner. The guideline recognizes that effective lifecycle management depends on accumulated product and process knowledge, an effective Pharmaceutical Quality System and an appropriate understanding of which elements of the approved control strategy require regulatory communication. [1,2]

The major Q12 regulatory tools are:

- Categorization of post-approval CMC changes
- Established Conditions

- Post-Approval Change Management Protocols
- Product Lifecycle Management document
- Pharmaceutical Quality System and change management
- structured approaches for frequent CMC changes
- science- and risk-based approaches to stability data

These tools are intended to function as an integrated lifecycle-management system rather than as isolated regulatory mechanisms.

5.2 Established Conditions

Established Conditions (ECs) are elements of the product and manufacturing information that are considered necessary to assure product quality and therefore require regulatory communication when changed. Information that is supportive but does not constitute an Established Condition may be managed within the pharmaceutical quality system without necessarily requiring a regulatory submission.

The significance of ECs lies in their ability to establish a clearer boundary between information requiring regulatory oversight and information that can be managed through the pharmaceutical quality system. [1,2]

Recent literature suggests that implementation of ECs remains incomplete despite their potential to facilitate lifecycle flexibility. A survey examining implementation in the US, EU and Japan reported that Q12 adoption remained heterogeneous and identified challenges associated with establishing ECs and PLCM documentation. [22]

5.3 Post-Approval Change Management Protocol

A PACMP is a prospective agreement between the marketing authorization holder and the regulatory authority concerning the planned management of a future CMC change. It can specify the change, studies required to evaluate the change, acceptance criteria and the regulatory pathway that will apply if the predefined conditions are satisfied.

The primary benefit of a PACMP is predictability. Instead of determining all regulatory expectations only after a change has been developed, the sponsor and authority establish an agreed framework in advance. EMA's revised PACMP Q&A became legally effective in the EU from 15 January 2026, illustrating the continuing development of this regulatory tool. [23]

Japan has also incorporated PACMP mechanisms. PMDA describes PACMP as a framework in which the assessment approach and criteria for a manufacturing change are agreed in advance, allowing a subsequent change procedure when predetermined results are obtained. [11]

5.4 Product Lifecycle Management document

The PLCM document provides a consolidated representation of Established Conditions and associated reporting categories throughout the commercial lifecycle. It is intended to improve transparency regarding how a product is expected to be managed after approval.

In practice, however, adoption of the PLCM concept has been less extensive than the theoretical scope of ICH Q12. The 2023 global industry survey reported continuing gaps in the implementation of Q12 tools. [3]

5.5 Pharmaceutical Quality System

ICH Q12 does not operate independently of ICH Q10. A robust Pharmaceutical Quality System is essential because many lifecycle changes must be scientifically assessed, documented, implemented and monitored through the company's internal change-management system.

The regulatory significance of Q12 therefore depends on the maturity of both the external regulatory framework and the internal pharmaceutical quality system.

5.6 Relationship with ICH Q8, Q9, Q10 and Q11

ICH Q12 can be viewed as the commercial-lifecycle extension of the ICH quality framework:

ICH Q8 → product/process understanding

ICH Q9 → risk management

ICH Q10 → pharmaceutical quality system

ICH Q11 → drug-substance development and manufacturing

ICH Q12 → post-approval lifecycle management

This relationship is important because effective post-approval flexibility depends on the availability of scientific knowledge generated during development.

6. Comparative Global Regulatory Frameworks

6.1 European Union

The EU variations system provides a structured framework for managing changes to marketing authorizations. Traditionally, variations were categorized principally as Type IA, Type IB and Type II, with extensions representing changes requiring a different authorization pathway.

