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Implementation Science in the Pharmaceutical Industry: Why we Know which Innovations Work but Still Cannot Implement Them - A Comparative Review of the United States, the European Union, and International Regulatory Contexts

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Abstract

Even though there have been major scientific developments in the fields of pharmaceutical analytical chemistry, manufacturing science, and regulatory science over the last twenty years, the incorporation of validated innovations into routine industrial practice remains slow, irregular, and incomplete. Although Quality by Design (QbD), Process Analytical Technology (PAT), continuous manufacturing (CM), Real-Time Release Testing (RTRT), and artificial intelligence (AI) are backed by strong scientific bases and have clear regulatory routes, their adoption differs greatly from product to product, facility to facility, and region to region. This structured narrative review uses implementation science, a field that systematically examines methods for integrating evidence into everyday practice, to examine innovations in pharmaceutical analytical and manufacturing processes. The review brings together the regulatory environments in the United States (21 CFR Parts 210/211, the FDA Emerging Technology Program, Quality Management Maturity), in the European Union (EudraLex Volume 4, Annex 1 on sterile manufacturing, the reform of EU pharmaceutical legislation), and in international frameworks (ICH Q8–Q14, M7, Q3D; WHO GMP; PIC/S Annex 11). Based on the Consolidated Framework for Implementation Research (CFIR), the RE-AIM evaluation model, and the Expert Recommendations for Implementing Change (ERIC) compilation, the review links implementation strategies to the various domains of pharmaceutical innovation. It examines FDA drug shortage reporting, analyzes 1,766 FDA Warning Letters (from 2016 to 2023), examines biosimilar uptake, and reviews regulatory submissions for continuous manufacturing. The review concludes with an implementation science framework tailored to the pharmaceutical industry, an example KPI dashboard, and 12 evidence-based recommendations. The main point is that, for a number of well-established innovations, the ability to implement them is now the main barrier to their routine adoption.

Keywords: Implementation science; Quality by Design; Process Analytical Technology; Continuous manufacturing; ICH Q14; ICH Q13; FDA Emerging Technology Program; EU GMP Annex 1; Pharma 4.0; Knowledge translation; Regulatory science; Pharmaceutical quality system.

1. INTRODUCTION

Over the past few decades, there has been significant scientific progress in pharmaceutical analytical chemistry. Regulatory bodies have launched a number of major initiatives, such as the FDA's "Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach" (U.S. Food and Drug Administration, 2004b), the FDA's guidance on Process Analytical Technology (U.S. Food and Drug Administration, 2004a), and the ICH Quality series Q8 through Q14 (International Council for Harmonisation, 2008; International Council for Harmonisation, 2009; International Council for Harmonisation, 2012; International Council for Harmonisation, 2019; International Council for Harmonisation, 2022a; International Council for Harmonisation, 2023a; International Council for Harmonisation, 2023c). Additional advances have involved the adoption of modernized validation frameworks such as ICH Q2(R2) (International Council for Harmonisation, 2023d) and ICH Q14 (International Council for Harmonisation, 2023c), the updated impurity controls in ICH Q3D(R2) (International Council for Harmonisation, 2022b) and ICH M7(R2) (International Council for Harmonisation, 2023b), and the Harmonisation of continuous manufacturing as set out in ICH Q13 (International Council for Harmonisation, 2022a; U.S. Food and Drug Administration, 2023c). The European regulatory framework has backed these developments with Quality by Design assessment programs (European Medicines Agency, 2017; European Medicines Agency, 2024c), the revised EU Good Manufacturing Practice Annex 1 for sterile products (European Commission, 2023), and EudraLex Volume 4 Annex 11 on computerized systems (European Commission, 2011). Contributions to international Harmonisation have also come from the World Health Organization (World Health Organization, 2024) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (PIC/S, 2022). Nevertheless, the implementation of risk-based development, real-time process control, advanced analytics, model-informed decision-making, and continuous flow processing is still uneven among different product lines and manufacturing networks (Arden *et al*., 2021; Burcham *et al*., 2018; Fisher *et al*., 2022; Grangeia *et al*., 2020; Lee *et al*., 2015; Messina, 2025; National Academies of Sciences, Engineering, and Medicine, 2021; Wahlich, 2021; Yu & Kopcha, 2017; Yu *et al*., 2014).

This paradox is central to implementation science, a discipline that began in public health and clinical research to understand why evidence-based interventions often fail to achieve widespread adoption (Bauer *et al*., 2015; Eccles & Mittman, 2006; Nilsen, 2015). According to Eccles and Mittman (2006), implementation science is "the scientific study of methods designed to promote the systematic incorporation of research findings and other evidence-based practices into routine practice" (Eccles & Mittman, 2006). Despite progress having been made through the creation of frameworks such as the Consolidated Framework for Implementation Research (CFIR) (Damschroder *et al*., 2009; Damschroder *et al*., 2022), RE-AIM (Glasgow *et al*., 1999; Glasgow *et al*., 2019), and the Expert Recommendations for Implementing Change (ERIC) (Powell *et al*., 2015), its application in pharmaceutical development and manufacturing is still limited (Messina, 2025). As a result, the industry still holds a large amount of validated knowledge that is not consistently incorporated into everyday operations.

The impact of the discrepancy between knowledge and practice is significant. The estimated amount of capitalized research and development costs per new medicine varies widely, with commonly quoted figures ranging from about USD 1 billion to USD 2.6 billion (DiMasi *et al*., 2016; Mullard, 2014; Wouters *et al*., 2020). There has been a fall in pharmaceutical R&D productivity over many decades, a trend known as Eroom's Law (OECD, 2023; Scannell *et al*., 2012). Ongoing drug shortages are linked to weaknesses in manufacturing, quality, and the supply chains (U.S. Food and Drug Administration, 2019; U.S. Food and Drug Administration, 2025b). An examination of 1,766 FDA Warning Letters issued between 2016 and 2023 showed that there are still problems with data integrity within the ALCOA/ALCOA+ categories and that after 2020 there has been a greater emphasis on endurance, availability, and completeness, although a causal relationship was not proven (Park & Kwon, 2026; U.S. Food and Drug Administration, 2024g). These results underline the importance of having robust, predictive, and information-rich analytical and manufacturing control systems as well as the organizational abilities needed to maintain them (Alosert *et al*., 2022; Arden *et al*., 2021; Burcham *et al*., 2018; Fisher *et al*., 2022; Grangeia *et al*., 2020; Lee *et al*., 2015; Sovány *et al*., 2024; Wahlich, 2021; Wu *et al*., 2025; Yu & Kopcha, 2017; Yu *et al*., 2014; Yu *et al*., 2019).

The review examines how implementation science is applied to pharmaceutical analytical and manufacturing innovation in the United States, the European Union, and other international regulatory environments. It sets out four objectives. The first is to map out the current regulatory situation concerning Quality by Design (QbD), Process Analytical Technology (PAT), Real-Time Release Testing (RTRT), Continuous Manufacturing (CM), Artificial Intelligence/Machine Learning (AI/ML), and the ICH Q14 analytical procedure development. The second objective is to adapt the CFIR, RE-AIM, ERIC, and Knowledge-to-Action frameworks to the context of regulated pharmaceutical manufacturing. The third involves drawing together evidence from the FDA's Emerging Technology Program (U.S. Food and Drug Administration, 2024e), the FDA Drug Shortages Report to Congress (U.S. Food and Drug Administration, 2025b), the Quality Management Maturity program (U.S. Food and Drug Administration, 2022; U.S. Food

and Drug Administration, 2024c), the mutual-recognition frameworks (European Medicines Agency, 2024b; U.S. Food and Drug Administration, 2024f), peer-reviewed manufacturing studies (Arden *et al*., 2021; Burcham *et al*., 2018; Fisher *et al*., 2022; Grangeia *et al*., 2020; Lee *et al*., 2015; Niazi, 2025; Sovány *et al*., 2024; Wahlich, 2021; Wu *et al*., 2025), and institutional reports (National Academies of Sciences, Engineering, and Medicine, 2021). The fourth objective is to put forward twelve evidence-based recommendations, together with an illustrative KPI dashboard, to implement implementation science within pharmaceutical organizations.

The article is structured as follows: Section 1.1 describes the method used for the review. Section 2 defines implementation science and distinguishes it from related fields. Section 3 examines the regulatory environment in the United States, the European Union, and international frameworks. Section 4 investigates gaps between evidence and practice in analytical and manufacturing innovation. Section 5 lists the technical, regulatory, organizational, workforce, supply-chain, and economic barriers. Section 6 offers an implementation framework adapted for the pharmaceutical sector. Section 7 includes selected real-world evidence. Section 8 outlines the strategies and recommendations. Section 9 addresses AI/ML, digital transformation, and future implementation needs. Section 10 contains the concluding remarks.

1.1. Review Approach and Evidence Selection

The article is a structured narrative review rather than a systematic review or a meta-analysis. The evidence used includes peer-reviewed publications, primary regulatory and pharmacopeial documents, and reports issued by governmental, intergovernmental, academic, or professional organizations. It has excluded commercial vendor websites, general news articles, market-promotional reports, and trade publications. The selected sources were those most directly relevant to pharmaceutical implementation, analytical lifecycle management, manufacturing innovation, regulatory pathways, data integrity, quality systems, and established implementation science frameworks. Since the literature is highly varied and there is limited publicly available information on failed industry projects, no pooled adoption rates have been calculated, and no formal assessment of potential bias has been conducted.

2. DEFINING IMPLEMENTATION SCIENCE IN PHARMACEUTICAL INNOVATION

Although there is some overlap, implementation science is conceptually different from translational research, dissemination science, and quality improvement. While translational research focuses on translating biomedical innovations from laboratory discoveries to clinical application, implementation science examines how evidence-based interventions are incorporated into routine, ongoing, real-world practice (Bauer *et al*., 2015; Eccles & Mittman, 2006; Nilsen, 2015). Dissemination science examines the communication of knowledge, whereas implementation science focuses on the outcomes resulting from such dissemination (Graham *et al*., 2006; Lane & Flagg, 2010). Quality improvement (QI) operates at the level of the process, whereas implementation science is grounded in theory and aims for generalizability (Nilsen, 2015; Nilsen *et al*., 2023).

In the pharmaceutical industry, three operational definitions are used to define the scope of implementation science. The first of these is that implementation science systematically examines ways to incorporate scientifically validated innovations—such as analytical methods, manufacturing platforms, and regulatory pathways—into routine laboratory and plant operations (Messina, 2025). The second defines an "innovation" as a practice backed by adequate scientific evidence and with an established regulatory pathway for a particular application. Examples of such innovations are Quality by Design (QbD), Process Analytical Technology (PAT), Real-Time Release Testing (RTRT), Continuous Manufacturing (CM), and ICH-conformant analytical procedure lifecycle management (Burcham *et al*., 2018; European Medicines Agency, 2012; Fisher *et al*., 2022; Goodwin *et al*., 2018; Grangeia *et al*., 2020; International Council for Harmonisation, 2008; International Council for Harmonisation, 2009; International Council for Harmonisation, 2012; International Council for Harmonisation, 2019; International Council for Harmonisation, 2022a; International Council for Harmonisation, 2023a; International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d; Lee *et al*., 2015; Sovány *et al*., 2024; U.S. Food and Drug Administration, 2004a; U.S. Food and Drug Administration, 2004b; Wahlich, 2021; Yu & Kopcha, 2017; Yu *et al*., 2014). The third states that "implementation" occurs when the innovation is incorporated into standard operating procedures, the pharmaceutical quality system, regulatory submissions, and continuous competency development (Damschroder *et al*., 2009; Damschroder *et al*., 2022; International Council for Harmonisation, 2008).

