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Pharmaceutical Regulatory Affairs: Global Perspectives

Rajesh Kumar Banerjee^{1*}, Ananya Priya Deshpande², Vikram Arjun Menon³

¹ PhD, Department of Pharmaceutical Nanotechnology, National Institute of Pharmaceutical Education and Research (NIPER), Mohali, India

² PhD, Centre for Targeted Drug Delivery, Indian Institute of Technology Delhi, India

³ PhD, Institute for Cancer Nanomedicine, Tata Memorial Centre, Mumbai, India

* Corresponding Author: **Rajesh Kumar Banerjee**

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Abstract

The pharmaceutical industry operates within an increasingly complex global regulatory environment that governs every stage of drug development, approval, and post-marketing surveillance. Regulatory affairs professionals must navigate diverse requirements across multiple jurisdictions while ensuring patient safety, product quality, and timely market access. This article examines the current landscape of pharmaceutical regulation from a global perspective, focusing on critical themes that shape contemporary regulatory practice. Key areas explored include the evolution of regulatory harmonization through initiatives such as the International Council for Harmonisation, strategies for effective regulatory dossier preparation across different regions, maintenance of quality compliance throughout the product lifecycle, implementation of robust pharmacovigilance systems, and utilization of expedited approval pathways for innovative therapies. The analysis addresses how regulatory convergence and reliance mechanisms are reducing duplication while maintaining rigorous standards, and how digital transformation is reshaping regulatory processes through electronic submissions, real-world evidence utilization, and artificial intelligence applications. The article also examines persistent challenges including resource constraints in emerging markets, complexity of biosimilar and advanced therapy regulation, and the need for adaptive frameworks to accommodate rapid scientific innovation. Understanding these regulatory dynamics is essential for optimizing global drug development timelines, ensuring equitable patient access to novel therapeutics, and maintaining the delicate balance between innovation acceleration and comprehensive safety evaluation. The future of pharmaceutical regulation will likely emphasize greater international collaboration, risk-based approaches, and technology-enabled regulatory science.

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Introduction

Pharmaceutical regulatory affairs represents a specialized discipline that serves as the critical interface between drug development organizations and governmental health authorities worldwide. The primary mandate of regulatory systems is to protect public health by ensuring that medicinal products meet stringent standards for safety, efficacy, and quality before reaching patients^[1]. However, the regulatory landscape has evolved considerably from its historical origins, transforming from predominantly national frameworks into an interconnected global system characterized by increasing harmonization, mutual

recognition, and scientific collaboration [2]. This evolution reflects both the internationalization of pharmaceutical research and development as well as recognition that duplicative regulatory requirements impose substantial burdens on drug developers without proportionate benefits for patient safety [3].

The contemporary regulatory environment presents numerous challenges for pharmaceutical companies seeking to develop and commercialize products across multiple markets. Different regulatory agencies maintain distinct requirements for clinical trial design, manufacturing standards, dossier formats, and post-approval obligations, necessitating sophisticated regulatory strategies that balance global efficiency with local compliance [4]. Regulatory timelines directly impact patient access to innovative therapies, making the optimization of approval processes a critical concern for both industry and public health stakeholders [5]. Furthermore, the rapid advancement of biomedical science has introduced novel therapeutic modalities including gene therapies, cell-based treatments, and personalized medicine approaches that challenge traditional regulatory paradigms designed primarily for small molecule drugs [6].

International harmonization efforts have achieved significant progress in reducing regulatory fragmentation, most notably through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, which has developed consensus guidelines adopted by regulatory authorities across the Americas, Europe, and Asia [7]. Parallel initiatives including the Pharmaceutical Inspection Co-operation Scheme and regional regulatory cooperation programs have further promoted convergence in manufacturing standards and inspection practices [8]. Despite these advances, meaningful differences persist across regulatory jurisdictions, particularly between highly resourced agencies in developed markets and emerging regulatory authorities in low- and middle-income countries [9].

The regulatory profession itself has evolved substantially, with modern regulatory affairs specialists requiring multidisciplinary expertise spanning clinical science, manufacturing operations, quality management, legal compliance, and strategic planning [10]. Professional competency frameworks and certification programs have emerged to standardize training and recognize qualified practitioners, reflecting the increasing sophistication and strategic importance of regulatory affairs within pharmaceutical organizations [11]. Regulatory intelligence, defined as the systematic gathering and analysis of regulatory information to inform strategic decision-making, has become an essential capability for navigating the complex global regulatory environment [12].

This article provides a comprehensive examination of pharmaceutical regulatory affairs from a global perspective, analyzing key regulatory frameworks, harmonization initiatives, lifecycle management strategies, quality and compliance requirements, pharmacovigilance obligations, and emerging trends that are reshaping the regulatory landscape. Understanding these foundational elements is essential for regulatory professionals, drug developers, and policy makers seeking to optimize the development and approval of safe and effective medicines for patients worldwide.

Global Regulatory Frameworks and Key Agencies

Pharmaceutical regulation is administered through a network of national and regional regulatory authorities that establish and enforce standards for medicinal products within their respective jurisdictions. The United States Food and Drug Administration stands as one of the oldest and most influential regulatory agencies globally, tracing its origins to the Pure Food and Drug Act of 1906 and substantially strengthened through subsequent legislation including the Federal Food, Drug, and Cosmetic Act of 1938 and the amendments introduced following the thalidomide tragedy [13]. The FDA maintains comprehensive regulatory oversight spanning drug discovery through post-marketing surveillance, with organizational divisions dedicated to specific product categories including the Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health [14].

The European Medicines Agency operates within a unique regulatory framework that combines centralized and decentralized procedures across the European Union member states. Established in 1995, the EMA coordinates the scientific evaluation of medicines through a network of national competent authorities and expert committees, with the Committee for Medicinal Products for Human Use serving as the primary scientific body for human medicines [15]. The centralized procedure, mandatory for certain innovative products including biotechnology-derived medicines and orphan drugs, results in a single marketing authorization valid across all EU member states, while the decentralized and mutual recognition procedures allow for coordinated national approvals [16]. Following Brexit, the United Kingdom established the Medicines and Healthcare products Regulatory Agency as an independent authority, introducing additional complexity to the European regulatory landscape [17].

