



ONE MEDICINE, MANY RULES: GLOBAL HARMONIZATION AND REGULATORY FRAGMENTATION IN DRUG APPROVALS

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Abstract

The globalization of pharmaceutical markets has intensified the need for a unified regulatory approach to facilitate timely access to safe, effective, and affordable generic medicines. Despite advances in international regulatory harmonization, significant fragmentation persists among global drug approval systems, creating challenges for pharmaceutical development, post-approval management, and lifecycle optimization. This research critically examines the current regulatory landscape governing generic drug approvals across major global regions, highlighting both convergence and divergence in regulatory expectations. The study is structured into five analytical chapters covering regulatory frameworks in ASEAN countries, post-approval change management practices in the United States and European Union, regulatory submission requirements in Australia, and comparative bridging strategies across Australia, Canada, Europe, Russia, and ASEAN nations. Special emphasis is placed on post-approval variation procedures, regulatory timelines, documentation requirements, and risk-based classification systems adopted by different authorities. Industry-based case studies are incorporated to evaluate practical challenges and strategic solutions for global product development. Findings indicate that while harmonization initiatives such as ICH guidelines have improved regulatory consistency, region-specific procedural requirements, data expectations, and approval pathways continue to hinder the development of a single globally acceptable drug product. The research underscores the importance of proactive regulatory planning, reliance-based submissions, and strategic bridging approaches to minimize duplication, reduce development costs, and accelerate global market access. This study contributes to regulatory science by proposing integrated regulatory strategies aimed at balancing global harmonization with regional regulatory autonomy, ultimately supporting efficient generic drug development and improved patient access worldwide.

Keywords:

Global regulatory harmonization; Generic drug approval; Post-approval variations; Regulatory fragmentation; Bridging strategies; Pharmaceutical regulatory affairs

INTRODUCTION

1.1 Global Development of Medicines: From Local to International Markets

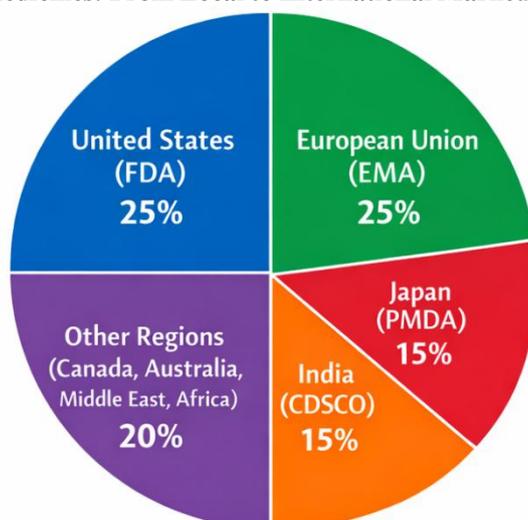


Figure 1: Global Regulatory Variation in Drug Approvals (2026)

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The pharmaceutical industry has shifted from locally focused drug development to a globally interconnected system. Modern medicines are often developed through multinational research programs, manufactured using globally sourced materials, and intended for marketing in several countries simultaneously. Scientifically, a drug remains the same regardless of where it is manufactured or marketed. However, the regulatory requirements governing its approval vary from country to country. This creates a fundamental challenge in global pharmaceutical development, commonly described as “*One Medicine, Many Rules.*”

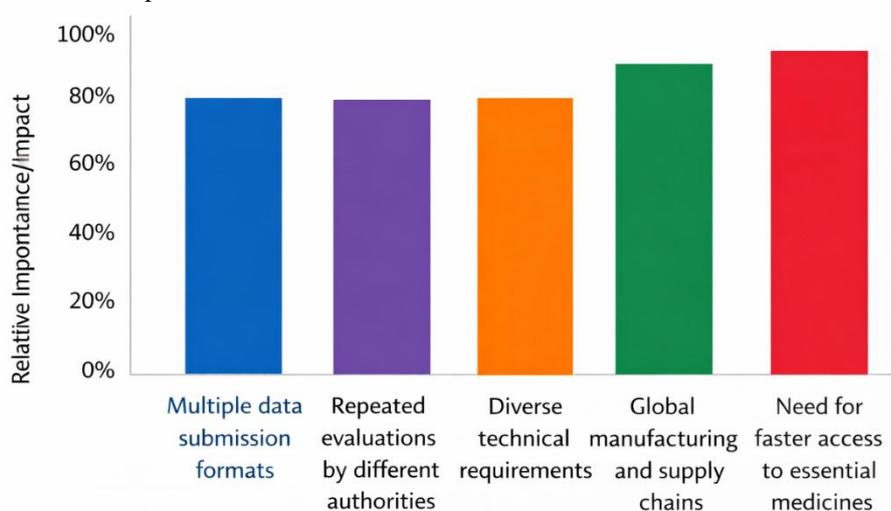
Every national regulatory authority is responsible for ensuring that medicines are safe, effective, and of acceptable quality for its population. While this responsibility is universal, the methods used to achieve it differ. Variations in legal frameworks, regulatory experience, healthcare priorities, and risk assessment approaches lead to differences in approval procedures. As a result, pharmaceutical companies must address multiple regulatory systems even when submitting identical scientific data for the same product.

“Despite ongoing international harmonization initiatives and increasing regulatory collaboration, these differences continue to shape global drug approval strategies even in recent periods.”