Implementation science looks at four closely related areas of study: the innovation itself, the internal environment (that is, the organization), the external environment (which includes regulators, payers, patients, and the supply chain), and the implementation process (Damschroder *et al*., 2009; Damschroder *et al*., 2022). The foundational research by Eccles and Mittman (Eccles & Mittman, 2006) has been turned into three main types of frameworks: process models, for example the Knowledge-to-Action cycle (Field *et al*., 2014; Graham *et al*., 2006; Registered Nurses' Association of Ontario, 2024); determinant frameworks, such as the Consolidated Framework for Implementation Research (CFIR) (Birken *et al*., 2017; Damschroder *et al*., 2009;

Damschroder *et al*., 2022), the Theoretical Domains Framework, and PARIHS; and evaluation frameworks, such as RE-AIM (Glasgow *et al*., 1999; Glasgow *et al*., 2019). The ERIC compilation (Powell *et al*., 2015) lists 73 separate implementation strategies, ranging from "carry out a local needs assessment" to "develop educational materials" and "audit and provide feedback". These strategies can be adapted and combined to address specific implementation challenges.

A key lesson from clinical implementation science—directly applicable to the pharmaceutical industry—is that strategies should be based on barriers identified through empirical evidence rather than assumptions about obstacles. Powell *et al*. (2015) showed that a strategy that works in one setting might not be successful in another because of different contextual factors. For example, a regulatory facility in New Jersey and a contract manufacturer in Tamil Nadu may face different organizational limitations even when implementing the same ICH guideline. The importance of being context-sensitive is stressed by the FDA Quality Management Maturity initiatives (U.S. Food and Drug Administration, 2022; U.S. Food and Drug Administration, 2024c), the EU GMP expectations (European Commission, 2011; European Commission, 2023), and the WHO GMP frameworks (World Health Organization, 2024), all of which stress the need for robust organizational systems, knowledge, and continuous control.

Distinguishing implementation science from change management is essential. Change management is a managerial discipline that addresses the human and organizational dynamics associated with any change (Damschroder *et al*., 2009). In contrast, implementation science is a scientific discipline that employs theory, hypothesis testing, measurement, and evaluation to understand why specific evidence-based practices succeed or fail in particular contexts (Eccles & Mittman, 2006; Nilsen, 2015). These disciplines are complementary: implementation science provides the diagnostic framework, while change management delivers the intervention. In this review, the term "implementation science" is used in its scientific, evidence-driven sense, while recognizing that practical implementation invariably involves a change-management component.

3. COMPARATIVE REGULATORY LANDSCAPE: US, EU, AND GLOBAL

In the last twenty years, there has been a major change in the regulatory environment concerning pharmaceutical innovation. The regulatory framework for drugs marketed in different countries is jointly determined by the United States, the European Union, and the International Council for Harmonisation (ICH). Moreover, regulatory supervision is extended to other territories by the World Health Organization (WHO), the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the pharmacopeial standards.

3.1. United States — FDA framework.

The 2004 release of the FDA's "Pharmaceutical CGMPs for the 21st Century — A Risk-Based Approach" (U.S. Food and Drug Administration, 2004b) marked a major shift from a prescriptive, batch-and-test system to a science- and risk-based regulatory approach. This document brought forward the Process Analytical Technology (PAT) framework (U.S. Food and Drug Administration, 2004a), encouraged the implementation of Quality by Design (QbD) principles, and set the stage for the ICH Q8–Q10 guidelines. The Code of Federal Regulations, Title 21, Parts 210 and 211 (U.S. Food and Drug Administration, 2024d) are still the legally binding Current Good Manufacturing Practice (cGMP) requirements for finished pharmaceuticals. Later FDA initiatives have included the Emerging Technology Program (ETP) (U.S. Food and Drug Administration, 2024e), the Advanced Manufacturing program (U.S. Food and Drug Administration, 2024a), the Quality Metrics Reporting program (U.S. Food and Drug Administration, 2023d), the CDER Quality Management Maturity (QMM) Program (U.S. Food and Drug Administration, 2022; U.S. Food and Drug Administration, 2024c), a 2023 discussion paper on artificial intelligence (AI) in drug manufacturing (U.S. Food and Drug Administration, 2023a; U.S. Food and Drug Administration, 2023b), a 2024 framework for AI in drug development (U.S. Food and Drug Administration, 2024b), and a 2025 draft guidance on the credibility of AI models for regulatory decision-making (U.S. Food and Drug Administration, 2025a). The FDA Modernization Act 2.0 authorizes alternatives to animal testing (Han, 2023; U.S. Food and Drug Administration, 2025c). Together, these regulatory measures create a flexible, science-driven environment for innovation, even though they do not mandate that the industry adopt any particular innovations.

3.2. European Union — EMA and EC framework.

The European regulatory system has two main parts. EudraLex Volume 4 (European Commission, 2011; European Commission, 2023) sets out the Good Manufacturing Practice (GMP) requirements that apply across all EU Member States. Annex 11, the section dealing with computerized systems, is currently being revised in cooperation with the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (PIC/S, 2022). Annex 1, which covers sterile manufacturing, came into force in August 2023 and mandates the introduction of a contamination control strategy, enhanced quality risk management, and integrated lifecycle controls (European Commission, 2023). The European Medicines Agency carries out central scientific evaluations of innovative products and promotes evaluations based on Quality by Design (QbD) (European Medicines Agency, 2017; European Medicines Agency, 2024c). Recent proposals from the European Commission (2023) and the European

Parliament (2024), together with the view set out by Gamba *et al*. (2025), call for major changes to regulatory data protection, access incentives, scientific advice, and manufacturing policy.

3.3. Global — ICH, WHO, and PIC/S.

The main global framework for standardizing pharmaceutical quality is provided by the International Council for Harmonisation (ICH). The concept of design space and control strategy was introduced in ICH Q8(R2) (International Council for Harmonisation, 2009). Quality risk management was formalized in ICH Q9(R1) (International Council for Harmonisation, 2023a), while ICH Q10 (International Council for Harmonisation, 2008) established the pharmaceutical quality system as one that applies throughout the product's lifecycle. ICH Q11 (International Council for Harmonisation, 2012) applied the improved development principles to drug substances, and ICH Q12 (International Council for Harmonisation, 2019) addressed lifecycle management. ICH Q13 (European Medicines Agency, 2023a; International Council for Harmonisation, 2022a; U.S. Food and Drug Administration, 2023c) covers continuous manufacturing. ICH Q14, in conjunction with ICH Q2(R2) (European Medicines Agency, 2023b; International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d), defines the analytical procedure lifecycle framework. ICH Q3D(R2) (International Council for Harmonisation, 2022b) deals with elemental impurities, and the practical problems relating to risk assessment for existing products are discussed in the official guidance and in peer-reviewed literature (Prajapati, 2017; U.S. Food and Drug Administration, 2018). ICH M7(R2) (European Medicines Agency, 2024a; International Council for Harmonisation, 2023b) is responsible for mutagenic impurities. The World Health Organization's Good Manufacturing Practices (WHO GMP) (World Health Organization, 2024) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) frameworks (PIC/S, 2022) also help with international coordination.

3.4. Pharmacopoeial layer.

The analytical compendial framework is provided by the United States Pharmacopeia, comprising General Chapter 〈 1225 〉 on the validation of compendial procedures (United States Pharmacopeia, 2017b) and General Chapter 〈 1224〉 on the transfer of analytical procedures (United States Pharmacopeia, 2017a). Moreover, ICH Q14 and ICH Q2(R2) have set up a harmonized analytical lifecycle foundation that supplements the relevant pharmacopeial requirements.

3.5. Mutual recognition and convergence.

The Mutual Recognition Agreement between the FDA and the EU (European Medicines Agency, 2024b; U.S. Food and Drug Administration, 2024f) accelerates regulatory procedures by reducing the need for duplicate inspections of approved human medicines. The Pharmaceutical Inspection Co-operation Scheme (PIC/S) helps to achieve greater consistency in inspection practices (PIC/S, 2022). Nevertheless, substantial differences still exist in the use of lifecycle management tools. While ICH Q12 provides a global framework, the EU's implementation notes address the application of certain concepts in the region (European Medicines Agency, 2020; International Council for Harmonisation, 2019). The implementation of ICH Q14 is still in the process of being adopted by organizations and regions (International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d). A comparative overview is given in Table 1, and the regulatory timeline is shown in Figure 1.

Table 1: Comparative regulatory framework — US, EU, and Global instruments by innovation domain

Innovation domain	United States (FDA)	European Union (EMA / EC)	Global (ICH / WHO / PIC/S)
Quality by Design (QbD)	21 CFR 210/211 (U.S. Food and Drug Administration, 2024d); cGMPs 21st C. (U.S. Food and Drug Administration, 2004b)	EMA QbD assessment (European Medicines Agency, 2017; European Medicines Agency, 2024c)	ICH Q8(R2) (International Council for Harmonisation, 2009); ICH Q11 (International Council for Harmonisation, 2012)
Process Analytical Technology (PAT)	FDA PAT Guidance (U.S. Food and Drug Administration, 2004a)	EMA QbD/PAT pathway (European Medicines Agency, 2024c)	ICH Q8/Q10 (International Council for Harmonisation, 2008; International Council for Harmonisation, 2009)
Pharmaceutical Quality System	FDA Q10 Guidance (U.S. Food and Drug Administration, 2009)	EMA Q10 adopted	ICH Q10 (International Council for Harmonisation, 2008); WHO GMP (World Health Organization, 2024)
Quality Risk Management	FDA Q9 implementation	EMA Q9(R1) adopted	ICH Q9(R1) (International Council for Harmonisation, 2023a)
Lifecycle Management (PACMP)	FDA Q12 implementation (International Council for Harmonisation, 2019)	ICH Q12 with EU implementation note (European Medicines Agency, 2020)	ICH Q12 (International Council for Harmonisation, 2019)
Continuous Manufacturing	FDA ETP (U.S. Food and Drug Administration, 2024e); Q13 Guidance (U.S. Food and Drug Administration, 2023c)	EMA Q13 (European Medicines Agency, 2023a)	ICH Q13 (International Council for Harmonisation, 2022a)