Japan's Pharmaceuticals and Medical Devices Agency operates under the Ministry of Health, Labour and Welfare and represents the primary regulatory authority for the Asian market. The PMDA has undergone significant modernization in recent decades, implementing regulatory reforms aimed at accelerating drug approval timelines and enhancing alignment with international standards [18]. The agency has invested substantially in building review capacity and expertise, particularly for innovative therapeutic modalities, while maintaining rigorous safety standards informed by historical incidents including medication-related adverse events that have shaped Japanese regulatory culture [19].

Regulatory authorities in emerging markets demonstrate considerable heterogeneity in organizational structure, resource capacity, and regulatory maturity. The National Medical Products Administration in China has emerged as an increasingly important regulatory body, implementing substantial reforms to modernize drug approval processes, enhance transparency, and improve alignment with international standards [20]. India's Central Drugs Standard Control Organisation regulates the world's largest generic pharmaceutical manufacturing sector while managing unique challenges related to quality oversight across thousands of manufacturing facilities [21]. Brazil's National Health Surveillance Agency, South Africa's Medicines Control Council, and other regulatory authorities in middle-income countries continue to strengthen their regulatory systems

through capacity-building initiatives and international collaboration [22].

The World Health Organization plays a crucial coordinating role in the global regulatory ecosystem through its Prequalification Programme, which assesses the quality, safety, and efficacy of medicines and vaccines for procurement by UN agencies and GAVI, focusing primarily on products addressing diseases of public health importance in resource-limited settings [23]. WHO also administers initiatives aimed at strengthening regulatory capacity in developing countries, recognizing that functional national regulatory authorities represent essential infrastructure for health system performance and access to quality medicines [24]. Regional regulatory harmonization initiatives including the African Medicines Regulatory Harmonisation Programme, the Association of Southeast Asian Nations harmonization working groups, and the Pan American Health Organization's regional system have advanced convergence among member states [25].

Regulatory frameworks vary substantially in their legal foundations, organizational structures, and operational approaches, reflecting different policy priorities, resource constraints, and socio-political contexts. However, common core principles unite regulatory authorities worldwide, including commitment to science-based decision making, protection of public health as the paramount objective, transparency in regulatory processes, and proportionality in balancing benefits and risks of medicinal products [26]. The challenge for multinational pharmaceutical development is navigating this diversity while maintaining efficiency and ensuring that regulatory requirements serve their fundamental protective purpose without creating unnecessary barriers to patient access.

Harmonization, Reliance, and Regulatory Convergence

International harmonization of pharmaceutical regulation has progressed substantially over the past three decades, driven by recognition that divergent technical requirements increase development costs and delay patient access without corresponding improvements in product safety or efficacy. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, established in 1990 as a joint initiative of regulatory authorities and pharmaceutical industry associations from Europe, Japan, and the United States, has produced an extensive portfolio of guidelines addressing quality, safety, efficacy, and multidisciplinary topics [27]. These ICH guidelines, developed through expert working groups and consensus processes, have achieved broad implementation across ICH founding members and subsequent adopting authorities, creating substantial technical convergence in areas including stability testing, impurities specifications, analytical validation, nonclinical safety studies, and good clinical practice standards [28].

The ICH quality guidelines, designated by the Q prefix, establish harmonized standards for pharmaceutical development, manufacturing, and control. Notable examples include ICH Q8 on pharmaceutical development, which introduces quality by design principles, ICH Q9 on quality risk management, which provides a systematic framework for risk-based decision making, and ICH Q10 on pharmaceutical quality systems, which describes a comprehensive model for managing quality throughout the product lifecycle [29]. The safety guidelines address nonclinical testing requirements,

with ICH S series documents covering toxicology studies, carcinogenicity assessment, genotoxicity testing, and reproductive toxicology, while the efficacy guidelines focus on clinical trial design, statistical methodology, and specific therapeutic areas [30].

The Common Technical Document, described in ICH M4, represents perhaps the most practically significant harmonization achievement, establishing a standardized format and organization for regulatory submissions that is accepted by authorities in the ICH regions and many other countries [31]. The CTD structure organizes information into five modules covering administrative information, quality overall summaries, nonclinical overview and summaries, clinical overview and summaries, and detailed technical documentation, with the modular architecture facilitating both initial submissions and lifecycle variations [32]. Electronic submissions in eCTD format have further standardized the technical specifications for regulatory dossiers, enabling more efficient document management and review processes [33].

Regulatory reliance represents a complementary approach to harmonization in which regulatory authorities leverage the assessments and decisions of other trusted agencies to inform their own regulatory determinations. Reliance mechanisms range from recognition of foreign regulatory decisions, where one authority accepts another's approval as evidence supporting a local marketing authorization, to work-sharing arrangements where reviewing responsibilities are distributed among participating authorities [34]. The WHO has actively promoted reliance as a strategy for strengthening regulatory efficiency, particularly for authorities with limited review capacity, developing a framework that describes different levels of reliance from awareness of other decisions through full recognition [35].

Several regional regulatory cooperation initiatives have advanced harmonization and reliance among member states. The African Medicines Agency, established to coordinate regulatory activities across the African continent, builds upon earlier African Medicines Regulatory Harmonisation initiatives that created zonal coordination mechanisms and joint assessment procedures [36]. The East African Community Medicines Regulatory Harmonisation programme has achieved notable success in implementing joint reviews and mutual recognition of good manufacturing practice inspections among partner states [37]. Similar regional initiatives operate in the Caribbean, the Gulf Cooperation Council states, and other regions, each adapted to local context and institutional capacity [38].