1.2 Why Regulatory Harmonization Became Necessary

As global drug development expanded, the need for regulatory harmonization became increasingly evident. Submitting the same data in different formats, undergoing repeated evaluations, and meeting diverse technical requirements resulted in increased costs and delayed patient access to medicines. Regulatory harmonization aims to reduce these inefficiencies by aligning scientific and technical requirements across regions while maintaining public health protection.

Harmonization does not seek to eliminate national regulations but rather to establish common scientific standards. This approach allows regulators to rely on shared principles for evaluating drug quality, safety, and efficacy. Over time, harmonization has become a key tool for improving regulatory efficiency and supporting global pharmaceutical development.



Graph 1: Key Drivers of Regulatory Harmonization in Global Drug Development

The bar chart illustrates the main factors driving regulatory harmonization in the pharmaceutical industry: Hence chart shows that globalization, reliance models, patient access, cost reduction, and safety are the primary motivators for regulatory harmonization, with each factor represented by a distinct colour for easy visualization.

1. Globalization of Manufacturing (Blue Bar)

As drug production spans multiple countries, consistent standards are needed to ensure quality and safety across regions.

Reliance Pathways (Green Bar)

Regulatory authorities increasingly depend on assessments from trusted agencies, reducing duplication of work.

Faster Access to Essential Medicines (Orange Bar)

Harmonization helps speed up approvals, ensuring patients receive critical treatments sooner.

Reduction of Costs and Redundant Evaluations (Red Bar)

Aligning technical requirements minimizes repeated submissions and resource expenditure for pharmaceutical companies.

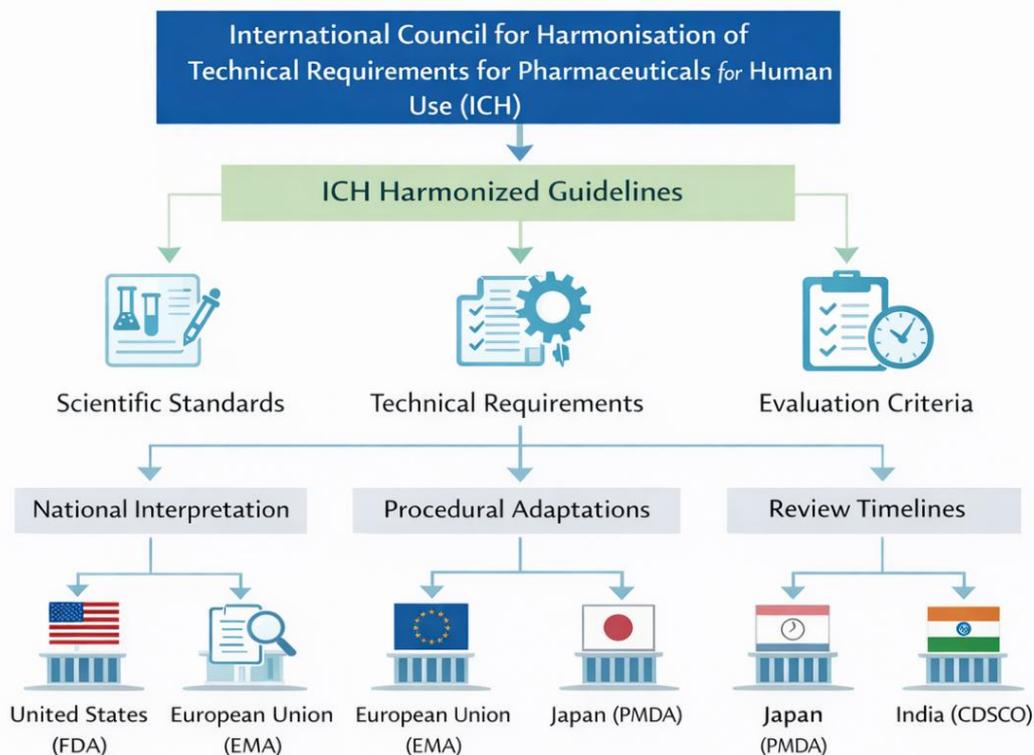
Public Health Protection (Purple Bar) Maintaining patient safety remains the core goal, even while harmonizing regulations internationally.

In recent years, regulatory harmonization has gained further importance due to globalization of manufacturing, increased reliance pathways, and the need for faster access to essential medicines.

1.3 Contribution of ICH to Scientific Alignment

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) plays a central role in global regulatory harmonization. ICH guidelines provide internationally accepted standards for pharmaceutical development, manufacturing, and evaluation. These guidelines help ensure that data generated during drug development are scientifically sound and acceptable to multiple regulatory authorities.

However, ICH guidelines are implemented at the national level, and regulatory authorities retain discretion in their application. Differences in interpretation, procedural requirements, and review timelines remain. Thus, while ICH provides a common scientific foundation, it does not result in identical regulatory outcomes across regions.



Flowchart 1: Contribution of ICH to Scientific Alignment

1. **ICH (Central Box, Dark Blue):** The International Council for Harmonisation sets globally accepted standards for drug development.

2. **ICH Harmonized Guidelines (Light Green Box):** Provides scientific standards, technical requirements, and evaluation criteria.