Innovation domain	United States (FDA)	European Union (EMA / EC)	Global (ICH / WHO / PIC/S)
Analytical Procedure Development	FDA Q14 / Q2(R2) implementation	EMA Q2(R2) (European Medicines Agency, 2023b)	ICH Q14 (International Council for Harmonisation, 2023c); ICH Q2(R2) (International Council for Harmonisation, 2023d)
Mutagenic Impurities	FDA M7 implementation	EMA M7(R2) (European Medicines Agency, 2024a)	ICH M7(R2) (International Council for Harmonisation, 2023b)
Elemental Impurities	FDA guidance (U.S. Food and Drug Administration, 2018)	EMA Q3D(R2) implementation	ICH Q3D(R2) (International Council for Harmonisation, 2022b)
AI/ML in CMC	FDA discussion paper and credibility guidance (U.S. Food and Drug Administration, 2023a; U.S. Food and Drug Administration, 2023b; U.S. Food and Drug Administration, 2024b; U.S. Food and Drug Administration, 2025a)	EMA AI lifecycle reflection paper (European Medicines Agency, 2024d)	ICH Q9/Q10 governance principles (International Council for Harmonisation, 2008; International Council for Harmonisation, 2023a)
Sterile Manufacturing	FDA aseptic-processing framework	EU Annex 1 (European Commission, 2023)	WHO/PIC/S GMP frameworks (PIC/S, 2022; World Health Organization, 2024)
Computerized Systems / Data Integrity	21 CFR Part 11 / CGMP (U.S. Food and Drug Administration, 2024d); enforcement context (Park & Kwon, 2026; U.S. Food and Drug Administration, 2024g)	Annex 11 (European Commission, 2011); revision coordinated with PIC/S (PIC/S, 2022)	PIC/S Annex 11 work (PIC/S, 2022)
Quality Management Maturity	CDER QMM (U.S. Food and Drug Administration, 2022; U.S. Food and Drug Administration, 2024c)	Inspection and PQS maturity mechanisms	WHO GMP / prequalification context (World Health Organization, 2024)

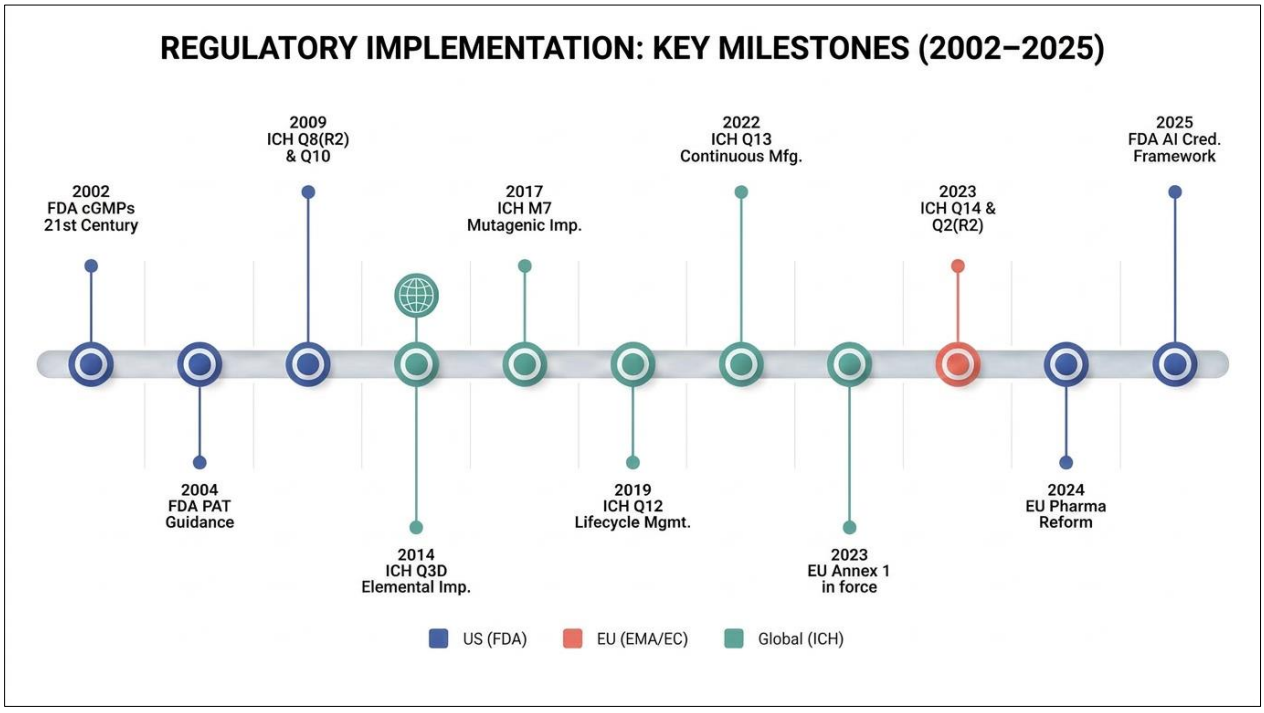

Figure 1: Regulatory Implementation Timeline, 2002 – 2025

4. EVIDENCE-TO-PRACTICE GAPS IN PHARMACEUTICAL INNOVATION

Since implementation science requires clear definitions of "evidence" and "practice", the level of maturity of various pharmaceutical innovations—despite established regulatory routes and substantial technical evidence—varies by product type, modality, organization, and jurisdiction. As a result, the main

problem is not that each innovation is not equally mature, but rather how contextual factors affect the process of getting validated applications into routine use.

4.1. Quality by Design.

Quality by Design (QbD) is supported by the frameworks of the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the International Council for Harmonisation (ICH) (European Medicines Agency, 2017; European Medicines Agency, 2024c; International Council for Harmonisation, 2008; International Council for Harmonisation, 2009; International Council for Harmonisation, 2012; U.S. Food and Drug Administration, 2004a; U.S. Food and Drug Administration, 2004b; Yu & Kopcha, 2017; Yu *et al*., 2014), as well as by systematic reviews of pharmaceutical development practices (Grangeia *et al*., 2020; Sovány *et al*., 2024). However, even with this level of support, the full implementation of design-space flexibility, lifecycle knowledge management, and post-approval tools is still inconsistent, particularly for legacy products and in situations where statistical or regulatory resources are limited. The available evidence provides a stronger basis for the technical feasibility than for the long-term, portfolio-wide implementation.

4.2. Process Analytical Technology.

In 2004, the U.S. Food and Drug Administration (U.S. Food and Drug Administration, 2004a) introduced Process Analytical Technology (PAT) to enable in-process measurement, multivariate control, and a better understanding of the process. Techniques such as near-infrared spectroscopy, Raman spectroscopy, focused-beam reflectance measurement, and multivariate control are technically well established for specific applications (Wu *et al*., 2025). However, there is still widespread but inconsistent commercial adoption because of the need for method lifecycle governance, data integrity controls, integration with plant systems, and the requirement for personnel who are skilled in interpreting and supporting the models (Alosert *et al*., 2022; Arden *et al*., 2021; European Commission, 2011; International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d; PIC/S, 2022).

4.3. Continuous Manufacturing.

The harmonized regulatory pathway for continuous manufacturing was established by ICH Q13 (European Medicines Agency, 2023a; International Council for Harmonisation, 2022a; U.S. Food and Drug Administration, 2023c). Commercial approvals and peer-reviewed studies have confirmed the technical feasibility of using continuous manufacturing for small-molecule products (Burcham *et al*., 2018; Lee *et al*., 2015; Niazi, 2025; Wahlich, 2021). An FDA audit of continuous-manufacturing submissions found no major regulatory obstacles associated with process changes or pre-approval inspections and noted that approval and time-to-market were shorter than with similar batch applications (Fisher *et al*., 2022). Economic modeling indicates that cycle time, inventory, and certain manufacturing costs can be reduced (Schaber *et al*., 2011). Nevertheless, the extent of adoption is still limited due to high capital requirements, difficulties in process integration, workforce capabilities, and the complexity of dealing with multi-region regulatory and supply-chain interfaces (Burcham *et al*., 2018; Fisher *et al*., 2022; Lee *et al*., 2015; National Academies of Sciences, Engineering, and Medicine, 2021; Plumb, 2005; Wahlich, 2021).

4.4. Real-Time Release Testing.

RTRT allows release decisions to be made based on validated process measurements and control strategies, rather than relying solely on testing the final product. The European Medicines Agency (EMA) has produced specific guidelines for use in RTRT cases (European Medicines Agency, 2012). Examples from full-scale commercial applications show how analytical technology (PAT), a thorough understanding of the process, and acceptance criteria established on a statistical basis can be used to make decisions about tablet content and content uniformity (Goodwin *et al*., 2018). Nevertheless, acceptance of the approach is still limited since the entire measurement system, the model lifecycle, the sampling method, data integrity, change control, and the fallback procedures all have to stay within a validated state (Alosert *et al*., 2022; European Medicines Agency, 2012; Goodwin *et al*., 2018; International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d; U.S. Food and Drug Administration, 2004a).

4.5. AI and machine learning.

The U.S. Food and Drug Administration has produced discussion papers and guidance documents concerning the application of artificial intelligence in both drug manufacturing and in regulatory decision-making (U.S. Food and Drug Administration, 2023a; U.S. Food and Drug Administration, 2023b; U.S. Food and Drug Administration, 2024b; U.S. Food and Drug Administration, 2025a). The European Medicines Agency has adopted a lifecycle reflection paper on artificial intelligence and machine learning (European Medicines Agency, 2024d). Peer-reviewed analyses have identified both the opportunities and the barriers associated with Industry 4.0, including data architecture, model governance, interoperability, human oversight, and regulatory acceptability (Alosert *et al*., 2022; Arden *et al*., 2021). With regard to applications in the fields of chemistry, manufacturing, and controls (CMC), the implementation gap is mainly due to data quality, model credibility, lifecycle monitoring, and organizational governance, not because of the availability of algorithms.

4.6. Analytical procedure lifecycle (ICH Q14 / Q2(R2)).

The analytical lifecycle framework, which encompasses the analytical target profile, science- and

risk-based development, robustness, ongoing performance monitoring, and structured change management, was introduced with the 2023 release of ICH Q14 and ICH Q2(R2) (European Medicines Agency, 2023b; International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d). Putting this framework into practice involves amending standard operating procedures, validation templates, documentation systems, statistical methodologies, and providing staff with additional training. Yet, at present, there is not enough publicly available data to determine what proportion of laboratories have fully transferred their analytical lifecycle programs. This lack of transparent information on the extent of adoption represents a major evidence gap.

4.7. Data integrity and ALCOA+.

Park and Kwon examined 1,766 FDA Warning Letters issued between 2016 and 2023, grouping findings related to data integrity according to the ALCOA and ALCOA+ principles. While their study highlighted continuing worries about endurance, availability, and completeness, it did not confirm the previously reported figures for laboratory control, out-of-specification (OOS) results, or stability failures (Park & Kwon, 2026). The FDA Warning Letter records serve as the main enforcement context (U.S. Food and Drug Administration, 2024g). The introduction of Industry 4.0 environments brings about additional data-integrity issues since the data, which occurs at high frequency and is closely interconnected, must remain attributable, complete, consistent, enduring, and available over its entire lifecycle (Alosert *et al*., 2022; European Commission, 2011; PIC/S, 2022; U.S. Food and Drug Administration, 2024d).

4.8. Elemental and mutagenic impurities.

The risk-based approach for controlling elemental impurities was established by ICH Q3D(R2) (International Council for Harmonisation, 2022b). On the other hand, ICH M7(R2) (European Medicines Agency, 2024a; International Council for Harmonisation, 2023b) introduced a risk-based assessment and control of DNA-reactive mutagenic impurities. Applying these guidelines to older products is difficult because effective risk assessments require a thorough understanding of the materials, processes, equipment, utilities, suppliers, and potential sources of variability (Prajapati, 2017; U.S. Food and Drug Administration, 2018). The major difficulty goes beyond analytical sensitivity and involves integrating risk assessment, supplier information, change control, and regulatory documentation throughout the product lifecycle.