The Access Consortium, comprising regulatory authorities from Australia, Canada, Singapore, Switzerland, and the United Kingdom, represents an innovative collaboration among agencies in smaller markets seeking to leverage collective expertise and avoid duplication in regulatory reviews. The consortium has implemented work-sharing pathways for certain applications and information exchange mechanisms that inform regulatory decision making while preserving each authority's independence in reaching final determinations [39]. The proliferation of such collaborative arrangements reflects growing acceptance that regulatory efficiency and scientific rigor are compatible objectives that can be advanced through international cooperation.

Despite substantial progress, challenges to complete harmonization persist. Differences in local epidemiology, medical practice patterns, genetic populations, and healthcare

infrastructure may justify some degree of regulatory variation across markets. Regulatory authorities face political pressures and public expectations that may conflict with full harmonization, particularly when foreign regulatory decisions appear to conflict with local risk tolerance or policy priorities ^[40]. Furthermore, harmonization of technical requirements does not necessarily translate to harmonized regulatory timelines, as review processes, resource allocation, and procedural requirements vary substantially across authorities. Continued advancement of harmonization and reliance will require sustained commitment from regulatory authorities, industry stakeholders, and international organizations, along with investments in capacity building to ensure that all regulatory authorities can effectively participate in and benefit from convergence initiatives.

Regulatory Strategy Across the Product Lifecycle

Effective regulatory strategy begins long before the submission of a marketing authorization application, extending across the entire product lifecycle from early development through generic competition and product discontinuation. Strategic regulatory planning requires anticipating requirements across target markets, identifying critical path activities that determine development timelines, and proactively engaging with regulatory authorities to obtain guidance and reduce uncertainty ^[41]. The regulatory strategy must be integrated with broader commercial and development objectives, ensuring that regulatory activities support rather than constrain business goals while maintaining scientific and ethical integrity ^[42].

Early-phase regulatory strategy focuses on establishing the regulatory classification of the investigational product, determining applicable regulatory pathways, and planning the nonclinical and clinical development programs to satisfy anticipated approval requirements. The selection of target indications, patient populations, and clinical endpoints has profound regulatory implications that extend throughout development, as authorities evaluate benefit-risk balance in the context of available therapeutic alternatives and unmet medical need within the proposed indication ^[43]. Sponsors must consider whether regulatory incentives such as orphan drug designation, pediatric investigation plans, or expedited review pathways may be available and strategically valuable, as these designations typically must be obtained during development rather than at the time of marketing authorization application ^[44].

Regulatory interactions with health authorities represent critical opportunities to obtain feedback on development plans, discuss proposed trial designs, and address scientific or regulatory concerns before making substantial resource commitments. Pre-investigational new drug meetings in the United States, scientific advice procedures in Europe, and equivalent consultation mechanisms in other jurisdictions allow sponsors to present development plans and receive regulatory input on issues including nonclinical testing strategies, clinical trial endpoints, statistical analysis plans, and chemistry, manufacturing, and controls development. The quality of preparation for these interactions and the strategic framing of questions substantially influences the value derived from regulatory guidance, making these milestone meetings focus points for regulatory planning. Global development strategies must address the sequencing of regulatory submissions across markets, considering factors

including commercial priorities, clinical trial site selection, data requirements, and approval timeline expectations. Some sponsors pursue sequential submissions beginning with the United States or Europe and subsequently filing in other markets once approvals are obtained in reference regions, while others implement simultaneous global submission strategies seeking approvals across multiple markets in parallel. The optimal approach depends on product characteristics, competitive dynamics, and resource constraints, with no single strategy universally appropriate across all development programs.

Lifecycle management of approved products requires ongoing regulatory activities including submission of manufacturing changes, approval of line extensions and new indications, maintenance of labeling to reflect accumulating safety and efficacy data, and compliance with post-approval commitments including safety studies and risk management programs. Regulatory intelligence regarding competitor activities, evolving regulatory requirements, and changing scientific standards informs lifecycle strategy, while regulatory expertise ensures that variations and supplements are appropriately categorized and submitted according to applicable procedures. The increasing use of real-world evidence to support regulatory decision making creates new opportunities for lifecycle management, allowing sponsors to leverage post-marketing data to expand indications, modify dosing recommendations, or address safety signals.

Product discontinuation, while often overlooked in regulatory strategy discussions, requires careful planning and regulatory compliance. Authorities typically require advance notification of product discontinuances to allow for patient transition to alternative therapies, and some jurisdictions impose obligations to maintain supply during specified transition periods or to transfer marketing authorizations to other companies willing to maintain supply. Strategic considerations regarding generic competition, including timing of regulatory submissions by generic manufacturers and brand-name company responses to generic entry, have important regulatory dimensions related to patent listings, regulatory exclusivities, and authorized generic arrangements.

The evolution of regulatory science and the introduction of novel approval mechanisms including accelerated approval, conditional marketing authorizations, and adaptive pathways require regulatory strategies that can capitalize on these opportunities while managing associated obligations and uncertainties. Companies must evaluate whether pursuing expedited pathways aligns with development capabilities and commercial objectives, recognizing that accelerated approvals typically require confirmatory studies that represent substantial post-approval commitments. Regulatory strategy must be dynamic and responsive to changing circumstances, with defined decision points and contingency plans that allow adaptation as development programs progress and new information becomes available.

Quality, Manufacturing, and GMP Compliance

Quality assurance represents a fundamental pillar of pharmaceutical regulation, with comprehensive requirements governing manufacturing processes, analytical testing, quality control, and quality management systems. Good manufacturing practice standards establish enforceable requirements for personnel qualification, facility design and maintenance, equipment calibration and maintenance, raw

material control, production operations, quality control testing, documentation, and complaint handling. Although GMP requirements share common principles globally, the specific regulatory expectations and inspection practices vary across jurisdictions, requiring manufacturers to maintain compliance with standards applicable to each market where products are distributed.