3. **National Implementation (Gray Boxes with Flags):**

Scientific standards, technical requirements, and evaluation criteria are applied differently in each country (US–FDA, EU–EMA, Japan–PMDA, India–CDSCO).

Procedural adaptations, review timelines, and national interpretation vary.

1. Outcome: While ICH ensures a common scientific foundation, regional differences remain, so regulatory outcomes are not identical.

2. Recent Updates (Note): Q12 (Lifecycle Management) and M10 (Bioanalytical Method Validation) reflect evolving scientific knowledge and regulatory expectations.

In recent years, ICH has continued to update guidelines, including Q12 for lifecycle management and M10 for bioanalytical method validation, reflecting evolving scientific knowledge and regulatory expectations. Despite these updates, regional adaptations and differing enforcement timelines mean that full global convergence of regulatory outcomes remains a challenge.

1.4 Role of WHO in Supporting Global Regulatory Convergence

The World Health Organization (WHO) focuses on improving global public health by strengthening regulatory systems worldwide. WHO provides technical guidance, promotes reliance-based approaches, and supports regulatory capacity building, particularly in developing countries. Through initiatives such as prequalification and essential medicines programs, WHO encourages the use of internationally accepted standards.

At the same time, WHO recommendations are adapted by individual countries to suit local healthcare needs. These adaptations, although necessary, contribute to regulatory variability. Consequently, WHO supports

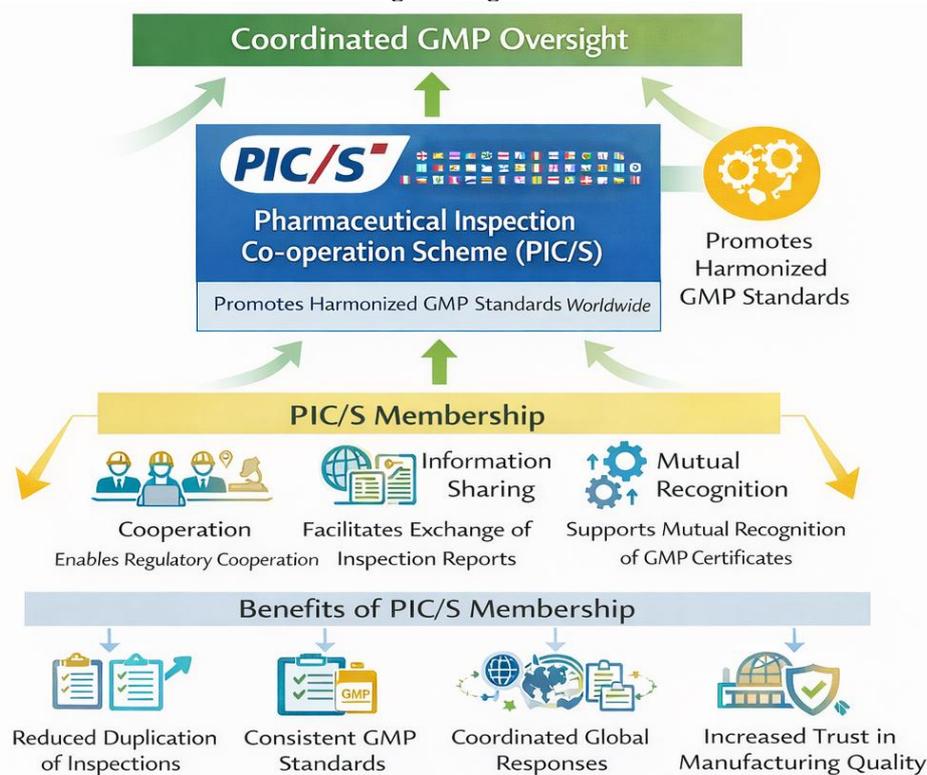
convergence rather than strict harmonization, acknowledging the need for flexibility across diverse regulatory environments.



Flow chart 2: Overview of Global Regulatory Convergence

In recent years, WHO has played a pivotal role in facilitating accelerated access to critical medicines and vaccines during global health emergencies, such as the COVID-19 pandemic, by promoting reliance on prequalified products and collaborative regulatory reviews. These efforts demonstrate WHO’s continuing influence in fostering convergence while accommodating local regulatory priorities.

1.5 PIC/S and Harmonization of Manufacturing Oversight



Flowchart 3: PIC/S in GMP Harmonization

Manufacturing quality is a critical component of drug approval and ongoing compliance. The Pharmaceutical Inspection Co-operation Scheme (PIC/S) addresses this aspect by promoting harmonized Good Manufacturing Practice (GMP) inspection standards. PIC/S enables cooperation and information sharing among regulatory inspectorates, reducing duplication of inspections and increasing confidence in manufacturing quality.

Despite these benefits, PIC/S does not override national regulatory authority decisions. Differences in inspection scheduling, compliance interpretation, and post-approval change requirements continue to exist. Therefore, while PIC/S enhances convergence in manufacturing standards, it does not eliminate regulatory fragmentation.

In recent years, PIC/S has facilitated coordinated inspections and mutual recognition of GMP compliance during global health emergencies and increased cross-border pharmaceutical trade, helping regulators maintain product quality while reducing unnecessary duplication and delays.