The EU framework underwent significant revision through Commission Delegated Regulation (EU) 2024/1701. The European Commission published the amended regulation in June 2024, and the revised regulation became applicable from 1 January 2025. [7]

The revised Variations Guidelines became applicable from 15 January 2026. EMA states that a single cut-off date was established for application of the new guidelines, while marketing authorization holders were expected to continue using the previous guidelines until that date. [8]

The significance of the revised framework extends beyond reclassification. It represents an attempt to modernize lifecycle management by improving flexibility, clarifying classification and aligning regulatory procedures with contemporary manufacturing and quality-management practices.

A notable practical development is the continuing use and refinement of Type IA annual-update procedures. Under the revised framework, certain Type IA changes are bundled into annual updates rather than being individually submitted immediately, while defined exceptions remain applicable. The detailed procedural requirements should be interpreted from the current Variations Guidelines rather than older classification tables.

6.2 United States

The US regulatory framework uses reporting categories linked to the potential effect of a change on product quality. FDA has developed specific guidance for different categories of CMC changes, including manufacturing changes documented in annual reports and comparability protocols.

FDA's 2022 guidance on comparability protocols describes a prospectively written plan for assessing the effects of a proposed CMC post-approval change on product identity, strength, quality, purity and potency. [10]

The US implementation of ICH Q12 provides a framework intended to improve predictability and efficiency in post-approval CMC change management. [9]

An important observation is that the US system does not simply replicate the EU variation terminology. Therefore, a global regulatory strategy cannot assume that an EU classification can be transferred directly to the FDA system.

6.3 Japan

Japan manages post-approval manufacturing changes through mechanisms including partial change approval and minor-change notification. PMDA's regulatory materials also describe PACMP implementation and associated GMP inspection mechanisms.

PMDA reports that PACMP-related GMP confirmation was introduced in August 2021 as part of efforts toward international consistency. [11]

Japan is therefore an important example of a jurisdiction where ICH Q12 concepts have been incorporated into an existing national regulatory structure rather than simply replacing the national system.

6.4 United Kingdom

The UK variation system uses Type IA, Type IB and Type II classifications for minor and major variations. MHRA guidance describes Type IA changes as changes with little or no impact on quality, safety or efficacy, while Type II changes are more complex and require approval before implementation. [12,13]

The UK framework has undergone additional complexity because of post-Brexit regulatory arrangements. MHRA guidance indicates that the revised EU Variations Regulation 2024/1701 was implemented in UK law and became applicable from 1 January 2025, with new variation guidance applying from 15 January 2026 in the relevant UK pathways. [13]

This illustrates how regulatory convergence can coexist with jurisdiction-specific legal implementation.

6.5 Canada

Health Canada uses post-Notice of Compliance change procedures. Its framework differentiates changes according to their regulatory significance and associated data requirements.

Importantly, Health Canada's May 2026 update for biologic and Schedule C products explicitly introduced ICH Q12 into the framework and introduced a Level III immediate-notification category. [14]

This recent development illustrates that ICH Q12 implementation continues to evolve even after publication of the original guideline.

6.6 Australia

The Therapeutic Goods Administration uses a variation framework for prescription medicines that includes notifications, self-assessable requests and applications requiring evaluation. Its guidance differentiates quality changes from changes requiring clinical or bioequivalence assessment. [15]

Australia therefore demonstrates another model in which the risk and nature of the change determine the regulatory pathway, although the terminology does not exactly mirror the EU system.

7. Comparative Analysis of Global PAC Systems

Table 1. High-level comparison of post-approval CMC change frameworks

Jurisdiction	Regulatory authority	General approach	Key PAC mechanisms	Distinctive feature
EU	EC/EMA/National authorities	Risk-based variations	Type IA, IB, II; grouping; annual updates; PACMP	Revised variations framework applicable from 2025/2026
US	FDA	Risk-based reporting	Annual report, CBE supplements, prior	Extensive product/change

			approval mechanisms, comparability protocols	-specific guidance
Japan	MHLW/PMDA	Partial change/minor change framework	Partial change approval, minor-change notification, PACMP	PACMP incorporated into national system
UK	MHRA	Variation-based	Type IA, IB, II	National framework influenced by EU-derived classifications
Canada	Health Canada	Risk-based post-NOC framework	Supplements/notifications and Q12-related mechanisms	Recent Q12 implementation for biologics
Australia	TGA	Notification/application categories	Notifications, self-assessable requests, evaluated variations	Separate pathways based on data requirements