4.9. Method transfer and global laboratories.

The structured approaches to the transfer of analytical procedures and the management of their lifecycle are provided by USP General Chapter 〈 1224 〉 (United States Pharmacopeia, 2017a) and ICH Q14 (International Council for Harmonisation, 2023c). For a transfer to be successful, it is necessary to have a thorough understanding of the method, to clearly communicate the critical method variables, to take into account the capabilities of the receiving laboratory, to ensure that adequate training is given, to use a strong comparative or co-validation design, and to have clearly defined acceptance criteria. Since there is currently no publicly available data which supports a universal global transfer success rate, action should focus on improving knowledge transfer and on risk-based planning instead of assuming that a procedure which has been formally validated will perform exactly the same in all laboratories (International Council for Harmonisation, 2008; International Council for Harmonisation, 2023c; United States Pharmacopeia, 2017a). Taken together, these evidence-to-practice examples are conceptualized as a persistent know-do gap (Figure 2) and progressive attrition across implementation stages (Figure 3).

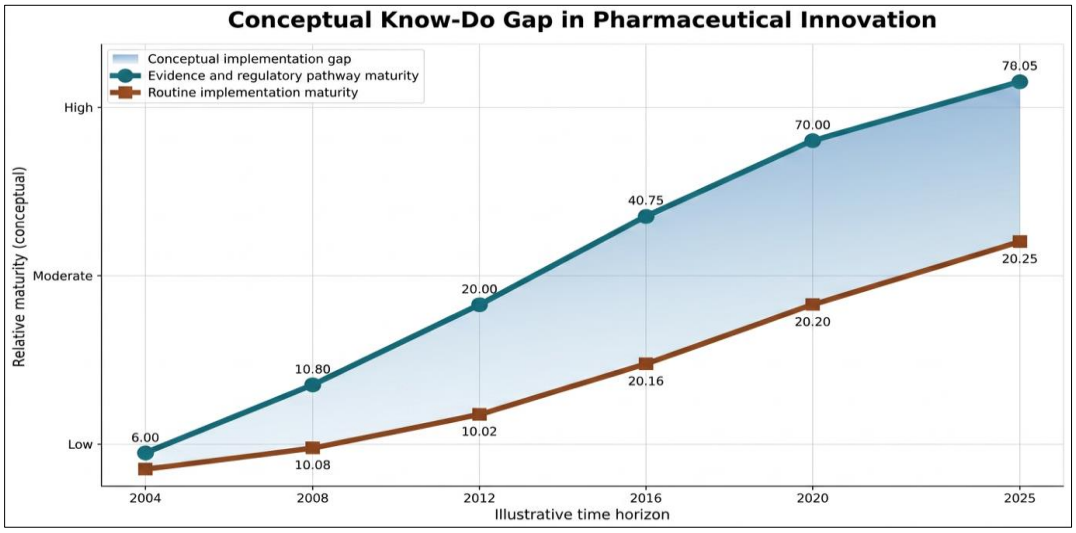

Figure 2. Conceptual Know-Do Gap in Pharmaceutical Innovation

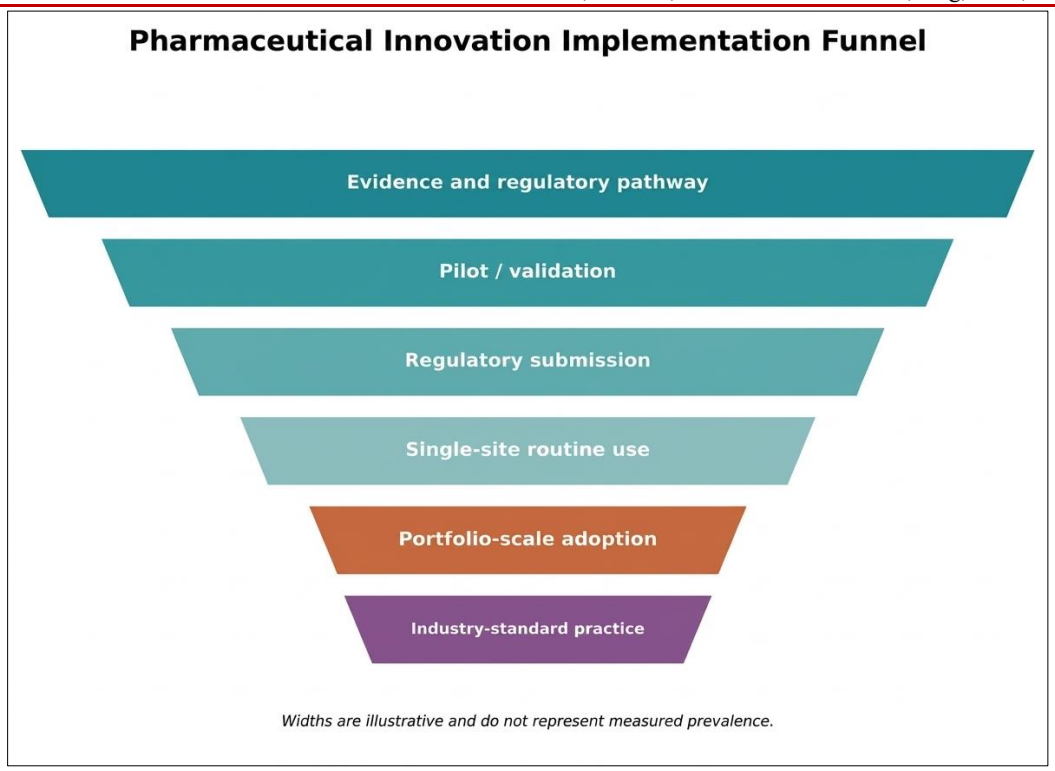

Figure 3: Conceptual Pharmaceutical Innovation Implementation Funnel

5. MULTILEVEL BARRIERS TO IMPLEMENTATION

The obstacles to implementing pharmaceutical innovations are usually divided into several closely related areas: technical and scientific, regulatory, organizational and cultural, workforce, economic, and supply chain. The importance of each of these areas depends on factors such as the type of product, geographic location, technological environment, and jurisdiction. As a result, effective implementation generally requires a coordinated set of strategies (Curran *et al*., 2012; Damschroder *et al*., 2009; Messina, 2025; National Academies of Sciences, Engineering, and Medicine, 2021; Powell *et al*., 2015).

5.1. Technical and scientific barriers.

Even though the basic scientific principles behind Quality by Design (QbD), Process Analytical Technology (PAT), Continuous Manufacturing (CM), Artificial Intelligence and Machine Learning (AI/ML), and ICH Q14 have been well established for particular applications, there are still significant technical difficulties when it comes to integrating these approaches. To comply with ICH Q2(R2) and ICH Q14 regarding the validation of in-line and multivariate measurements, it is necessary to develop custom validation strategies and implement continuous lifecycle monitoring (International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d). The use of high-frequency, interconnected, model-driven data places further demands on existing Laboratory Information Management Systems (LIMS), chromatography data systems, data architecture, and data governance (Alosert *et al*., 2022; Arden *et al*., 2021; European Commission, 2011; PIC/S, 2022; U.S. Food and Drug Administration, 2024d). Moreover, Real-Time Release Testing (RTRT) requires that the measurement and control systems remain in a validated state throughout the whole product lifecycle (European Medicines Agency, 2012; Goodwin *et al*., 2018).

5.2. Regulatory barriers.

Even though the FDA, EMA, and ICH have removed many prescriptive obstacles to innovation, the implementation process still requires a careful approach to the regulatory expectations specific to each jurisdiction. The acceptance of design space, the procedures for making changes after approval, and the implementation of ICH Q12 across regions all differ among regulatory environments (European Medicines Agency, 2017; European Medicines Agency, 2020; International Council for Harmonisation, 2019; Yu *et al*., 2014). According to EU Annex 1, organizations must adopt a contamination control strategy throughout the company and implement the corresponding pharmaceutical quality system controls (European Commission, 2023). Mutual recognition agreements (European Medicines Agency, 2024b; U.S. Food and Drug Administration, 2024f) eliminate some redundant inspections but do not apply to all products, jurisdictions, or decisions regarding advanced technology.

5.3. Organizational and cultural barriers.

Organizational barriers encompass risk aversion, fragmented knowledge management, inconsistent quality-system maturity, competing

priorities, and limited expertise in statistics, chemometrics, informatics, and model lifecycle management (Arden *et al*., 2021; Messina, 2025; National Academies of Sciences, Engineering, and Medicine, 2021; U.S. Food and Drug Administration, 2022; U.S. Food and Drug Administration, 2024c). The FDA's Quality Management Maturity (QMM) program aims to assess advanced quality-management practices that support reliable performance, rather than mandating specific technologies (U.S. Food and Drug Administration, 2022; U.S. Food and Drug Administration, 2024c). Evidence from warning letters highlights persistent data-integrity vulnerabilities; however, these findings should not be construed as evidence of a single organizational cause (Park & Kwon, 2026; U.S. Food and Drug Administration, 2024g).

5.4. Economic barriers.

The introduction of continuous manufacturing, together with end-to-end process analytical technology (PAT), generally entails substantial capital investment, process redesign, validation, and systems integration. The economic results are affected by factors including product volume, process architecture, inventory policy, level of facility utilization, and regulatory timelines (Burcham *et al*., 2018; Fisher *et al*., 2022; Lee *et al*., 2015; National Academies of Sciences, Engineering, and Medicine, 2021; Plumb, 2005; Schaber *et al*., 2011). Evidence on biosimilars shows that reimbursement policies, procurement practices, competitive conditions, and market structure significantly affect adoption, even when scientific comparability has been established (Carl *et al*., 2022).

5.5. Knowledge management as a cross-cutting barrier.

The ICH Q10 guideline (International Council for Harmonisation, 2008; U.S. Food and Drug Administration, 2009) regards knowledge management as a key factor in supporting pharmaceutical quality systems. In reality, though, knowledge related to analytical development, validation, deviation management, stability studies, process operations, and regulatory activities is often scattered across separate systems. The ISPE Pharma 4.0 operating model (ISPE, 2020) and recent Industry 4.0 analyses (Alosert *et al*., 2022; Arden *et al*., 2021) stress the need for an integrated data architecture, contextualized information, strong governance, and effective human supervision. The main difficulty in implementing this is integrating these elements while ensuring data integrity and maintaining validated-state control.

5.6. Workforce barriers and the analytical skills gap.

The introduction of ICH Q14, which covers Process Analytical Technology (PAT), Real-Time Release Testing (RTRT), Continuous Manufacturing (CM), and artificial intelligence (AI)-supported systems, calls for a wider range of skills than the conventional single-method, batch-and-test methods. Important skills in this context are experimental design, multivariate calibration, statistical inference, model maintenance, data governance, software validation, and change control (Alosert *et al*., 2022; Arden *et al*., 2021; Goodwin *et al*., 2018; International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d; Wu *et al*., 2025). Although implementation strategies such as train-the-trainer programs, communities of practice, supervised pilots, and cross-functional collaboration are possible, their effectiveness must be established through empirical evidence rather than assumed (Damschroder *et al*., 2009; Powell *et al*., 2015).