1.6 Why Regulatory Fragmentation Still Exists

Even with harmonization efforts, regulatory fragmentation persists due to differences in administrative processes, legal requirements, and regulatory decision-making. Fragmentation is evident in areas such as approval timelines, post-approval variations, labelling requirements, and pharmacovigilance obligations.

1.6.1 Differences in National Legal Frameworks

Each country maintains its own legal authority to regulate medicines. Laws governing clinical trials, marketing approvals, and manufacturing licenses vary widely, reflecting local policy priorities, healthcare systems, and risk tolerance. These differences prevent complete standardization of regulatory processes.

1.6.2 Variability in Administrative Procedures

Approval timelines, documentation requirements, and submission formats differ across regulatory agencies. While ICH and WHO provide common scientific standards, the practical implementation of these standards is often region-specific. For instance, dossier structure, electronic submission formats, and inspection procedures may vary significantly.

1.6.3 Divergence in Risk Assessment Approaches

Regulatory authorities may interpret safety, efficacy, or quality data differently based on local population needs, epidemiology, or healthcare infrastructure. Some countries adopt more conservative approaches, leading to additional studies or stricter post-marketing surveillance requirements.

1.6.4 Impact on Pharmaceutical Companies

For pharmaceutical companies, particularly generic manufacturers, regulatory fragmentation increases operational complexity. Companies must prepare multiple submissions for the same product, manage region-specific changes, and comply with varying post-approval requirements. This results in higher development costs and delayed market entry.

1.6.5 Consequences for Patient Access

Fragmentation directly affects patient access to affordable medicines. Delays in approval or inconsistent regulatory requirements can slow the availability of new therapies, especially in low- and middle-income countries. This underscores the ongoing tension between ensuring safety and efficacy and promoting timely access to essential medicines.

1.6.6 Challenges in Generic Drug Approvals

Generic drug approvals face several challenges due to differences in regulatory requirements across countries. The key challenges include:

1. Variation in Bioequivalence Requirements

Regulatory authorities differ in bioequivalence study design, acceptance criteria, and study conditions. A study accepted in one country may not be sufficient in another, leading to repeated studies and increased costs.

2. Reference Listed Drug (RLD) Selection Issues

The reference product must be approved and available locally. Differences in reference product acceptance across regions often require additional justification or bridging studies.

3. Differences in Generic Approval Pathways

Some countries provide streamlined abbreviated pathways, while others impose additional technical or administrative requirements, increasing regulatory complexity.

4. Post-Approval Change Management Complexity

Classification of manufacturing, formulation, or analytical changes varies among regulatory agencies. Minor changes in one region may require extensive review in another.

5. Regulatory Timeline Variability

Approval timelines differ significantly between regions, making it difficult to plan simultaneous global product launches.

6. Diverse Documentation and Submission Formats

Differences in dossier structure, electronic submission systems, and country-specific documentation increase preparation time and resource utilization.

7. Manufacturing Inspection and GMP Differences

Although GMP standards are harmonized to some extent, inspection frequency, interpretation, and compliance expectations vary across regions.

8. Intellectual Property and Data Exclusivity Constraints

Patent linkage systems and data exclusivity periods differ among countries, affecting the timing of generic market entry.

9. Pharmacovigilance and Post-Marketing Requirements

Safety reporting timelines, databases, and risk management expectations vary, adding to post-approval compliance burden.

10. Increased Cost and Delayed Market Entry

The combined effect of regulatory fragmentation leads to duplicated efforts, higher development costs, and delayed access to affordable medicines.

1.7 Strategic Importance of Global Regulatory Planning

The complexity and diversity of global regulatory requirements make structured planning essential for pharmaceutical companies. Strategic regulatory planning enables efficient navigation of multiple regulatory systems, ensuring timely approvals and compliance.

To manage regulatory diversity, pharmaceutical companies now adopt structured global regulatory strategies. These strategies involve early planning, use of harmonized guidelines, regulatory intelligence, and bridging approaches that support approvals across multiple regions. Regulatory planning now extends throughout the product lifecycle, from development to post-approval change management.

By current period, regulatory strategy is recognized as a critical function within pharmaceutical development, directly influencing timelines, costs, and global market access. Effective regulatory planning allows companies to balance compliance with efficiency in an increasingly complex regulatory environment.

1.7.1 Early Regulatory Planning

Early integration of regulatory considerations into the drug development process is now standard practice. Companies evaluate target markets, anticipate regulatory requirements, and design clinical programs that meet the needs of multiple jurisdictions simultaneously. Early planning minimizes duplication of studies and accelerates global submissions.

1.7.2 Use of Harmonized Guidelines

Pharmaceutical companies rely heavily on internationally recognized standards, such as ICH guidelines, to generate robust scientific data. Adherence to these guidelines increases the likelihood of acceptance by multiple regulatory authorities and reduces the risk of rejection due to technical inconsistencies.

1.7.3 Regulatory Intelligence and Risk Mitigation

By recent studies, regulatory intelligence has become a critical component of global planning. Companies monitor evolving regulations, guidance documents, and agency precedents to anticipate challenges. Risk-based strategies are applied to address potential regulatory hurdles, including differences in clinical trial requirements, labelling expectations, and post-approval obligations.

1.7.4 Bridging and Reliance Approaches

Bridging studies and reliance mechanisms are increasingly used to facilitate approvals in multiple regions. Companies submit data generated in one region to support applications in another, reducing the need for redundant trials. Regulatory reliance, where authorities leverage the assessment of other trusted agencies, has gained prominence as a tool to improve efficiency and patient access.