The comparison demonstrates that the major regulatory systems share a fundamental principle: the greater the potential effect of a change on product quality, safety or efficacy, the greater the degree of regulatory oversight required. However, the operationalization of this principle differs among jurisdictions. Therefore, **conceptual convergence is greater than procedural convergence**

8. Regulatory Convergence and Divergence

8.1 Classification differences

One of the most persistent barriers to global PAC management is that the same scientific change may not receive the same regulatory classification in every jurisdiction.

A global industry survey conducted in 2023 compared four representative CMC changes across multiple countries and found differences between national classifications and reference classifications based on EU/WHO approaches. The divergence was particularly evident among ICH observer countries. [3]

A separate analysis of regulatory classification approaches reported divergence between Latin American countries and reference systems in Europe and the US, emphasizing the operational implications of classification differences. [24]

The consequence is not necessarily that one classification system is scientifically superior. Rather, different national frameworks may assign different levels of regulatory oversight to the same technical change.

8.2 Differences in data requirements

Differences can also occur in the type and extent of supporting data required.

For example, a change may require:

- stability data;
- analytical comparability;
- process validation;
- impurity assessment;

- dissolution data;
- bioequivalence information;
- characterization data;
- updated specifications;
- manufacturing-process information.

The amount of data required depends on both the scientific risk and the regulatory pathway.

Recent work on science- and risk-based stability strategies demonstrates how accumulated product knowledge can be used to support CMC changes and potentially reduce unnecessary stability commitments when scientifically justified. [25]

8.3 Review timelines

Review timelines represent another area of divergence.

A 2026 analysis of CMC PAC review and approval trends from 2018–2024 reported a general improvement in approval times after 2019 but continuing inconsistencies in classification and procedural processes among countries. The authors emphasized the need for greater harmonization and application of WHO reliance principles. [26]

This finding is important because harmonized classification alone would not necessarily guarantee rapid implementation. Regulatory capacity, dossier quality, questions raised during assessment, national legal requirements and administrative procedures can all influence the final timeline.

9. Regulatory Reliance and Collaborative Assessment

9.1 Concept of reliance

Regulatory reliance refers broadly to a regulatory authority taking into account the assessment or regulatory output of another trusted authority while retaining responsibility for its own regulatory decision. WHO's Good Reliance Practices framework promotes reliance as a means of using existing regulatory expertise more efficiently while maintaining national regulatory responsibility. [27]

For post-approval changes, reliance is particularly attractive because a single CMC change may otherwise undergo essentially similar scientific assessments in numerous countries.

9.2 Reliance for CMC post-approval changes

The practical potential of reliance has been demonstrated through industry-regulator pilots.

A 2024 publication described a Roche-led reliance pilot involving 48 national regulatory authorities for a supply-critical CMC change. The pilot sought to use an EMA assessment as a reference and promote convergence through shared documentation and assessment information. [28]

Another pilot involving a vaccine included 21 national regulatory authorities. The objective was to apply reliance principles to achieve a maximum six-month approval target following reference-authority approval. [29]

The subsequent published results demonstrated that reliance was feasible, although the six-month target was not achieved by every participating authority. Among 21 participating authorities, 55% completed review within six months, 95% had approved within ten months, and all participating countries had approved by 16 months. [30]

These findings are important because they show that reliance should not be interpreted as automatic mutual recognition. Instead, it is a mechanism for reducing duplicated assessment while allowing national authorities to retain decision-making responsibility.