5.7. Supply-chain and supplier-quality barriers.

The active pharmaceutical ingredients (APIs), the excipients, the primary packaging, the contract laboratories, and the contract manufacturers are all part of the pharmaceutical supply chain, and this chain operates in a number of different jurisdictions (U.S. Food and Drug Administration, 2019; U.S. Food and Drug Administration, 2025b; World Health Organization, 2024). The ICH Q9(R1) and ICH Q10 guidelines set out frameworks for risk-based supplier and lifecycle management (International Council for Harmonisation, 2008; International Council for Harmonisation, 2023a). Moreover, PIC/S and various mutual recognition arrangements help achieve regulatory convergence (European Medicines Agency, 2024b; PIC/S, 2022; U.S. Food and Drug Administration, 2024f). Although drug-shortage reports and enforcement records show weaknesses in manufacturing, quality, and the supply chains, these sources do not offer evidence that a specific proportion of the problems can be attributed solely to supplier quality (Park & Kwon, 2026; U.S. Food and Drug Administration, 2019; U.S. Food and Drug Administration, 2024g; U.S. Food and Drug Administration, 2025b).

5.8. Cost-of-quality versus cost-of-non-quality.

Recalls, deviations, batches that are rejected, the need for remediation, supply disruptions, and a loss of market access all lead to significant direct and indirect costs (Fisher *et al*., 2022; National Academies of Sciences, Engineering, and Medicine, 2021; OECD, 2023; Scannell *et al*., 2012; Schaber *et al*., 2011; U.S. Food and Drug Administration, 2019; U.S. Food and Drug Administration, 2025b). The size of these costs varies according to the particular product and the specific event. The current body of literature has not determined a general ratio between the cost of poor quality and the amount invested in preventive quality measures. An effective way to implement this is to explicitly include quality risk, supply continuity, and lifecycle costs in the processes for making capital and portfolio decisions (U.S. Food and Drug Administration, 2022; U.S. Food and Drug Administration, 2024c). The principal barrier classes and representative evidence are summarized in Table 2.

Table 2: Multilevel barriers to pharmaceutical implementation, with representative evidence

Barrier class	Specific barrier	Representative evidence
Technical / Scientific	Multivariate validation and lifecycle monitoring under ICH Q14 / Q2(R2)	(International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d; Wu *et al*., 2025)
Technical / Scientific	Data integrity for high-frequency and interconnected PAT data	(Alosert *et al*., 2022; European Commission, 2011; PIC/S, 2022; U.S. Food and Drug Administration, 2024d)
Technical / Scientific	RTRT requires validated measurement, model, control, and fallback strategies	(European Medicines Agency, 2012; Goodwin *et al*., 2018; International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d; U.S. Food and Drug Administration, 2004a)
Regulatory	Region-specific implementation of ICH Q12 and post-approval tools	(European Medicines Agency, 2020; International Council for Harmonisation, 2019)
Regulatory	Organization-wide contamination-control implementation under EU Annex 1	(European Commission, 2023)
Regulatory	Q3D/M7 risk-assessment challenges for legacy products and supply chains	(International Council for Harmonisation, 2022b; International Council for Harmonisation, 2023b; Prajapati, 2017; U.S. Food and Drug Administration, 2018)
Organizational / Cultural	Risk aversion, competing priorities, and variable quality-system maturity	(Messina, 2025; National Academies of Sciences, Engineering, and Medicine, 2021; U.S. Food and Drug Administration, 2022; U.S. Food and Drug Administration, 2024c)
Organizational / Cultural	Fragmented knowledge and data architecture	(Alosert *et al*., 2022; Arden *et al*., 2021; International Council for Harmonisation, 2008; ISPE, 2020; U.S. Food and Drug Administration, 2009)
Organizational / Cultural	Persistent data-integrity vulnerabilities without a single proven cause	(Alosert *et al*., 2022; Park & Kwon, 2026; U.S. Food and Drug Administration, 2024g)
Workforce	Statistical, multivariate, informatics, and model-lifecycle competency needs	(Alosert *et al*., 2022; Arden *et al*., 2021; International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d; Wu *et al*., 2025)
Economic	Capital, integration, validation, and lifecycle costs for CM/PAT	(Burcham *et al*., 2018; Fisher *et al*., 2022; Lee *et al*., 2015; National Academies of Sciences, Engineering, and Medicine, 2021; Plumb, 2005; Schaber *et al*., 2011)
Economic	Market and procurement conditions influencing biosimilar uptake	(Carl *et al*., 2022)
Supply chain	Heterogeneous supplier and manufacturing-network capability	(PIC/S, 2022; U.S. Food and Drug Administration, 2019; U.S. Food and Drug Administration, 2025b; World Health Organization, 2024)

6. A PHARMA-ADAPTED IMPLEMENTATION SCIENCE FRAMEWORK

We have developed a framework for pharmaceutical implementation science that combines the scope of the Consolidated Framework for Implementation Research (CFIR) (Damschroder *et al*., 2009; Damschroder *et al*., 2022), the evaluative capabilities of the RE-AIM framework (Glasgow *et al*., 1999; Glasgow *et al*., 2019), the strategic classification provided by the Expert Recommendations for Implementing Change (ERIC) (Powell *et al*., 2015), and the lifecycle structure outlined in ICH Q10 (International Council for Harmonisation, 2008). Figure 4 shows this framework, which is made up of five interconnected domains. The major implementation-science frameworks and their pharmaceutical adaptations are summarized in Table 3.

6.1. Outer setting.

The area in question includes all the external factors that affect the company, such as regulators, pharmacopoeias, payers, procurement systems, patients, suppliers, and public health requirements (European Commission, 2011; European Commission, 2023; European Medicines Agency, 2012; European Medicines Agency, 2017; European Medicines Agency, 2023a; European Medicines Agency, 2023b; European Medicines Agency, 2024a; European Medicines Agency, 2024b; European Medicines Agency, 2024c; European Medicines Agency, 2024d; International Council for Harmonisation, 2008; International Council for

Harmonisation, 2009; International Council for Harmonisation, 2011; International Council for Harmonisation, 2012; International Council for Harmonisation, 2019; International Council for Harmonisation, 2022a; International Council for Harmonisation, 2022b; International Council for Harmonisation, 2023a; International Council for Harmonisation, 2023b; International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d; PIC/S, 2022; U.S. Food and Drug Administration, 2004a; U.S. Food and Drug Administration, 2004b; U.S. Food and Drug Administration, 2018; U.S. Food and Drug Administration, 2019; U.S. Food and Drug Administration, 2023c; U.S. Food and Drug Administration, 2024f; World Health Organization, 2024). The external influences consist of formal guidelines and programs such as the FDA Quality Metrics (U.S. Food and Drug Administration, 2023d), the FDA Quality Management Maturity (QMM) (U.S. Food and Drug Administration, 2022; U.S. Food and Drug Administration, 2024c), EU Annex 1 (European Commission, 2023), mutual recognition agreements (European Medicines Agency, 2024b; U.S. Food and Drug Administration, 2024f), and the expectations established by the World Health Organization (WHO) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (PIC/S, 2022; World Health Organization, 2024).

6.2. Inner setting.

The internal environment includes the organization itself, such as its leadership, structural features, networks, communication methods, culture, climate, readiness, and available resources (Damschroder *et al*., 2009; Damschroder *et al*., 2022). The four enablers mentioned in ICH Q10—management responsibility, knowledge management, quality risk management, and continual improvement—are part of this area (International Council for Harmonisation, 2008; U.S. Food and Drug Administration, 2009). Although some interventions begin with changes in the external environment, most are carried out within the internal setting.

6.3. Innovation.

Innovations have features that may help or hinder their adoption, such as relative advantage, complexity, trialability, observability, and adaptability (Damschroder *et al*., 2009; Damschroder *et al*., 2022). In the pharmaceutical sector, these characteristics vary depending on the specific application. For example, Quality by Design (QbD) provides flexibility across the lifecycle but demands thorough statistical and regulatory integration. Process Analytical Technology (PAT) enhances process observability but requires strict governance of models, data, and systems. Artificial Intelligence and Machine Learning (AI/ML) offer adaptability, although they do give rise to concerns regarding transparency, bias, and lifecycle monitoring (Alosert *et al*., 2022; Arden *et al*., 2021; European Medicines Agency, 2024d; Grangeia *et al*., 2020; Sovány *et al*., 2024; Wu *et al*., 2025).

6.4. Individuals.

Scientists, qualified individuals, operators, assessors, data scientists, and quality professionals all provide knowledge, beliefs, feelings of self-efficacy, a sense of role identity, and practical limitations which affect the process of adoption (Birken *et al*., 2017; Damschroder *et al*., 2009; Damschroder *et al*., 2022). While the individual domain is usually examined less directly than technical performance, ICH Q10 regards personnel competence and management responsibility as essential elements of the pharmaceutical quality system (International Council for Harmonisation, 2008).

6.5. Implementation process.

The structure for implementation activities is provided by the cyclical Plan – Engage – Execute – Reflect/Evaluate process, as set out in the updated Consolidated Framework for Implementation Research (CFIR) (Damschroder *et al*., 2022) and the Knowledge-to-Action framework (Field *et al*., 2014; Graham *et al*., 2006; Registered Nurses' Association of Ontario, 2024). In pharmaceutical environments subject to regulation, the cycle must specifically take into account validation, change control, the impact on the regulatory dossier, and planning for the post-approval phase in accordance with the ICH Q12 guidelines (International Council for Harmonisation, 2019).

The implementation is carried out by adapting the 73 Expert Recommendations for Implementing Change (ERIC), compiled by Powell and colleagues (Powell *et al*., 2015). Of these, 51 strategies can be directly applied to pharmaceutical settings, 18 need to be adapted, and 4 are not directly applicable. These categories are the result of the authors' conceptual evaluation and have not yet undergone formal validation by expert consensus. In practice, projects should involve selecting an innovation, carrying out a CFIR-based diagnostic assessment, choosing a bundle of strategies that is aligned with the ERIC framework, and then assessing Reach, Effectiveness, Adoption, Implementation fidelity, and Maintenance using the RE-AIM framework (Damschroder *et al*., 2009; Damschroder *et al*., 2022; Glasgow *et al*., 1999; Glasgow *et al*., 2019; Powell *et al*., 2015). A full strategy-level mapping should be provided as supplementary material when submitting it to a journal. An author-developed qualitative mapping of ERIC-aligned strategies to the major pharmaceutical implementation barriers is shown in Figure 5.

The main idea of the framework is that pharmaceutical implementation should be addressed empirically. The barriers had to be systematically identified, strategies had to be matched to relevant contextual factors, fidelity had to be assessed, and

outcomes had to be checked against predetermined endpoints. This type of evidence-based approach is preferable to choosing strategies based on tradition, vendor preference, or arbitrary judgment.