1.7.5 Lifecycle Regulatory Management

Regulatory strategy now encompasses the entire product lifecycle from early development to post-marketing changes. Companies plan for variations, renewals, and compliance updates across different markets to maintain uninterrupted global access. Lifecycle management ensures consistency, reduces regulatory risk, and supports sustainable market growth.

1.7.6 Strategic Value for Global Market Access

Effective regulatory planning is directly linked to timelines, cost-efficiency, and competitive advantage. Companies that successfully implement global strategies can achieve faster market entry, streamline compliance, and optimize resource allocation. By recent period, regulatory planning is recognized not only as a compliance function but as a strategic enabler of global pharmaceutical success.

1.8 Moving Forward: From Harmonization to Practical Convergence

Complete global harmonization remains difficult to achieve due to national sovereignty and public health priorities. Instead, the focus is shifting toward regulatory convergence, where authorities collaborate, rely on trusted assessments, and share information while maintaining independent decision-making.

Advances in regulatory science, digital submissions, and reliance models are expected to further support convergence. International organizations such as ICH, WHO, and PIC/S will continue to guide this transition, helping regulators and industry navigate global regulatory complexity.

While global harmonization remains an aspirational goal, achieving it fully is constrained by national sovereignty, differing healthcare priorities, and legal frameworks. Consequently, the pharmaceutical sector is increasingly embracing regulatory convergence a practical approach that balances collaboration with local autonomy.

1.8.1 Emphasis on Reliance and Collaboration

Regulatory convergence encourages authorities to rely on the scientific assessments and decisions of trusted regulatory agencies. Collaborative review processes, joint scientific advice, and shared evaluation platforms reduce duplication of effort while maintaining rigorous safety and efficacy standards.

1.8.2 Role of Digitalization

Digital regulatory submissions, real-time data sharing, and electronic Common Technical Document (eCTD) formats are transforming global regulatory interactions. By streamlining submissions and enabling better data transparency, digital tools support faster decision-making and facilitate convergence across regions.

1.8.3 Strengthening International Frameworks

International organizations such as ICH, WHO, and PIC/S continue to provide guidance, technical standards, and best practices that underpin convergence. WHO's prequalification program, PIC/S's GMP inspection guidance, and ICH's harmonized technical guidelines serve as common reference points for both regulators and industry.

1.8.4 Future Directions

By current study, regulatory convergence is expected to expand through:

- Greater adoption of reliance pathways, especially in developing countries.
- Increased alignment of post-approval requirements, labelling, and pharmacovigilance standards.
- Wider integration of regulatory science innovations, including model-informed drug development and real-world evidence.

This shift toward convergence supports global pharmaceutical development by improving efficiency, reducing costs, and enhancing timely access to medicines without compromising local regulatory authority or public health priorities.

1.9 Rationale of the Study

The global pharmaceutical industry operates under the paradox of "One Medicine, Many Rules," where scientifically identical products face diverse regulatory requirements across different countries. This study investigates the current landscape of global drug approvals, focusing on the effectiveness of harmonization initiatives and the roles of ICH, WHO, and PIC/S in promoting scientific alignment.

Despite efforts toward harmonization, regulatory fragmentation persists, creating operational, financial, and timeline challenges for pharmaceutical companies and potentially delaying patient access to medicines. By analysing these dynamics, the study aims to provide a comprehensive understanding of the challenges inherent in global regulatory frameworks and highlight strategies for efficient, compliant, and cost-effective regulatory planning.

Ultimately, the research seeks to inform policymakers, regulatory authorities, and industry stakeholders on approaches that balance public health protection with practical convergence, facilitating timely global access to safe and effective medicines.

2. AIM, OBJECTIVES AND PLAN OF STUDY

2.1 Aim

The aim of this study is to critically analyse global regulatory harmonization and regulatory fragmentation in generic drug approvals through a comparative evaluation of major regulatory frameworks, post-approval management practices, and bridging strategies, with the objective of proposing integrated regulatory approaches to support efficient global generic drug development and market access.

2.2 Objectives of the Study

The specific objectives of the present research are:

1. To study the evolution of global pharmaceutical development and the concept of "One Medicine, Many Rules."
2. To examine major global regulatory frameworks governing generic drug approvals across different regions.
3. To evaluate the role of international harmonization initiatives such as ICH, WHO, and PIC/S in promoting regulatory convergence.
4. To identify key areas of regulatory fragmentation, including approval pathways, documentation requirements, timelines, and post-approval variations.
5. To analyse post-approval change management practices in selected regulatory jurisdictions.
6. To assess regulatory submission requirements in different regions and their impact on global generic drug development.
7. To study bridging and reliance strategies adopted to facilitate approvals across multiple regulatory authorities.
8. To evaluate industry challenges through case-based regulatory analysis.

9. To propose integrated regulatory strategies that balance harmonization with regional regulatory autonomy.

2.3 Plan of Work

The present research work is designed as a qualitative, comparative, and document-based study focusing on global regulatory harmonization and regulatory fragmentation in drug approval processes, with special emphasis on generic medicines. The study will be conducted through a systematic review and comparative analysis of regulatory frameworks, guidelines, and approval pathways across major regulatory jurisdictions, including the United States, European Union, ASEAN countries, Australia, Canada, and Russia.