The Pharmaceutical Inspection Co-operation Scheme facilitates international cooperation on GMP inspections and enforcement, with participating authorities from over fifty countries sharing inspection reports, coordinating inspection activities, and working toward convergence in GMP standards and inspection practices. The PIC/S guide to good manufacturing practice, which aligns substantially with ICH quality guidelines and EU GMP standards, serves as a reference for many member authorities. Despite harmonization efforts, meaningful differences persist in specific GMP requirements, particularly regarding aspects such as validation expectations, cleaning validation acceptance criteria, and process validation approaches.

The pharmaceutical quality system, as described in ICH Q10, provides a model for managing quality throughout the product lifecycle, encompassing development, technology transfer, commercial manufacturing, product discontinuation, and knowledge management. The quality system includes management responsibilities, quality risk management, change management, management review, and internal audit functions, with objectives including achieving product realization, establishing and maintaining a state of control, and facilitating continual improvement. Implementation of robust quality systems supports both regulatory compliance and operational excellence, reducing the likelihood of quality defects, manufacturing deviations, and product recalls that impose substantial costs on manufacturers and potentially compromise patient safety.

Analytical method validation ensures that test methods reliably measure what they purport to measure with appropriate accuracy, precision, specificity, linearity, and robustness. The ICH Q2 guideline establishes harmonized validation requirements for analytical procedures used in pharmaceutical testing, while ICH Q14 provides contemporary guidance on analytical procedure development incorporating analytical quality by design principles. Specification setting for drug substances and drug products must ensure that materials meeting the specifications consistently deliver products that meet quality, safety, and efficacy requirements, with specifications typically addressing identity, assay, impurities, physical properties, and performance characteristics such as dissolution.

Stability testing provides evidence regarding how the quality of a drug substance or drug product varies with time under the influence of environmental factors such as temperature, humidity, and light, establishing shelf life and storage conditions for marketed products. ICH Q1A through Q1F guidelines establish comprehensive stability testing requirements, including long-term and accelerated testing conditions, photostability testing, and stability testing in container closure systems. Stability programs must be maintained throughout the product lifecycle, with ongoing stability studies confirming that commercial batches continue to meet specifications throughout their shelf lives.

Quality by design represents a paradigm shift in pharmaceutical development and manufacturing, emphasizing systematic understanding of product and

process characteristics, defining design space within which process parameters can vary without impacting quality, and implementing control strategies based on sound science and quality risk management. QbD approaches, described in ICH Q8, Q9, and Q10, enable more flexible regulatory approaches including the possibility of post-approval changes within the approved design space without requiring regulatory submissions. Implementation of QbD requires substantial upfront investment in process understanding but can generate long-term benefits including reduced process variability, increased process efficiency, and enhanced regulatory flexibility.

Manufacturing changes, whether involving production sites, manufacturing processes, analytical methods, specifications, or other aspects of chemistry, manufacturing, and controls, require evaluation to determine regulatory classification and submission requirements. Changes may be categorized as minor, moderate, or major variations depending on their potential impact on product quality, safety, or efficacy, with regulatory authorities prescribing different notification and approval requirements for each category. Change management processes must ensure that appropriate scientific assessment is completed, regulatory submissions are prepared when required, and implementation occurs only after necessary regulatory clearances are obtained.

Clinical Trial Regulation and Ethical Oversight

Clinical trials of investigational medicinal products are subject to comprehensive regulatory oversight designed to protect trial participants while ensuring that trials generate reliable scientific evidence. Regulatory requirements for clinical trials span authorization to conduct trials, oversight of trial conduct, adverse event reporting, data integrity, and informed consent, with some aspects regulated by health authorities and others primarily governed by research ethics committees. The balance between regulatory authority oversight and ethics committee review varies across jurisdictions, with some countries maintaining dual review systems and others consolidating authority in a single regulatory body.

Investigational new drug applications or clinical trial applications must be submitted to regulatory authorities before initiating clinical studies in most jurisdictions, providing authorities opportunity to review proposed trial protocols, investigator qualifications, nonclinical safety data, manufacturing information for investigational products, and proposed informed consent documents. In the United States, the IND becomes effective thirty days after submission unless the FDA places the application on clinical hold, while European Member States implement varied procedures with some operating under tacit consent timelines and others requiring explicit authorization. The content requirements for clinical trial applications have been substantially harmonized through ICH E6 good clinical practice guideline and ICH M3 on nonclinical safety studies for the conduct of human clinical trials.

Good clinical practice standards establish ethical and scientific quality requirements for designing, conducting, recording, and reporting clinical trials, ensuring that the rights, safety, and wellbeing of trial participants are protected and that clinical trial data are credible and accurate. The ICH E6 guideline on good clinical practice represents the internationally recognized standard, establishing principles and requirements for institutional review boards,

investigators, sponsors, and monitors involved in clinical research. GCP requirements address informed consent processes, protocol development, investigator qualifications and responsibilities, sponsor oversight, monitoring activities, adverse event management, data management, and documentation practices.

Ethics committee or institutional review board review provides independent evaluation of the scientific merit and ethical acceptability of proposed clinical research, with particular focus on ensuring that risks to participants are minimized and reasonable in relation to anticipated benefits, that informed consent processes are adequate, and that participant selection is equitable. The composition, procedures, and authority of ethics committees vary internationally, although common standards emphasize independence, multidisciplinary expertise, and systematic review procedures. Some countries operate centralized ethics review systems for multicenter trials, while others require separate review by ethics committees at each participating institution, impacting timelines and administrative burden for trial sponsors.

Informed consent represents a fundamental ethical requirement for clinical research, ensuring that potential participants receive comprehensive information about trial purposes, procedures, risks, benefits, alternatives, and rights, and provide voluntary agreement to participate based on adequate understanding. Regulatory standards for informed consent address the content that must be disclosed, the process for obtaining consent, documentation requirements, and special considerations for vulnerable populations including children, pregnant women, and individuals with impaired decision-making capacity. The increasing complexity of clinical trials and informed consent documents has raised concerns about participant comprehension, leading to initiatives focused on improving the clarity and accessibility of consent materials.