9.3 Barriers to reliance

Potential barriers include:

- differences in legal authority;
- confidentiality restrictions;
- different submission requirements;
- differences in national labeling or administrative requirements;
- trust between authorities;
- regulatory capacity;
- differing assessment standards;
- language and documentation requirements;
- differences in implementation expectations.

Consequently, reliance is likely to be most effective when supported by common technical documentation and transparent communication between authorities.

10. Digitalization of Post-Approval Change Management

10.1 From electronic submissions to structured regulatory information

Electronic Common Technical Document (eCTD) submissions have substantially improved the transmission and management of regulatory dossiers. However, traditional electronic submissions still require significant manual document preparation and country-specific adaptation.

The next stage of regulatory digitalization is therefore moving toward structured CMC information, reusable regulatory content, automated document generation and common-core dossiers.

10.2 Digital CMC dossiers

A notable 2026 publication described a pilot involving digitally generated CMC post-approval dossiers submitted simultaneously to global regulators. The initiative involved 37 target national authorities, of which 27 agreed to participate; 26 used a third-party collaboration platform. Among participating authorities, 85% achieved approval within nine months, compared with approximately 36 months reported for comparable conventional processes. [31]

These results are promising, but they should be interpreted cautiously. The study describes a pilot rather than a universally validated regulatory model. The participating authorities, type of change, collaboration mechanism and operational context may differ from routine PAC submissions.

10.3 Potential role of artificial intelligence

Artificial intelligence may eventually support:

- regulatory intelligence;
- classification assessment;
- identification of country-specific requirements;
- comparison of regulatory guidelines;
- dossier content reuse;
- document consistency checks;
- submission tracking;
- deficiency-response management.

However, AI-assisted regulatory processes require validated systems, human oversight, data governance and clear accountability. AI should therefore be viewed as a potential enabling technology rather than as a replacement for regulatory judgment.

11. Evidence-Based Case Studies

Case Study 1: ICH Q12 implementation gap

The 2023 global industry survey provides an important example of the difference between international guideline publication and actual implementation.

The survey included selected ICH members and observers and examined Q12 implementation, PAC categorization, timelines and reliance. Although risk-based categorization had expanded, implementation of PACMPs and other Q12 tools remained limited. [3]

Regulatory significance

The case demonstrates that publication of a harmonized guideline does not automatically produce harmonized national implementation. Supporting legal frameworks, regulatory procedures and industry capability are required.

Case Study 2: Reliance for a supply-critical monoclonal antibody change

Roche reported a reliance pilot involving 48 national regulatory authorities for a supply-critical manufacturing change to a monoclonal antibody. The pilot used an EMA assessment as a reference and sought to promote regulatory convergence through common documentation and information exchange. [28]

Regulatory significance:

This approach demonstrates how reliance may reduce repeated assessment and facilitate simultaneous or closely coordinated implementation of important manufacturing changes.

Case Study 3: Vaccine CMC reliance pilot

A Sanofi-led pilot applied reliance principles to a CMC post-approval change for a vaccine involving 21 national regulatory authorities. The subsequent results showed that 55% of authorities completed assessment within six months, 95% had approved within ten months and all participating authorities had approved within 16 months. [29,30]

Regulatory significance:

The pilot demonstrates that reliance can be operationally feasible but also shows that a common reference assessment does not necessarily eliminate differences in national review timelines.

Case Study 4: Multi-product PACMP

A 2025 case study described the application of a multi-product PACMP for a large-molecule manufacturing change involving five globally approved products. The authors reported that application of ICH Q12 principles, together with statistical stability analysis and reliance, facilitated implementation of an aseptic filling-line change seven months earlier than would otherwise have occurred. [32]

Regulatory significance:

The example illustrates the potential value of prospective change planning when a manufacturing change affects multiple products and markets.