6.6. Worked illustration: implementing ICH Q14 in a multi-site analytical organization.

A multinational company specializing in generic drugs, which has five sites across three regulatory areas, implemented the ICH Q14 and ICH Q2(R2) guidelines (International Council for Harmonization, 2023c; International Council for Harmonization, 2023d) within its method development department. The implementation was carried out using a well-structured four-step approach. In the first step, Planning, the company established analytical target profiles for its top 20 products, assessed the current level of method validation against ICH Q14 requirements, and developed a 24-month plan. In the second step, Engagement, the company identified clinical-style opinion leaders at each site (that is, senior method-development scientists), established a cross-site community of practice, and secured sponsorship from the Quality Council in line with the ICH Q10 requirement on management responsibility (International Council for Harmonisation, 2008). In the third step, Execution, the company applied ERIC strategies such as train-the-trainer programs, audit-and-feedback systems, structured reviews of the analytical risk-assessment documents, alignment with ICH Q9(R1) risk management (International Council for Harmonisation, 2023a), and pre-submission contact with the FDA's Emerging Technology Program for the most innovative methods (U.S. Food and Drug Administration, 2024e). The fourth step, Reflection and Evaluation, monitored the RE-AIM endpoints: Reach (the percentage of method-development projects that used ATPs), Effectiveness (the cycle time to validation and the out-of-specification rate), Adoption (the percentage of sites), Implementation (the audit-fidelity score), and Maintenance (the level of continued adoption at 12 and 24 months) (Glasgow *et al*., 1999; Glasgow *et al*., 2019). This structured framework converts the general regulatory expectations into a measurable, auditable, and lifecycle-managed implementation program.

6.7. Hybrid effectiveness-implementation designs.

In the pharmaceutical field, implementation projects typically use study designs that combine effectiveness and implementation research (Curran *et al*., 2012). In Hybrid Type 1 studies, effectiveness is the main focus, and implementation data are also collected. Type 2 studies examine both effectiveness and implementation simultaneously, whereas Type 3 studies focus on the implementation strategy and monitor relevant outcomes. A multi-site continuous-manufacturing study in this area can assess the performance of critical quality attributes (CQAs), the regulatory and operational timelines, adoption fidelity, and sustainment (Burcham *et al*., 2018; Curran *et al*., 2012; Fisher *et al*., 2022; Wahlich, 2021). However, such study designs are seldom found in the pharmaceutical implementation literature and therefore offer a major methodological opportunity.

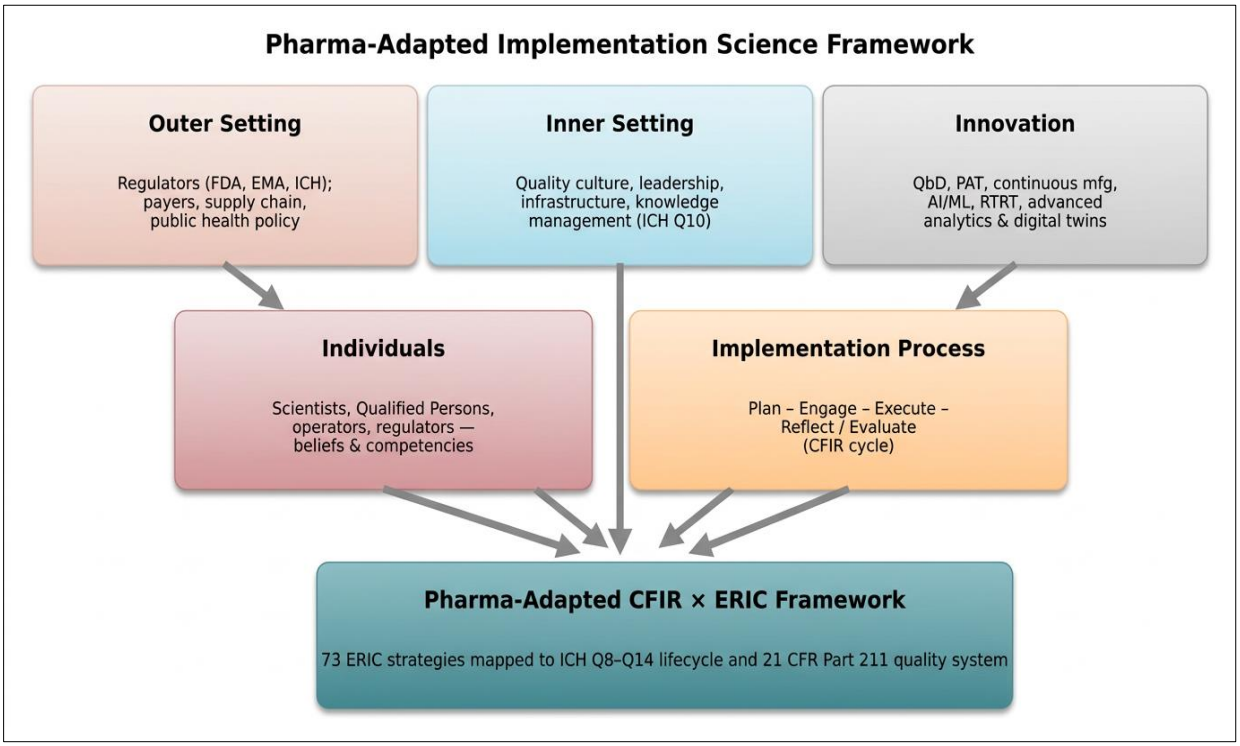

Figure 4: Pharma-Adapted Implementation Science Framework.

Table 3: Implementation science frameworks adapted to pharmaceutical innovation.

Framework	Primary focus	Pharmaceutical adaptation	Key reference
CFIR	Determinants across outer setting, inner setting, innovation, individuals, and process	Regulators and payers in outer setting; ICH Q10 system in inner setting	(Damschroder *et al*., 2009; Damschroder *et al*., 2022)
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance	Product/site reach, CQA and quality outcomes, adoption, fidelity, sustainment	(Glasgow *et al*., 1999; Glasgow *et al*., 2019)
ERIC	73 discrete implementation strategies	Author-developed mapping: 51 direct, 18 adapted, 4 not directly applicable; validation still needed	(Powell *et al*., 2015)
Knowledge-to-Action	Cyclical movement from knowledge to sustained action	Maps to pharmaceutical lifecycle and change management	(Field *et al*., 2014; Graham *et al*., 2006; Registered Nurses' Association of Ontario, 2024)
Theoretical Domains Framework	Behavioural determinants at individual level	Applied to scientist, operator, assessor, and quality-professional behaviour	(Birken *et al*., 2017)
PARIHS	Evidence × Context × Facilitation	Applied to GMP context and regulatory facilitation	(Rycroft-Malone, 2004)
Hybrid effectiveness-implementation studies	Type 1, 2, and 3 hybrid approaches	Can evaluate technical outcomes and implementation in parallel	(Curran *et al*., 2012)

7. REAL-WORLD IMPLEMENTATION DATA: CASE STUDIES AND EMPIRICAL EVIDENCE

Empirical data obtained from the United States, Europe, and a number of international situations show, on the one hand, the difficulties involved in implementation and, on the other hand, the benefits of using explicit implementation strategies. Yet, since public reporting remains incomplete and inconsistent across regions, these examples can only be regarded as case evidence and do not provide a full evaluation of the extent of global adoption.

7.1. FDA Drug Shortages — Calendar Year 2024 Report to Congress.

By the end of 2024, the U.S. Food and Drug Administration (FDA) had 125 drug shortages still ongoing (U.S. Food and Drug Administration, 2025b). Analyses conducted by the FDA have found that problems related to manufacturing quality, market conditions, and weaknesses in the supply chain are major reasons for these shortages (U.S. Food and Drug Administration, 2019; U.S. Food and Drug Administration, 2025b). These results indicate that simply modernizing regulation does not guarantee a reliable supply. It is still not known, though, whether drugs produced using Quality by Design (QbD), Process Analytical Technology (PAT), or continuous manufacturing are missing from the shortage lists.

7.2. FDA Warning Letters analysis (2016–2023).

Park and Kwon enumerated 1,766 FDA Warning Letters issued from 2016 through 2023 and categorized data-integrity findings using ALCOA/ALCOA+ principles (Park & Kwon, 2026). They reported no statistically significant overall pre- versus post-pandemic difference, while selected categories—including endurance, availability, and completeness—showed year-over-year increases after 2020. The average number of data-integrity violations per company increased in 2023, but the authors cautioned that causality could not be inferred. FDA's Warning Letter database provides the enforcement record (U.S. Food and Drug Administration, 2024g).

7.3. ICH Q13 continuous manufacturing implementation.

The ICH Q13 procedure reached Step 4 in 2022 (European Medicines Agency, 2023a; International Council for Harmonisation, 2022a; U.S. Food and Drug Administration, 2023c). An FDA audit of continuous-manufacturing submissions found no major regulatory obstacles associated with process changes or pre-approval inspections and reported that the mean or median times for approval and market entry were shorter than for similar batch applications (Fisher *et al*., 2022). Peer-reviewed literature and economic analyses have confirmed the technical feasibility and the possible operational advantages, although they also point out challenges involving integration, capital investment, workforce development, and lifecycle management (Burcham *et al*., 2018; Lee *et al*., 2015; Plumb, 2005; Schaber *et al*., 2011; Wahlich, 2021).

7.4. Biosimilar adoption divergence.

A comparative analysis of biosimilar uptake and pricing was carried out by Carl *et al*. (2022) in the United

States, Germany, and Switzerland. One year after their market entry, the highest product-level uptake was about 36% for bevacizumab in the United States, 48% for adalimumab in Germany, and 25% for rituximab in Switzerland. The uptake patterns differed by molecules, country, launch conditions, pricing, and policy. The findings show the significance of external factors, even though the products and market conditions were different.

7.5. EU Annex 1 implementation.

Since August 2023, the EU GMP Annex 1 has required that a contamination control strategy be documented and integrated throughout the facility, processes, personnel, utilities, monitoring, and quality-system controls (European Commission, 2023). Carrying out this regulation requires considerable work in risk assessment, documentation, training, qualification, and governance. However, at present, there is not enough publicly available evidence to identify a dominant cost category among manufacturers.

7.6. ICH Q14/Q2(R2) early adoption.

The ICH Q14 and ICH Q2(R2) guidelines achieved Step 4 in 2023 (International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d). Even though companies are updating their analytical development, validation, monitoring, and change-management practices, there remains a lack of publicly available, representative data on the extent of adoption. For this reason, no global percentage for laboratory re-platforming or the use of the analytical target profile is provided in this review.

7.7. AI/ML in pharmaceutical analytics.

The U.S. Food and Drug Administration (FDA) has released a discussion paper on AI manufacturing, established a resource center for drug development, and put forward draft guidance regarding model credibility (U.S. Food and Drug Administration, 2023a; U.S. Food and Drug Administration, 2023b; U.S. Food and Drug Administration, 2024b; U.S. Food and Drug Administration, 2025a). The European Medicines Agency (EMA) has produced a lifecycle reflection paper (European Medicines Agency, 2024d). Peer-reviewed analyses of Industry 4.0 point to opportunities in automation and decision support, as well as challenges concerning data integrity, interoperability, model governance, workforce capability, and regulatory confidence (Alosert *et al*., 2022; Arden *et al*., 2021). There is no evidence to support the idea of a single global digital maturity score for the pharmaceutical industry.

Table 4 presents the selected cases. In each of these cases, adoption results from a combination of factors in the inner and outer settings. The evidence fails to show a single universal causal pathway.