Adverse event reporting requirements obligate investigators and sponsors to report serious adverse events to regulatory authorities and ethics committees within specified timeframes, allowing authorities to assess evolving safety information and take action if necessary to protect trial participants or modify trial conduct. The definitions of adverse events, serious adverse events, and suspected unexpected serious adverse reactions have been harmonized internationally, along with expectations for expedited reporting and periodic safety reporting. The volume of safety reports generated in large clinical trial programs has prompted discussions about optimizing reporting requirements to focus on clinically significant safety signals while reducing administrative burden associated with reports that provide limited new information.

Clinical trial registries and results databases enhance transparency by making information about ongoing and completed trials publicly accessible, addressing concerns about selective reporting and publication bias that may distort the medical literature and clinical decision making. Regulatory requirements or policies in the United States, Europe, and many other jurisdictions mandate registration of clinical trials and disclosure of summary results, typically through platforms such as ClinicalTrials.gov or the European Union Clinical Trials Register. Sponsors must implement processes to ensure timely and accurate registration and results reporting while protecting commercially confidential information and participant privacy.

Pharmacovigilance and Post-Marketing Surveillance

Pharmacovigilance encompasses the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems, with systematic post-marketing surveillance essential for identifying safety signals that may not be apparent during pre-approval clinical development programs. The limitations of clinical trials, including restricted patient populations, limited durations of exposure, controlled conditions of use, and finite sample sizes, mean that important safety information frequently emerges only after marketing authorization when larger and more diverse patient populations receive treatment under real-world conditions. Spontaneous adverse event reporting systems represent the foundation of pharmacovigilance in most countries, allowing healthcare professionals, patients, and pharmaceutical companies to report suspected adverse drug reactions to regulatory authorities for evaluation and signal detection. Major spontaneous reporting databases include the FDA Adverse Event Reporting System in the United States, EudraVigilance in Europe, and numerous national databases operated by regulatory authorities worldwide. Statistical signal detection methodologies applied to spontaneous reporting databases can identify disproportionate reporting patterns suggestive of potential safety signals requiring further investigation, although spontaneous reporting has well-recognized limitations including substantial underreporting and inability to establish causation or quantify incidence rates.

Individual case safety reports must be submitted by marketing authorization holders to regulatory authorities when they become aware of serious adverse events, with regulatory requirements specifying timelines for expedited reporting of serious and unexpected reactions and periodic submission of safety update reports summarizing all adverse event information received during defined intervals. The ICH E2A through E2F guidelines have harmonized pharmacovigilance requirements including definitions, reporting standards, periodic safety update report formats, and development safety update reports, substantially reducing divergent requirements that historically imposed duplicative reporting burdens on multinational pharmaceutical companies.

Risk management planning has evolved from a reactive approach focused on responding to identified safety signals toward proactive risk minimization strategies implemented at the time of product launch. Risk management plans, required by regulatory authorities in the United States, Europe, and many other jurisdictions, systematically document what is known and unknown about product safety, describe planned pharmacovigilance activities, and detail risk minimization measures beyond routine product labeling that may be necessary to ensure safe and effective use. Risk minimization interventions range from targeted education programs for prescribers and patients through restricted distribution programs that impose controls on who may prescribe or dispense certain high-risk products.

Post-authorization safety studies may be required by regulatory authorities as conditions of approval or may be initiated voluntarily by marketing authorization holders to address safety questions that emerge during the product lifecycle. Study designs may include observational studies leveraging healthcare databases, disease registries, primary data collection studies, or clinical trials, with methodological

rigor and study size determined by the specific safety question being addressed. Regulatory authorities have increasingly exercised authority to require post-marketing studies, particularly for products approved through expedited pathways or for products where important safety questions remain unanswered at the time of initial authorization.

Benefit-risk evaluation represents a central concept in pharmacovigilance and regulatory decision making, recognizing that all medicinal products carry some degree of risk and that regulatory judgments must weigh demonstrated and potential benefits against identified and potential harms in the context of available therapeutic alternatives and severity of the condition being treated. Structured benefit-risk assessment frameworks have been developed to make benefit-risk evaluations more systematic, transparent, and consistent, although substantial judgment remains necessary in weighing incommensurable outcomes and addressing uncertainty. The benefit-risk balance may shift during the product lifecycle as additional safety or efficacy information accumulates, potentially leading to labeling modifications, risk minimization enhancements, indication restrictions, or in extreme cases product withdrawal.

Signal management processes ensure that potential safety signals identified through various sources including spontaneous reports, clinical trial data, published literature, or other information are systematically evaluated, with appropriate actions taken based on the strength of evidence and clinical significance of the signal. Signal management includes initial signal detection, signal validation to determine whether a causal association is biologically plausible and statistically supported, signal analysis to characterize the nature and magnitude of the risk, and signal disposition involving decisions about labeling updates, risk minimization measures, or additional studies. Effective signal management requires multidisciplinary expertise spanning epidemiology, clinical medicine, statistics, and regulatory affairs, along with efficient processes for information gathering and decision making.

Challenges, Emerging Trends, and Digital Transformation

The pharmaceutical regulatory environment faces numerous contemporary challenges that require adaptive responses from both regulatory authorities and industry stakeholders. Resource constraints affecting regulatory agencies, particularly in low- and middle-income countries, limit review capacity and inspection capabilities, potentially delaying approvals and constraining oversight of product quality and safety. Capacity building initiatives supported by the World Health Organization, bilateral development programs, and regional cooperation arrangements have made progress in strengthening regulatory systems, although substantial gaps persist in many countries.

The regulation of novel therapeutic modalities including cell and gene therapies, tissue-engineered products, and other advanced therapy medicinal products presents unique challenges due to product complexity, manufacturing variability, limited development experience, and uncertainties regarding long-term outcomes. Traditional regulatory frameworks developed primarily for chemically synthesized small molecules may not fully address the unique characteristics of biological products and advanced therapies, prompting authorities to develop specialized guidance and review procedures. The intersection of medical devices and

pharmaceuticals in combination products adds additional complexity requiring coordination between different regulatory divisions and potentially different approval pathways.