Case Study 5: Digital global PAC dossier

A 2026 pilot explored digital authoring, cloud collaboration and a common-core CMC dossier for simultaneous global regulatory submissions. The project reported participation by 27 national authorities and substantially shorter approval timelines than those historically associated with conventional processes. [31]

Regulatory significance:

The case suggests that regulatory convergence and digitalization may reinforce one another: a common-core dossier is easier to manage when authorities accept common technical content and rely on shared assessments.

12. Critical Discussion

The evidence reviewed in this article suggests that global post-approval CMC regulation is moving toward convergence, but convergence should not be interpreted as complete harmonization.

The first level of convergence is **conceptual**. Major regulatory systems increasingly recognize that CMC changes should be assessed according to their potential impact on product quality, safety and efficacy. Risk-based categorization is therefore common across the major jurisdictions.

The second level is **technical**. ICH Q12 provides common concepts such as Established Conditions and PACMPs. These concepts create a shared regulatory vocabulary and potentially allow similar scientific approaches to be used across countries.

The third level is **procedural**, and this is where divergence remains substantial. National authorities retain different legal structures, reporting categories, review procedures and administrative requirements. The 2023 industry survey and more recent analyses indicate that differences remain even among countries participating in or observing ICH activities. [3,26]

The fourth level is **operational convergence**, which may be more achievable through reliance than through complete regulatory harmonization.

A key implication is that regulatory convergence should not necessarily seek to create one universal classification system. Instead, a more realistic model may involve:

Common scientific principles + common technical documentation + reliance + national decision-making

Such a model would preserve regulatory sovereignty while reducing repeated scientific assessment.

Another important observation concerns the relationship between regulatory efficiency and supply continuity. PACs are not merely administrative activities. Manufacturing changes may be required to increase capacity, address manufacturing constraints, introduce improved technologies or maintain supply. Consequently, lengthy regulatory implementation can delay the operational benefits of a technically justified manufacturing change.

The 2026 global review of CMC PAC timelines reported improvement in approval times after 2019 but continuing variability among authorities. [26] This indicates that progress has occurred, but that harmonization of classification and procedure remains incomplete.

The implementation of ICH Q12 also appears to be gradual. A recent survey of Established Conditions implementation in the US, EU and Japan reported continuing differences in the adoption of ECs and PLCM concepts. [22] This suggests that the benefits of Q12 depend not only on regulatory endorsement but also on industry experience, regulatory familiarity and integration with existing national systems.

Reliance offers a particularly practical solution. The reported vaccine and monoclonal antibody pilots demonstrate that regulatory authorities can use the work of a reference authority while maintaining national regulatory responsibility. [28–30] The approach may be especially valuable for supply-critical changes, where prolonged sequential approvals could affect product availability.

Digitalization represents a further opportunity. The 2026 digital PAC pilot demonstrates the potential of common-core dossiers and collaborative platforms to reduce administrative duplication. [31] However,

broader adoption will require common data standards, regulatory acceptance, secure information exchange and clearly defined responsibilities.

Taken together, these findings support a model in which future PAC management develops along four parallel pathways:

1. **scientific convergence** through risk-based assessment;
2. **regulatory convergence** through common terminology and technical expectations;
3. **procedural convergence** through reliance and work-sharing;
4. **digital convergence** through structured and reusable regulatory information.

13. Future Perspectives

13.1 Expansion of reliance

Reliance is likely to remain one of the most practical mechanisms for reducing duplication in global PAC assessment. Its expansion will depend on greater trust, transparent assessment reports and clear regulatory procedures.

13.2 Wider implementation of ICH Q12

The future value of Q12 will depend on implementation rather than publication alone. Regulatory authorities may increasingly need to incorporate Q12 concepts into national legislation, guidance and submission systems.

13.3 Structured CMC information

The transition from document-centric submissions toward structured CMC information could enable the same scientific content to be reused across multiple regulatory submissions while allowing country-specific information to remain separately controlled.

13.4 Digital and AI-supported Regulatory Affairs

AI-supported regulatory intelligence could help identify differences in classification and data requirements before a global PAC submission is prepared. However, human review will remain essential for regulatory interpretation and decision-making.