7.8. Quality Management Maturity (QMM) — early evidence.

The Quality Management Maturity (QMM) program, organized by the FDA, is a voluntary initiative designed to improve quality management practices and examine the link between these practices and manufacturing performance and supply reliability (U.S. Food and Drug Administration, 2022; U.S. Food and Drug Administration, 2024c). Since the program is still in progress and because limited outcome data are currently available to the public, the QMM program should be seen more as an implementation-science experiment than as proof of a validated causal connection between QMM ratings and particular performance outcomes.

7.9. R&D productivity, Eroom's Law, and the cost of non-implementation.

The productivity of pharmaceutical research and development (R&D) has declined over many decades, a phenomenon known as Eroom's Law, with reasons that extend beyond chemistry, manufacturing, and controls (CMC) (OECD, 2023; Scannell *et al*., 2012). The estimates of R&D costs reported in the peer-reviewed literature vary widely depending on the methods and datasets employed (DiMasi *et al*., 2016; Mullard, 2014; Wouters *et al*., 2020). Manufacturing innovations could lead to shorter cycle times, lower inventory levels, reduced specific costs, and shorter regulatory timelines in suitable situations (Fisher *et al*., 2022; Schaber *et al*., 2011). Yet the extent to which implementation failure contributes to overall R&D productivity has not been measured. Even though the implementation gap is probably relevant to both productivity and access, it should not be presented as a quantified share of the total decline.

Table 4: Selected real-world pharmaceutical implementation case studies and outcomes.

Case/evidence source	Region	Implementation domain	Supported finding	Reference
FDA Drug Shortages 2024 Report	US	Quality and supply reliability	125 ongoing shortages at end-2024; manufacturing, quality, market, and supply vulnerabilities remain relevant	(U.S. Food and Drug Administration, 2019; U.S. Food and Drug Administration, 2025b)
FDA Warning Letters 2016–2023	Global	Data integrity	1,766 letters enumerated; selected ALCOA+ categories increased after 2020; causality not established	(Park & Kwon, 2026; U.S. Food and Drug Administration, 2024g)

Case/evidence source	Region	Implementation domain	Supported finding	Reference
FDA audit of CM submissions	US	Continuous manufacturing	No substantial regulatory barriers identified; shorter approval and market-entry timelines than matched batch applications	(Fisher *et al*., 2022)
Peer-reviewed CM evidence	US / Global	Continuous manufacturing	Commercial feasibility with continuing capital, integration, workforce, and lifecycle challenges	(Burcham *et al*., 2018; Lee *et al*., 2015; Plumb, 2005; Schaber *et al*., 2011; Wahlich, 2021)
Biosimilar uptake comparison	US / Germany / Switzerland	Market adoption	Uptake differed by molecule, country, policy, pricing, and launch conditions	(Carl *et al*., 2022)
EU Annex 1	EU	Sterile manufacturing	Contamination control strategy and integrated PQS implementation required	(European Commission, 2023)
ICH Q14 / Q2(R2)	Global	Analytical lifecycle	Global framework established; representative adoption metrics remain sparse	(European Medicines Agency, 2023b; International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d)
FDA QMM	US	Quality-system maturity	Voluntary program exploring mature practices and manufacturing performance	(U.S. Food and Drug Administration, 2022; U.S. Food and Drug Administration, 2024c)
Industry 4.0 evidence	Global	Digital manufacturing	Opportunities accompanied by data-integrity, interoperability, governance, and workforce barriers	(Alosert *et al*., 2022; Arden *et al*., 2021; ISPE, 2020)
FDA and EMA AI frameworks	US / EU	AI in development and CMC	Risk- and context-based credibility, governance, and lifecycle considerations are emerging	(European Medicines Agency, 2024d; U.S. Food and Drug Administration, 2023a; U.S. Food and Drug Administration, 2023b; U.S. Food and Drug Administration, 2024b; U.S. Food and Drug Administration, 2025a)

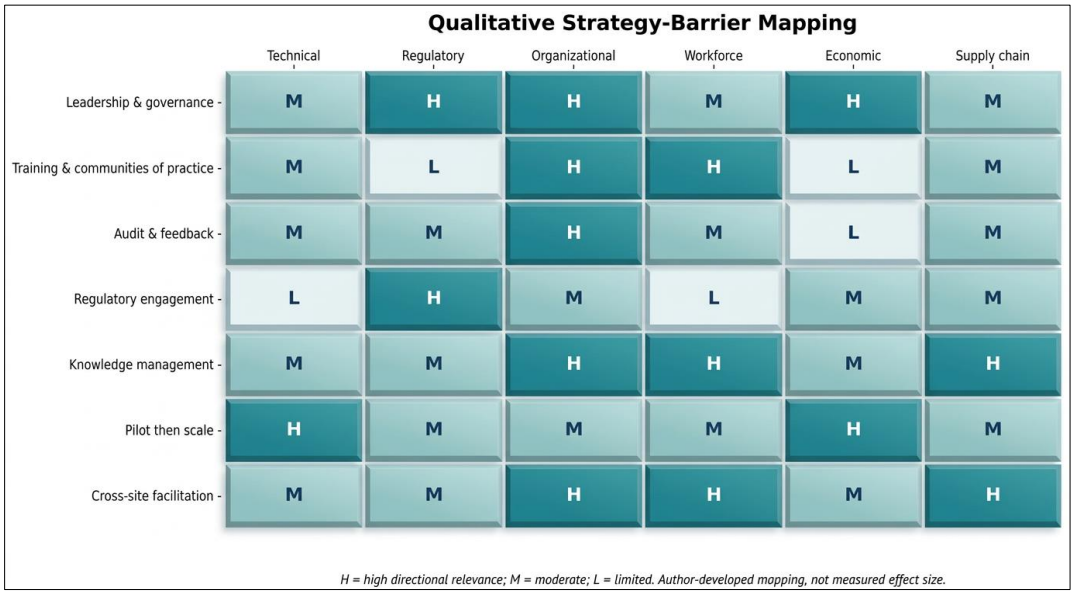

Figure 5: ERIC-Aligned Strategies for Pharmaceutical Implementation Barriers

8. STRATEGIES AND RECOMMENDATIONS

The report includes 12 recommendations based on existing evidence and is organized into three main groups of stakeholders: regulators, sponsor organizations, and the academic and pharmacopeial community. Each of the recommendations corresponds with the ERIC strategies and the relevant framework domains. However, the recommendations have not yet been assessed as a complete intervention package.

8.1. Recommendations for regulators (US, EU, Global).

R1. Quality Management Maturity (QMM) should be made into a specific incentive. The FDA's QMM concept (U.S. Food and Drug Administration, 2022; U.S. Food and Drug Administration, 2024c) should be put into practice with clearly defined benefits, such as accelerated approval of changes after the product has been licensed under ICH Q12, fewer inspections, and preferences in procurement being given to facilities that show a high level of QMM. Similarly, the EMA and ICH should also adopt comparable frameworks.

R2. In all ICH regions, transparent post-approval change pathways are required, as specified in ICH Q12. The existing asymmetry in the implementation of Q12—with full adoption taking place in the United States and only partial adoption in the European Union—constitutes a major obstacle (European Medicines Agency, 2020; International Council for Harmonisation, 2019).

R3. The FDA's AI credibility framework (U.S. Food and Drug Administration, 2025a) should be introduced as a tiered pathway for acceptance, coordinated with the EMA and the ICH, to enable the uptake of clearly low-risk applications of artificial intelligence without the need for individual regulatory negotiations.

R4. The principle of mutual recognition of inspections should be extended beyond the FDA-EU Mutual Recognition Agreement (European Medicines Agency, 2024b; U.S. Food and Drug Administration, 2024f) to include members of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (PIC/S, 2022) for advanced manufacturing technologies. Such an extension would reduce the costs of implementing procedures across multiple regions.

8.2. Recommendations for sponsor organizations (analytical, manufacturing, and quality leadership).

R5. Before any major innovation is rolled out, an implementation diagnostic based on the CFIR should be carried out. This method detects barriers that exist in both the internal and external environments at the facility, network, and supply-chain levels (Damschroder *et al*., 2009; Damschroder *et al*., 2022).

R6. A dedicated ERIC strategy bundle for the pharmaceutical sector should be created. The literature points to a core bundle among the 73 ERIC strategies, this comprising train-the-trainer programmes, facility-level audit and feedback, knowledge management in accordance with ICH Q10 (International Council for Harmonisation, 2008; U.S. Food and Drug Administration, 2009), the involvement of opinion leaders in technical operations, and structured pre-submission engagement under the FDA's ETP (U.S. Food and Drug Administration, 2024e).

R7. Rather than viewing ICH Q14 and ICH Q2(R2) (International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d) as tactical compliance projects, they should be regarded as strategic capabilities; it is essential to set up the analytical target profile, the lifecycle standard operating procedures, and the statistical infrastructure in order to support comprehensive analytical quality by design in all new method development.

R8. Real-time release testing (RTRT) pilot schemes should only be carried out in those situations where an adequate level of understanding of the process, the capability of process analytical technology, and lifecycle governance have been achieved (European Medicines Agency, 2012; Goodwin *et al*., 2018; International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d; U.S. Food and Drug Administration, 2004a). Before end-product testing is reduced, conventional release fallback procedures, model maintenance plans, data integrity controls, and change management procedures must be established.

R9. Data integrity has to be treated not only as an issue relating to implementation but also as a compliance obligation. Evidence from warning letters and analyses related to Industry 4.0 shows that sustainable remediation necessitates technical controls, a solid data architecture, governance, training, and management supervision (Alosert *et al*., 2022; Park & Kwon, 2026; U.S. Food and Drug Administration, 2024g).

R10. Set RE-AIM-aligned KPIs.

The key performance indicators include Reach (measured as a percentage of products), Effectiveness (which refers to the critical quality attribute or the outcome of a deviation), Adoption (given as a percentage of facilities), Implementation (as assessed by a fidelity audit), and Maintenance (involving continued use throughout the lifecycle). A proposed KPI dashboard is given in Table 5.

8.3. Recommendations for academia and the pharmacopeial community.

R11. In addition to technical demonstrations, empirical implementation studies should be published, and the pharmaceutical literature could benefit from hybrid effectiveness-implementation studies (Curran *et al*., 2012) that report on context, strategy, fidelity, adoption, sustainment, cost, and unintended consequences alongside technical performance.

R12. It is important to continue to ensure alignment among the USP, Ph. Eur., JP, ICH Q14, and ICH Q2(R2) frameworks (International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d; United States Pharmacopeia, 2017a; United States Pharmacopeia, 2017b). Any differences among the various pharmacopeias should be documented and addressed through risk-based transfer, validation, and lifecycle procedures, rather than assuming they are fully harmonized.

The twelve recommendations support one another. Recommendations R1 through R4 relate to the external environment; recommendations R5 through R10 relate to the internal environment; and Recommendations R11 and R12 help build the evidence base for further implementation. As shown in the matrix of strategies by barriers (Figure 5), those bundles which include elements from all three groups of actors are most likely to result in continued implementation.

8.4. Sequencing and prioritization.

The twelve recommendations should not all be implemented at the same time. According to implementation science frameworks, actions should be sequenced to take into account the organization's context, its readiness, and measurable learning outcomes (Curran *et al*., 2012; Damschroder *et al*., 2009; Damschroder *et al*., 2022; Powell *et al*., 2015). We therefore suggest a three-stage method. In the first wave, the emphasis is on establishing governance structures, identifying barriers, selecting measurable pilot projects, and developing the necessary basic capabilities. The second wave consists of extending proven approaches to a number of sites and product lines. The third wave is intended to embed lifecycle monitoring, achieve regulatory convergence, and promote continuous improvement.