Personalized medicine and companion diagnostics create regulatory challenges regarding the coordination of drug and diagnostic development, the design of clinical trials in biomarker-defined patient populations, and the regulation of diagnostics that guide therapeutic decisions. Regulatory authorities have developed frameworks for co-development of therapeutics and companion diagnostics, although practical implementation challenges persist regarding review coordination, approval timing, and post-market oversight. The expansion of pharmacogenomic information in drug labeling has been gradual, with ongoing debate about standards of evidence required to support genetic testing recommendations and the clinical utility of pharmacogenomic information for individual prescribing decisions.

Digital transformation is reshaping pharmaceutical regulation through electronic submission systems, computational modeling and simulation, real-world evidence generation, and artificial intelligence applications in drug development and regulatory review. Electronic common technical document submissions have become standard in major markets, improving submission efficiency and enabling structured data exchange between sponsors and reviewers. Regulatory authorities are exploring artificial intelligence and machine learning tools to enhance review processes, analyze pharmacovigilance data, and identify quality signals in manufacturing data, although validation of AI systems and ensuring transparency in AI-assisted regulatory decisions pose challenges.

Real-world evidence derived from electronic health records, claims databases, patient registries, and other sources of data generated during routine clinical practice has attracted substantial interest as a potential source of regulatory evidence to supplement traditional clinical trial data. Regulatory authorities have issued guidance describing considerations for using real-world evidence to support regulatory decision making, including data quality, study design, and statistical analysis requirements. Applications of real-world evidence span diverse uses including supporting new indication approvals, satisfying post-approval study commitments, and contributing to safety signal evaluation, although challenges remain regarding data standardization, confounding control, and establishing standards for when real-world evidence may substitute for randomized controlled trials.

Patient engagement in drug development and regulatory decision making has expanded substantially, with regulatory authorities implementing mechanisms for incorporating patient perspectives into benefit-risk evaluations, expedited program determinations, and regulatory policy development. Patient-focused drug development initiatives seek to systematically gather patient input on disease burden, treatment preferences, and risk tolerance, informing regulatory review and decision making. The appropriate weight to give patient preferences when they diverge from traditional clinical outcomes remains subject to ongoing discussion and methodological development.

Regulatory agility and adaptive approaches are increasingly necessary to keep pace with scientific innovation while maintaining appropriate safety and efficacy standards.

Adaptive licensing frameworks, implemented in various forms across jurisdictions, allow for iterative approval based on progressive evidence generation, with initial approval in restricted populations or under specific conditions followed by expansion as additional data become available. These approaches potentially accelerate patient access to innovative therapies while managing uncertainty through staged evaluation, although they require robust post-authorization evidence generation and willingness to restrict or withdraw products if confirmatory evidence is not forthcoming.

Globalization of clinical trials and pharmaceutical manufacturing supply chains introduces complexity in regulatory oversight, particularly regarding quality assurance of products manufactured in multiple countries and ensuring the integrity of clinical trial data generated at sites distributed across numerous jurisdictions. Regulatory reliance and mutual recognition of inspections can enhance efficiency while maintaining oversight, although variation in regulatory capacity and enforcement rigor across countries raises concerns about regulatory arbitrage and the adequacy of oversight for products destined for highly regulated markets. The COVID-19 pandemic highlighted both the potential for accelerated regulatory cooperation during public health emergencies and the persistent challenges of ensuring equitable global access to medical products.

Conclusion

Pharmaceutical regulatory affairs operates at the critical intersection of biomedical science, public health policy, and commercial pharmaceutical development, ensuring that medicines available to patients meet rigorous standards for quality, safety, and efficacy while facilitating timely access to therapeutic innovation. The global regulatory landscape has evolved substantially from fragmented national systems toward increasing harmonization, cooperation, and reliance, reducing unnecessary duplication while preserving regulatory sovereignty and local decision making authority. International standards developed through the International Council for Harmonisation and other multilateral initiatives have created substantial technical convergence, particularly in quality requirements, good clinical practice standards, and submission formats, although meaningful differences persist across jurisdictions in procedural requirements, review timelines, and specific regulatory expectations.

Effective regulatory strategy spans the product lifecycle from early development planning through post-marketing surveillance and product discontinuation, requiring integration of regulatory considerations with scientific, commercial, and operational decision making. The increasing availability of expedited approval pathways, adaptive licensing frameworks, and real-world evidence mechanisms provides opportunities for accelerating development and

approval while simultaneously imposing post-authorization obligations and requiring sophisticated benefit-risk management. Quality assurance through good manufacturing practice compliance, robust analytical methods, and comprehensive quality systems remains fundamental to pharmaceutical regulation, with quality-by-design approaches offering potential for enhanced process understanding and regulatory flexibility.

Pharmacovigilance and post-marketing surveillance recognize the inherent limitations of pre-approval evidence and the necessity of ongoing safety monitoring throughout the product lifecycle to detect, characterize, and manage safety signals as they emerge in larger and more diverse patient populations. Risk management has evolved from reactive signal response toward proactive risk minimization planning, while maintaining the flexibility to adapt to new safety information through labeling updates, risk minimization enhancements, and in some cases indication restrictions or product withdrawals when benefit-risk balance shifts unfavorably.

Contemporary challenges facing pharmaceutical regulation include the need to adapt frameworks designed for conventional pharmaceuticals to accommodate advanced therapy medicinal products, personalized medicine, and other novel modalities, to leverage emerging data sources including real-world evidence while maintaining scientific rigor, to incorporate patient perspectives while preserving evidence-based decision making, and to build regulatory capacity in resource-limited settings to ensure global access to quality medical products. Digital transformation through electronic systems, computational methods, and artificial intelligence applications offers potential to enhance regulatory efficiency and effectiveness, although validation, transparency, and data integrity must be ensured.