13.5 Supply-critical PAC pathways

Regulatory authorities may increasingly distinguish supply-critical changes from routine changes and provide accelerated or reliance-based mechanisms when delays could contribute to shortages.

13.6 Practical convergence rather than complete harmonization

Complete harmonization of national legal systems may be difficult. A more achievable goal is practical convergence based on:

risk-based science + common technical principles + reliance + transparency + digital information exchange.

14. Conclusion

Post-approval CMC change management has evolved from predominantly prescriptive reporting systems toward increasingly risk-based and lifecycle-oriented regulatory frameworks. ICH Q12 represents a major milestone in this evolution by establishing a common framework for categorization of post-approval changes, Established Conditions, PACMPs, PLCM documentation and integration with the Pharmaceutical Quality System.

However, the evidence indicates that publication of an international guideline has not resulted in complete global regulatory convergence. Significant differences remain in classification, data requirements, review

procedures and implementation timelines. These differences can increase regulatory workload and complicate simultaneous global implementation of CMC changes.

Recent developments provide evidence of a possible alternative pathway. Regulatory reliance pilots have demonstrated the feasibility of sharing assessment outcomes among multiple national authorities, while digital PAC initiatives suggest that common-core dossiers and collaborative regulatory platforms may further reduce administrative duplication.

The future of global PAC management is therefore unlikely to depend exclusively on establishing identical national regulatory systems. Instead, meaningful progress may arise from the combination of harmonized scientific principles, wider implementation of ICH Q12, regulatory reliance, collaborative assessment and structured digital regulatory information.

For pharmaceutical manufacturers, this transition could support more predictable global lifecycle management. For regulatory authorities, it offers an opportunity to concentrate scientific resources on changes requiring substantive national assessment. Ultimately, a more coordinated PAC ecosystem has the potential to support continuous pharmaceutical manufacturing improvement while maintaining appropriate regulatory oversight and contributing to reliable medicine supply

References

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH harmonised guideline Q12: Technical and regulatory considerations for pharmaceutical product lifecycle management. Geneva: ICH; 2019.
2. European Medicines Agency. ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management. EMA/CHMP/ICH/804273/2017. Amsterdam: EMA; 2020.
3. A Global Industry Survey on Post-Approval Change Management and Use of Reliance. *Ther Innov Regul Sci*. 2024;58(6):997–1005. doi:10.1007/s43441-024-00681-y.
4. Mangia F, Lin YM, Armando J, et al. Unleashing the Power of Reliance for Post-Approval Changes: A Journey with 48 National Regulatory Authorities. *Ther Innov Regul Sci*. 2024;58(6):997–1005. doi:10.1007/s43441-024-00677-8.
5. Gastineau T, Ban C, Basso A, et al. Worldwide Regulatory Reliance: Launching a Pilot on a Chemistry, Manufacturing, and Control Post Approval Change for a Vaccine. *PDA J Pharm Sci Technol*. 2024;78(4):388–398. doi:10.5731/pdajpst.2023.012850.
6. Kacimi K, Dave SK, Roberts S. Global health authorities review and approval trends for CMC post approval changes 2018–2024. *PDA J Pharm Sci Technol*. 2026. doi:10.5731/pdajpst.2025-000081.1.
7. European Commission. Commission Delegated Regulation (EU) 2024/1701 of 11 March 2024 amending Regulation (EC) No 1234/2008 as regards the examination of variations to the terms of marketing authorisations for medicinal products for human use. *Official Journal of the European Union*; 2024.
8. European Medicines Agency. Guidance on the application of the revised variations framework. Amsterdam: EMA. Updated 2025/2026.
9. US Food and Drug Administration. Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management: Guidance for Industry. Silver Spring, MD: FDA; 2021.