8.5. Measurement and reporting.

When carrying out pharmaceutical implementation projects, it is necessary to report outcomes while maintaining appropriate confidentiality measures. The reports should clearly separate technical effectiveness from implementation outcomes and include a full account of the context, the strategy, fidelity, reach, adoption, maintenance, resource use, and any unintended effects (Curran *et al*., 2012; Damschroder *et al*., 2009; Damschroder *et al*., 2022; Glasgow *et al*., 1999; Glasgow *et al*., 2019; Messina, 2025; Powell *et al*., 2015). The thorough reporting of these details enables successful and unsuccessful implementation experiences to be applied in other organizations.

Table 5: RE-AIM-aligned KPI dashboard for pharmaceutical implementation projects

RE-AIM dimension	Pharmaceutical KPI	Data source	Illustrative target—qualification required
Reach	% of in-scope products using the new method/process	Submission tracking, MES	Organization-defined staged target
Effectiveness	CQA capability; deviation and OOS trends	QMS, LIMS	Product- and risk-specific acceptance criteria
Effectiveness	Cycle time to validation or regulatory submission	Project tracker	Prespecified improvement versus baseline
Adoption	% of facilities implementing	Site survey, audit	Network-specific staged target
Adoption	% of applicable new methods using an ATP	Method portfolio review	Defined by analytical portfolio and maturity
Implementation	Audit fidelity score	Internal audit	Prespecified minimum with remediation plan
Implementation	Regulatory engagement for higher-risk innovation	Agency correspondence	Engagement when risk and novelty warrant
Maintenance	Sustained use at 12 and 24 months	Periodic management review	No unexplained regression; continued control
Maintenance	Knowledge management aligned with ICH Q10	Knowledge-platform metrics	Centralized, current, retrievable, auditable
Cross-cutting	Quality-management maturity trajectory	Internal/QMM assessment	Stable, evidence-supported improvement

The RE-AIM dimensions have been adapted from the research of Glasgow and his colleagues (Glasgow *et al*., 1999; Glasgow *et al*., 2019). The targets listed in Table 5 are merely illustrative suggestions which will need to be further qualified in light of organizational, product, and risk-specific considerations. It is not correct to regard these targets as validated universal standards.

9. FUTURE OUTLOOK: AI, DIGITAL TWINS, AND PHARMA 4.0

The implementation environment is expected to change significantly due to three converging trends over the next five years.

9.1. Pharma 4.0 and digital maturity.

The operating model for ISPE Pharma 4.0 (ISPE, 2020) together with peer-reviewed literature on Industry 4.0 (Alosert *et al*., 2022; Arden *et al*., 2021) envisions a future in which quality systems, manufacturing execution, laboratory informatics, process models, and regulatory knowledge are widely integrated. This integration is anticipated to increase agility and improve understanding of the processes. However, potential risks associated with implementation include interoperability failures, uncontrolled data transformations, cybersecurity threats, unclear accountability, and loss of control over the validated state.

9.2. AI/ML and model-informed lifecycle.

The lifecycle reflection paper issued by the European Medicines Agency (European Medicines Agency, 2024d), along with the U.S. Food and Drug Administration's discussion paper on AI in manufacturing, its guidelines on drug-development resources, and its draft credibility guidance (U.S. Food and Drug Administration, 2023a; U.S. Food and Drug Administration, 2023b; U.S. Food and Drug Administration, 2024b; U.S. Food and Drug Administration, 2025a), together form an emerging regulatory framework for model-informed decision-making. For this framework to be effectively implemented, it is necessary to take into account the context of use, ensure that the data is representative, verify model performance, maintain human oversight, provide comprehensive documentation, put in place robust change management procedures, and carry out ongoing monitoring (Alosert *et al*., 2022; Arden *et al*., 2021; European Medicines Agency, 2024d).

9.3. Regulatory convergence and divergence.

Advancements in ICH Harmonisation are still underway. The launch of ICH Q13 on continuous manufacturing (International Council for Harmonisation, 2022a) and the associated updates to Q14 and Q2(R2) (International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d) represent the most significant recent developments. However, regional differences are still visible. The EU Pharma Reform proposal (European Parliament, 2024; Gamba *et al*., 2025) and the 2023 Annex 1 (European Commission, 2023) show that the European regulatory approach at times goes beyond US initiatives and at other times lags behind them. The consequence is that implementation strategies must be adapted to each region, since the same innovations may encounter different internal and external obstacles in the United States, the European Union, India, China, Brazil, or sub-Saharan Africa. The alignment between the WHO Good Manufacturing Practice (GMP) framework (World Health Organization, 2024) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S, 2022) provides mechanisms for achieving regulatory coherence, but these measures do not fully eliminate existing divergences.

9.4. Workforce and competency transformation.

The workforce's capabilities are a key factor shaping current developments in the industry. Pharmaceutical analytical scientists are now required to combine compendial validation with the requirements set out in ICH Q2(R2)/Q14 (International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d; United States Pharmacopeia, 2017b) alongside advanced knowledge in the areas of experimental design, multivariate analysis, informatics, model governance, and risk-based lifecycle management. It is recommended that companies establish competencies specific to each role, establish supervised qualification routes, and implement continuous education programs, rather than relying solely on traditional instrument training.

9.5. Animal-testing alternatives and the FDA Modernization Act 2.0.

The organ-on-a-chip, in silico, and human-cell models fall within a field of implementation defined by the FDA Modernization Act 2.0 (Han, 2023) and the FDA's 2025 initiative to reduce its dependence on animal testing for certain products (U.S. Food and Drug Administration, 2025c). Even though this topic goes beyond the main area of focus, which is chemistry, manufacturing, and controls (CMC), it does show a similar implementation challenge in that regulatory approval together with technical potential are not enough to ensure that the applications will be validated, carried out routinely, or be relevant for making decisions.

9.6. Cross-cutting prediction.

In the following five years, the application of the ICH Q14 concepts is expected to grow, although low-risk AI-assisted applications may gain regulatory approval and there could be greater use of continuous manufacturing. However, there is currently no evidence to support accurate global percentage forecasts. Advances are likely to be uneven across different modalities, companies of different sizes, product lines, and regions (Arden *et al*., 2021; European Medicines

Agency, 2023a; European Medicines Agency, 2024d; Fisher *et al*., 2022; International Council for Harmonisation, 2023c; International Council for Harmonisation, 2023d; U.S. Food and Drug Administration, 2025a; Wahlich, 2021).

9.7. Equity, access, and global health implications.

The implications go beyond just productivity and also involve public health and issues of equity. The WHO Prequalification program (World Health Organization, 2024) and the PIC/S framework (PIC/S, 2022) offer routes to regulatory approval for low- and middle-income countries. That said, a significant technological gap still exists between manufacturing in innovator companies and that in emerging markets, as this review has pointed out. Because the International Council for Harmonisation (ICH) is expanding its membership and more regulatory authorities are joining PIC/S, there is an increasing opportunity to spread validated innovations in chemistry, manufacturing, and controls (CMC) to a broader number of markets. Even though implementation strategies which are effective in high-resource settings may need to be adapted, as shown in the field of implementation science (Damschroder *et al*., 2009; Nilsen *et al*., 2023), the basic frameworks can still be applied. All the initiatives aimed at tackling drug shortages, boosting biosimilar uptake, and improving pandemic preparedness depend on moving forward with global implementation efforts (Carl *et al*., 2022; U.S. Food and Drug Administration, 2019; U.S. Food and Drug Administration, 2025b; World Health Organization, 2024).

9.8. LIMITATIONS OF THIS REVIEW

There are several limitations associated with this structured narrative review. Publicly available evidence might give a distorted view by highlighting more successful pilot projects than those that have been discontinued, delayed, or failed. The existing body of evidence is mainly drawn from the United States, the European Union, and ICH-associated areas, with only limited empirical data from low-resource and non-ICH settings. Because there is a great deal of variation among the technologies, estimates of adoption outcomes, and the way results are reported, it is not possible to arrive at a defensible estimate of pooled adoption or to conduct a meta-analysis. Figures 2, 3, 4, and 5 are conceptual diagrams developed by the authors and are not quantitative syntheses of the evidence; the KPI thresholds in Table 5 are merely illustrative and not validated universal standards. The proposed ERIC adaptation has not yet been the subject of formal expert consensus or prospective validation. Overcoming these limitations will depend on conducting transparent, multi-site implementation studies, publishing both positive and negative results, and adopting a standard approach to reporting context, fidelity, adoption, sustainment, resource use, and unintended effects.

10. CONCLUSION

The pharmaceutical industry is at a crucial junction. Even though there is a great deal of evidence and well-defined regulatory routes available for a number of innovations, the routine introduction of these innovations remains slow, inconsistent, and incomplete. To resolve this paradox, the present review draws on implementation science. The analysis, which is based on peer-reviewed evidence, the main regulatory and pharmacopeial documents, and a selection of governmental, intergovernmental, and professional sources, contends that implementation capability is a major but by no means the only limitation on adoption.

The review includes a pharmaceutical-adapted CFIR × ERIC × RE-AIM framework (see Figure 4), a qualitative strategy–barrier mapping approach that was developed by the authors (see Figure 5), a comparative regulatory landscape (see Figure 1 and Table 1), a conceptual implementation funnel (see Figure 3), a conceptual know-do gap (see Figure 2), and twelve evidence-based recommendations. The degree to which each innovation has achieved regulatory and technical maturity depends on the specific application. As a result, implementation strategies have to be chosen and assessed in the relevant context.

The practical effects on pharmaceutical analytical scientists are considerable. ICH Q14 and ICH Q2(R2) have set out a lifecycle approach to analytical procedures (International Council for Harmonization, 2023c; International Council for Harmonization, 2023d). Process Analytical Technology (PAT), Real-Time Release Testing (RTRT), and continuous manufacturing each have clearly defined regulatory routes and have been shown to have practical applications (European Medicines Agency, 2012; Fisher *et al*., 2022; Goodwin *et al*., 2018; International Council for Harmonisation, 2022a; U.S. Food and Drug Administration, 2004a; U.S. Food and Drug Administration, 2023c; Wahlich, 2021). Emerging as well are frameworks for assessing the credibility of artificial intelligence and machine learning (AI/ML) (European Medicines Agency, 2024d; U.S. Food and Drug Administration, 2025a). The challenges that remain involve developing workforce capabilities, ensuring data integrity, advancing knowledge management, strengthening validation and governance, and promoting cross-functional collaboration to turn innovations into routine practice.

Implementation science provides a wide range of tools and approaches to aid these initiatives. Even though its use in the pharmaceutical industry has been postponed so far, it is now necessary. The effects of continued delay in action are clearly seen in current drug shortages, frequent quality failures, ongoing inefficiencies in research and development, and unequal global access. On the other hand, the costs of taking

action include investments in building capabilities, managing knowledge, and conducting rigorous evaluations. By prioritizing implementation and innovation, pharmaceutical companies and regulators will ensure that proven solutions are consistently implemented for each product, in each market, and throughout the product lifecycle.

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