The future of pharmaceutical regulation will likely emphasize greater international collaboration and reliance, risk-based and adaptive regulatory approaches that tailor oversight intensity to product characteristics and uncertainty levels, expanded use of real-world evidence to complement traditional clinical trial data, enhanced patient engagement in regulatory decision making, and continued evolution of regulatory science to maintain pace with biomedical innovation. Success will require sustained commitment from regulatory authorities, pharmaceutical industry stakeholders, and the broader scientific and policy communities to maintain the fundamental regulatory mission of protecting public health while enabling access to beneficial therapeutic innovations. As pharmaceutical science continues to advance and global health challenges evolve, regulatory affairs will remain an essential discipline ensuring that the promise of biomedical research translates into safe and effective medicines for patients worldwide.

Figures

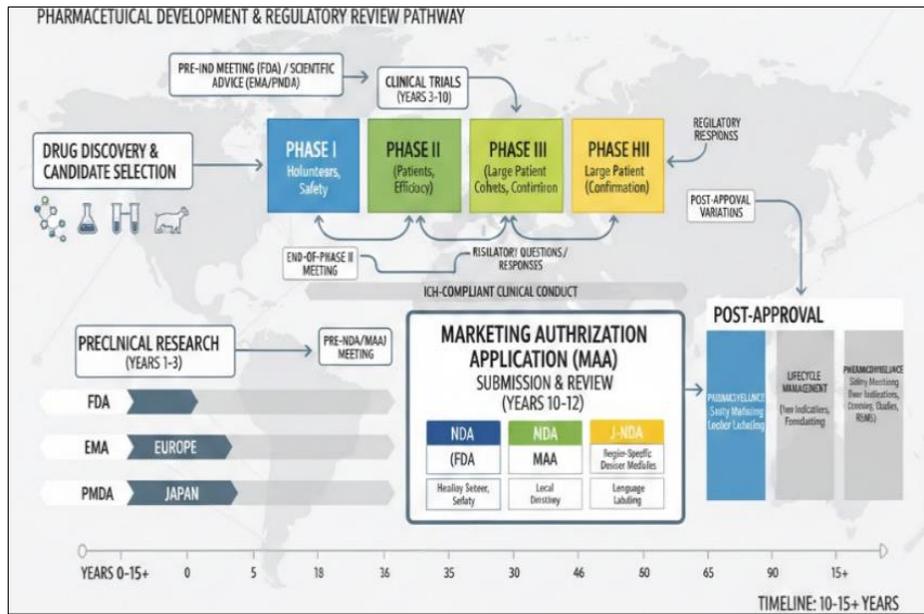


Fig 1: Global regulatory pathway from development to marketing authorization.

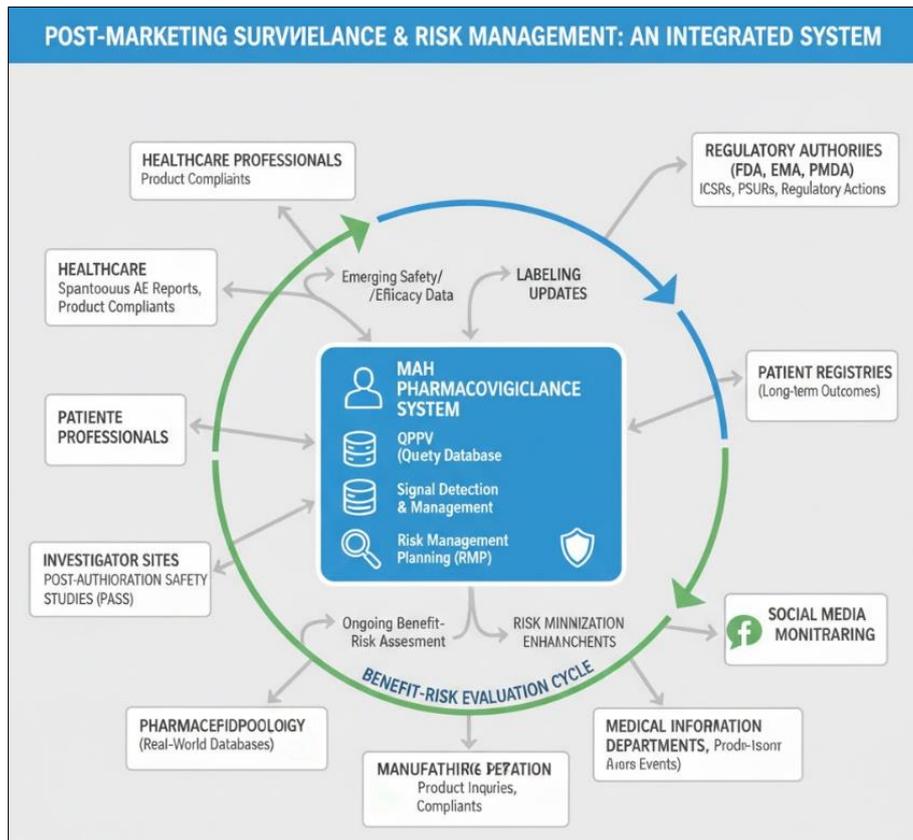


Fig 2: Post-approval lifecycle management and pharmacovigilance framework.