1. Selection of Research Design

The study will be conducted as a qualitative, descriptive, and comparative regulatory analysis focusing on global drug approval systems.

2. Identification of Regulatory Jurisdictions

Major regulatory regions including the United States, European Union, ASEAN countries, Australia, Canada, and Russia will be selected for comparative evaluation.

3. Collection of Regulatory Data

Regulatory guidelines, legislation, and official documents will be collected from recognized sources such as FDA, EMA, WHO, ICH, PIC/S, TGA, and Health Canada websites, along with peer-reviewed literature.

4. Review of Harmonization Initiatives

International harmonization efforts led by organizations such as ICH, WHO, and PIC/S will be critically reviewed to assess their role in regulatory convergence.

Comparative Analysis of Approval Requirements

Generic drug approval pathways, dossier formats, bioequivalence requirements, approval timelines, and documentation standards across selected regions will be systematically compared.

Evaluation of Regulatory Fragmentation

Key areas of regulatory divergence, including post-approval variation management, inspection practices, and administrative procedures, will be identified and analysed.

Assessment of Reliance and Bridging Approaches

The use of reliance-based submissions and bridging strategies adopted by regulatory authorities to reduce duplication and improve efficiency will be examined.

Analysis of Industry-Based Case Examples

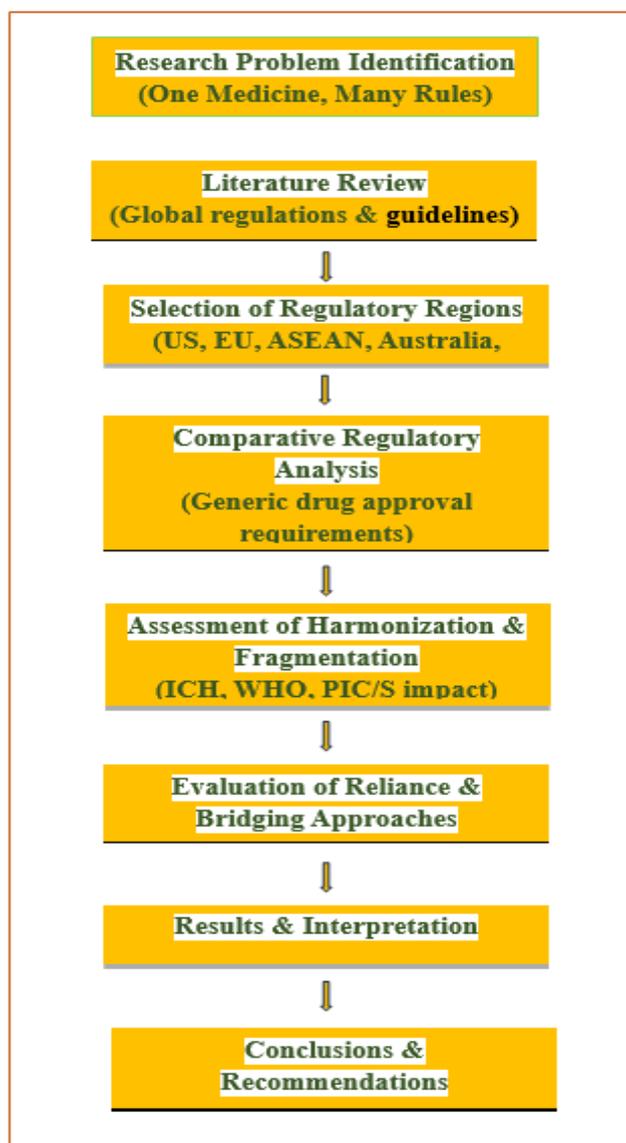
Selected real-world regulatory case examples will be analysed to highlight practical challenges faced during global generic drug development.

Synthesis of Findings

Observations from comparative analysis will be integrated to identify gaps, trends, and limitations in the current global regulatory landscape.

Development of Strategic Recommendations

Based on the findings, integrated regulatory strategies and practical recommendations will be proposed to enhance regulatory convergence and facilitate efficient global drug approvals.



Flow Chart 4: Plan of Work

3. LITERATURE REVIEW

3.1 Overview of Global Pharmaceutical Regulation

The regulation of medicines is a fundamental public health function aimed at ensuring the safety, efficacy, and quality of pharmaceutical products. Although the scientific properties of a drug remain constant, regulatory approval requirements vary widely across countries due to differences in legal frameworks, healthcare priorities, and regulatory maturity. Several studies have highlighted that global pharmaceutical development is increasingly affected by regulatory diversity, leading to delays in market access and increased development costs (Rago & Santoso, 2008).

Globalization has transformed drug development into a multinational process involving multi-country clinical trials, global manufacturing networks, and international supply chains. However, despite this scientific globalization, regulatory systems remain largely national, giving rise to the concept commonly described as “*One Medicine, Many Rules.*”

3.2 Evolution of Regulatory Harmonization

Regulatory harmonization emerged as a response to inefficiencies caused by divergent national regulatory requirements. Prior to harmonization efforts, pharmaceutical companies were required to submit multiple country-specific dossiers, often containing the same scientific data presented in different formats. This duplication resulted in increased regulatory burden and delayed patient access to medicines.