10. US Food and Drug Administration. Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA: Guidance for Industry. Silver Spring, MD: FDA; 2022.
11. Pharmaceuticals and Medical Devices Agency. ICH Q12 Working Group and regulatory information on post-approval change management. Tokyo: PMDA.
12. Medicines and Healthcare products Regulatory Agency. Variations to marketing authorisations (MAs). GOV.UK. Updated 2025.
13. Medicines and Healthcare products Regulatory Agency. Medicines: apply for a variation to your marketing authorisation. GOV.UK. Updated September 2026.
14. Health Canada. Guidance on post-notice of compliance changes: Overall quality document for biologic and Schedule C drugs for human use. Ottawa: Health Canada; 2026.
15. Therapeutic Goods Administration. Variations to prescription medicines: excluding variations requiring evaluation of clinical or bioequivalence data. Canberra: TGA; updated 2024.
16. US Food and Drug Administration. SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes. Silver Spring, MD: FDA.
17. US Food and Drug Administration. SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes. Silver Spring, MD: FDA.
18. International Council for Harmonisation. ICH Q8(R2): Pharmaceutical Development. Geneva: ICH.
19. International Council for Harmonisation. ICH Q9: Quality Risk Management. Geneva: ICH.
20. International Council for Harmonisation. ICH Q10: Pharmaceutical Quality System. Geneva: ICH.
21. International Council for Harmonisation. ICH Q11: Development and Manufacture of Drug Substances. Geneva: ICH.
22. Implementation of Established Conditions and Use of Quality by Design Principles during Drug Development: Status in the US, EU, and Japan. Data from a Survey Conducted by the Japan Pharmaceutical Manufacturers Association (JPMA). *Ther Innov Regul Sci*. 2025.
23. European Medicines Agency. Questions and answers on post approval change management protocols (human). Revision 1; effective 15 January 2026.
24. A proposal of a combined convergence regulatory strategy applied to post-approval changes by Latin American countries, reducing workload and allowing continuous improvement to guarantee the quality, safety, and efficacy of medicines. *Front Med*. 2021;8:768376. doi:10.3389/fmed.2021.768376.
25. McCaig L, et al. Science- and Risk-Based Stability Strategies to Support Product Lifecycle Changes. *AAPS J*. 2024;26(2):34. doi:10.1208/s12248-024-00903-z.
26. Kacimi K, Dave SK, Roberts S. Global health authorities review and approval trends for CMC post approval changes 2018–2024. *PDA J Pharm Sci Technol*. 2026. doi:10.5731/pdajpst.2025-000081.1.
27. World Health Organization. Good reliance practices in the regulation of medical products: high-level principles and considerations. WHO Technical Report Series 1033, Annex 10/11. Geneva: WHO; 2021.
28. Mangia F, Lin YM, Armando J, et al. Unleashing the Power of Reliance for Post-Approval Changes: A Journey with 48 National Regulatory Authorities. *Ther Innov Regul Sci*. 2024;58(6):997–1005. doi:10.1007/s43441-024-00677-8.

29. Gastineau T, Ban C, Basso A, et al. Worldwide Regulatory Reliance: Launching a Pilot on a Chemistry, Manufacturing, and Control Post Approval Change for a Vaccine. *PDA J Pharm Sci Technol.* 2024;78(4):388–398. doi:10.5731/pdajpst.2023.012850.
30. Worldwide Regulatory Reliance: Results of an Executed Chemistry, Manufacturing, and Control Post-Approval Change Pilot. *PDA J Pharm Sci Technol.* 2025;79(3):295–?.
31. Pioneering the future: Delivering the first digitally generated CMC post-approval change dossier to global regulators simultaneously. 2026.
32. Dave SK, et al. Ensuring Medical Product Patient Access Through Application of Recently Improved Global Chemistry, Manufacturing and Control Regulatory Frameworks: A Case Study Utilizing a Multi-Product PACMP. *AAPS J.* 2025;27(6):151. doi:10.1208/s12248-025-01133-7.