Tables

Table 1: Comparison of regulatory requirements across major global regions

Aspect	United States (FDA)	European Union (EMA)	Japan (PMDA)	Emerging Markets
Primary legislation	Federal Food Drug and Cosmetic Act, Public Health Service Act	Regulation 726/2004, Directive 2001/83/EC	Pharmaceutical Affairs Law, Pharmaceuticals and Medical Devices Act	Varies by country, often adapted from ICH guidelines
Marketing authorization routes	New Drug Application, Biologics License Application, 505(b)(2) pathway	Centralized procedure, decentralized procedure, mutual recognition procedure, national procedure	New Drug Application, abbreviated pathways for generics and biosimilars	Predominantly national procedures with some regional harmonization
Dossier format	eCTD based on ICH M4 with US-specific module 1	eCTD based on ICH M4 with EU-specific module 1	eCTD based on ICH M4 with Japan-specific module 1 and ethnic factors documentation	Variable, often CTD-based with local adaptations
Clinical trial authorization	IND effective 30 days after submission unless clinical hold	Clinical trial application with approval timelines varying by member state	Clinical trial notification with 30-day review period	Varies, often requiring explicit approval with variable timelines
Ethnic factors considerations	Generally not required unless specific population concerns identified	Required assessment of need for studies in European population	Extensive requirements for Japanese population pharmacokinetic and dose-response data	Variable requirements, some countries requiring local clinical data
Pediatric requirements	Pediatric Research Equity Act mandates pediatric studies unless waived	Paediatric Investigation Plan required for most new applications	Pediatric development plan required for innovative products	Generally limited pediatric requirements
Review timelines	10 months standard review, 6 months priority review for NDA	210 days for CHMP opinion in centralized procedure	12 months standard review, 9 months for priority review	Highly variable, ranging from 6 months to several years
Post-approval variations	Supplements categorized as prior approval, changes being effected, annual report	Variations categorized as Type IA, IB, and II with corresponding procedures	Partial change applications with categorization by significance	Variable procedures, often adapted from ICH or reference authority approaches
Pharmacovigilance	Periodic Adverse Experience Reports, Risk Evaluation and Mitigation Strategies when required	Periodic Safety Update Reports, Risk Management Plans mandatory	Periodic Safety Update Reports, Risk Management Plans for designated products	Variable requirements, often following ICH guidelines where capacity permits
Inspection approach	For-cause and surveillance inspections of manufacturing sites and clinical trial sites	Coordinated inspections by EMA and national competent authorities	PMDA inspections supplemented by reliance on foreign inspections for approved sites	Variable capacity, increasing reliance on WHO prequalification or reference authority inspections

Table 2: Key challenges and solutions in global regulatory affairs

Challenge	Description	Current Solutions	Future Directions
Divergent regulatory requirements	Different technical requirements, dossier formats, and procedural expectations across jurisdictions increase development complexity and costs	ICH harmonization guidelines, Common Technical Document format, regional harmonization initiatives, regulatory convergence programs	Extended ICH membership to additional countries, enhanced implementation of existing ICH guidelines, development of new guidelines for emerging technologies
Limited regulatory capacity in emerging markets	Resource constraints and insufficient technical expertise in many regulatory authorities delay approvals and limit oversight capability	WHO prequalification program, reliance mechanisms allowing leveraging of reference authority reviews, capacity building initiatives, collaborative registration procedures	Increased investment in regulatory system strengthening, technology transfer for electronic systems, regional centers of regulatory excellence, expanded reliance frameworks
Novel therapeutic modalities	Advanced therapies including gene therapies, cell-based treatments, and personalized medicines challenge traditional regulatory paradigms	Specialized regulatory pathways, dedicated review divisions, adaptive licensing frameworks, enhanced pre-submission interactions, registry-based approaches	Evolution of regulatory frameworks based on accumulating experience, development of modality-specific guidance, enhanced international coordination for novel products
Balancing speed and rigor	Pressure to accelerate approvals for innovative therapies while maintaining appropriate safety and efficacy standards	Expedited pathways including breakthrough designation, accelerated approval, conditional authorization, priority review, rolling review mechanisms	Risk-based approaches tailoring evidence requirements to benefit-risk context, expanded use of real-world evidence, adaptive trial designs, Bayesian statistical frameworks
Data integrity and trial conduct quality	Concerns about reliability of clinical trial data, particularly from sites in emerging markets, and prevention of fabrication or manipulation	Risk-based monitoring approaches, centralized data review, investigator training programs, inspection of clinical trial sites, data analytics to detect anomalies	Advanced analytics and artificial intelligence to identify data integrity signals, blockchain and other technologies for tamper-evident data recording, enhanced international inspection cooperation
Pharmacovigilance signal detection	Volume of spontaneous reports and challenges distinguishing true signals from noise in large safety databases	Disproportionality analysis methods, data mining algorithms, active surveillance using healthcare databases, patient registries, signal management prioritization frameworks	Machine learning approaches for signal detection, integration of multiple data sources, enhanced international signal sharing, patient-reported outcome collection through digital platforms
Supply chain complexity and quality assurance	Globalized manufacturing with active pharmaceutical ingredients and finished products produced across multiple countries complicates oversight	Mutual recognition of good manufacturing practice inspections, Pharmaceutical Inspection Co-operation Scheme, supply chain mapping requirements, serialization and track-and-trace systems	Expanded mutual recognition agreements, real-time manufacturing data sharing with regulators, continuous manufacturing with enhanced process analytics, blockchain for supply chain transparency
Regulatory requirements for companion diagnostics	Coordination of drug and diagnostic development, appropriate evidence standards for biomarker-based patient selection	Parallel review pathways coordinating drug and diagnostic evaluation, co-development guidance, biomarker qualification programs	Standardized frameworks for analytical and clinical validation of diagnostics, registry-based evaluation approaches, regulatory acceptance of next-generation sequencing panels
Patient access disparities	Substantial delays between initial approval in developed markets and availability in low- and middle-income countries	WHO prequalification enabling procurement for global health programs, voluntary licensing agreements, regulatory reliance enabling faster local approvals, collaborative registration procedures	Enhanced reliance mechanisms, abbreviated pathways for products approved by reference authorities, regional cooperation to create larger markets, tiered pricing and access programs
Adapting to digital health technologies	Medical software, digital therapeutics, artificial intelligence diagnostic and decision support tools, remote monitoring, and digital endpoints challenge traditional regulatory frameworks	Software as a Medical Device guidance, predetermined change control plans allowing iterative updates, real-world performance monitoring, regulatory sandboxes for novel technologies	Harmonized international frameworks for digital health regulation, standards for AI validation and transparency, frameworks for continuous learning systems, patient-generated health data qualification

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