The establishment of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) marked a major milestone in regulatory harmonization. Studies have demonstrated that ICH guidelines have significantly improved consistency in quality, safety, and efficacy

requirements among major regulatory regions, particularly the United States, European Union, and Japan (ICH, 2019).

3.3 Role of ICH in Scientific Alignment

ICH guidelines provide harmonized technical standards for pharmaceutical development, including quality (Q), safety (S), efficacy (E), and multidisciplinary (M) guidelines. Literature indicates that adoption of ICH guidelines has reduced variability in dossier structure, stability requirements, and clinical trial design across ICH member regions.

However, several authors have emphasized that ICH harmonization is primarily scientific rather than procedural. While data requirements may be aligned, differences persist in submission procedures, review timelines, and post-approval obligations (Kopp & Regul, 2017). Recent guidelines such as ICH Q12 (Lifecycle Management) aim to address regulatory divergence in post-approval changes, but full global convergence has not yet been achieved.

3.4 Contribution of WHO to Regulatory Convergence

The World Health Organization (WHO) plays a vital role in promoting regulatory convergence, particularly in low- and middle-income countries. WHO supports regulatory strengthening through technical guidance, training, and reliance-based approaches. The WHO Prequalification Programme has been widely recognized as an effective tool for ensuring access to quality-assured generic medicines, especially for global health programs. Literature suggests that WHO's approach focuses on convergence rather than strict harmonization, allowing countries to adapt international standards to local public health needs. During global health emergencies such as the COVID-19 pandemic, WHO-led collaborative regulatory reviews significantly accelerated access to vaccines and essential medicines, demonstrating the effectiveness of reliance mechanisms (WHO, 2021).

3.5 PIC/S and Harmonization of Manufacturing Standards

Manufacturing quality is a critical component of drug approval. The Pharmaceutical Inspection Co-operation Scheme (PIC/S) aims to harmonize Good Manufacturing Practice (GMP) inspection standards among participating countries. Studies indicate that PIC/S membership improves regulatory confidence in manufacturing compliance and reduces duplication of inspections.

Despite these benefits, PIC/S does not eliminate national regulatory autonomy. Differences in inspection frequency, enforcement practices, and post-approval manufacturing changes continue to contribute to regulatory fragmentation (PIC/S, 2020).

3.6 Regulatory Fragmentation in Drug Approvals

Several studies have identified regulatory fragmentation as a major barrier to efficient global drug development. Fragmentation arises from differences in national legislation, administrative procedures, risk assessment approaches, and post-approval requirements. Even among highly regulated regions, approval timelines and documentation expectations vary significantly.

Generic drug approvals are particularly affected by fragmentation due to varying bioequivalence requirements, reference product selection, and post-approval change classification systems. Literature highlights that these differences often lead to repeated studies and delayed generic market entry, ultimately impacting patient access and healthcare costs (Vogel et al., 2018).

3.7 Reliance and Bridging Approaches in Global Regulation

Recent literature emphasizes the growing importance of reliance-based regulatory models, where regulatory authorities use the scientific assessments of trusted agencies to support local decisions. Bridging strategies, including the use of foreign clinical and bioequivalence data, are increasingly adopted to reduce duplication and improve efficiency.

Authors note that reliance mechanisms are particularly beneficial for emerging regulatory systems, enabling faster access to medicines while maintaining regulatory oversight. However, successful reliance depends on trust, transparency, and regulatory capacity (Luigetti et al., 2020).

3.8 Gaps Identified in Existing Literature

While numerous studies discuss harmonization initiatives and regulatory frameworks, limited literature provides a comprehensive comparative analysis of multiple regulatory regions with a specific focus on generic drug approvals and post-approval change management. Additionally, practical challenges faced by industry during global submissions are often under-represented.

These gaps highlight the need for integrated research that examines both harmonization efforts and persistent fragmentation, with a focus on strategic regulatory planning for global generic drug development.

3.9 Summary of Literature Review

The literature clearly indicates that global regulatory harmonization has improved scientific alignment through initiatives led by ICH, WHO, and PIC/S. However, regulatory fragmentation remains due to national legal frameworks, administrative differences, and divergent risk assessment practices. Generic drug approvals are particularly impacted by these challenges. This review establishes the foundation for the present study, which aims to analyse regulatory convergence and fragmentation across multiple jurisdictions and propose strategic solutions for efficient global drug approvals.

And Some of Review of literature are:

1. **Mahajan & Basarkar (2025)** analysed and compared generic drug approval processes in the United States, Europe, India, and Australia, highlighting significant differences in regulatory criteria, approval timelines, and submission requirements across these regions. The study reveals how divergent frameworks increase complexity for global market entry and emphasizes the need for harmonized regulatory strategies to facilitate generic approvals.
2. **Regulatory frameworks and filing discrepancies (2025)** investigated regulatory systems in the US, EU, India, Japan, and China by analysing ANDA deficiencies in FDA submissions between 2014 and 2024. It identified common deficiencies in bioequivalence, chemistry, and labelling and emphasized that lack of harmonization in filing requirements contributes to delays and inefficiency in generic drug approvals, highlighting areas for regulatory convergence.
3. **Dangy-Caye et al. (2025)** conducted a global analysis of pharmaceutical regulatory activities by major international bodies including ICH, WHO, and PIC/S, mapping their contributions to convergence and reliance mechanisms. The study demonstrates that collaborative guidance, standards, and norms from these authorities support alignment of regulatory policies, particularly in quality, public health, and pharmacovigilance domains.
4. **Li et al. (2025)** reviewed the international harmonization of pharmaceutical regulation with a special focus on China's involvement, exploring key challenges and coordination practices in a global health context. The research emphasizes that while harmonization efforts are growing, national interpretations and procedural variations continue to challenge seamless alignment of regulatory expectations.
5. **Global Regulatory Harmonization Strategies (2025)** discussed major factors that complicate harmonization, such as variability in legal frameworks, clinical trial standards, ethical requirements, and inconsistent adoption of international guidelines. The article highlights that differences in regulatory and administrative practices remain major barriers to achieving true global alignment in drug approval systems.
6. **Global Harmonization in Drug Approval (2025)** examined the diversity of regulatory and clinical trial requirements across multiple countries including the USA, Japan, and India. The review points out that despite shared scientific principles, differences in expedited review pathways, pharmacovigilance systems, and post-marketing standards hinder streamlined global drug approvals and slow patient access.
7. **FDA International Regulatory Harmonization overview (2025)** outlined the role of ICH and FDA's harmonization efforts, emphasizing that internationally harmonized guidelines in safety, quality, and efficacy help reduce unnecessary duplication of clinical trials and regulatory reviews. It also discusses the benefits of aligned technical requirements for efficient global product approval.
8. **FDA's Generic Drug Harmonization Efforts (2025)** described initiatives such as Parallel Scientific Advice and global generic drug programs designed to support concurrent regulatory discussions between FDA and EMA, aiming to minimize redundant testing and improve coordination between agencies during global generic drug development.
9. **Comparison of drug approvals by EMA and FDA (2025)** evaluated differences in approval characteristics between the FDA and EMA over a decade, revealing that differences in regulatory pathways, such as faster and more flexible review options in the US, reflect ongoing divergence despite harmonization initiatives. This study highlights how structural and procedural differences shape regulatory outcomes.
10. **Critical view of ASEAN harmonization (2025)** focused on regulatory requirements for generic drug submissions in ASEAN countries, noting that despite regional harmonization efforts, variation in national regulations and submission practices continues to impede the full realization of harmonized approval processes in the region.
11. **Deshmukh et al. (2025)** reviewed fast-track generic drug approval pathways in the US, Switzerland, UK, and Japan, comparing criteria, documentation requirements, and review timelines. The authors highlight that accelerated review mechanisms differ significantly between regulators, leading to varied timelines and reliance frameworks that affect global submission planning.
12. **Cross-regional ANDA deficiencies analysis (2025)** analysed FDA ANDA filings from 2014 to 2024 and found bioequivalence, chemistry, and labelling as common deficiencies. It emphasizes differences in filing requirements among regulatory authorities, suggesting that harmonizing certain technical standards can reduce repeated rejections.
13. **Downing et al. (2017)** compared new drug approvals across FDA, EMA, and Swissmedic between 2007 and 2016, demonstrating significant differences in approval timing and indication outcomes. Results indicate ongoing divergence in regulatory outcomes despite harmonization efforts.
14. **Harmonizing regulatory frameworks (2026)** discusses persistent regional divergences in regulatory interpretations of ICH guidelines, highlighting that regulatory culture, risk tolerance, and national sovereignty influence approval requirements and cause inefficiencies and additional costs.

15. **Global Regulatory Harmonization Strategies (2025)** outlines major barriers to harmonization, including variability in legal processes, clinical trial regulations, and limited reliance model adoption in emerging markets, reinforcing how these differences complicate multi-region drug approvals.
16. **Real-world safety harmonization study (2024)** compared Risk Management Plans (RMPs) and Risk Evaluation and Mitigation Strategies (REMS) between regulators, showing differences in risk management expectations, which demonstrates fragmentation in post-market safety requirements.
17. **FDA International Regulatory Harmonization overview (2025)** describes the role of ICH in uniting regulatory authorities globally to reduce duplication and align scientific standards, emphasizing the benefits of harmonized guidelines for improving regulatory efficiency.
18. **FDA's Generic Drug Harmonization Efforts (2025)** highlights the FDA's Generic Drug Cluster initiative within ICH, which fosters dialogue among regulators to understand and align regulatory requirements for generic approvals worldwide.
19. **Global Harmonization in Drug Approval (2025)** explored clinical trial diversity and regulatory variances across the USA, India, and Japan, reporting that differing expedited pathways and post-marketing obligations continue to hamper true harmonization.
20. **Suankit et al. (2023)** examined harmonization efforts between developed and developing countries, focusing on regulatory collaborations such as ASEAN harmonization, indicating that emerging markets are adopting but adapting guidelines to their contexts.
21. **Parallel Scientific Advice programs (2021–23)** analysed the FDA-EMA Parallel Scientific Advice initiative for complex generics, showing how concurrent scientific dialogues can facilitate regulatory understanding and reduce divergence in expectations.
22. **FDA vs EMA generic application White Paper (2026)** described differences in legislative requirements and approval timelines for generic drugs, illustrating that FDA and EMA frequently do not approve the same generic products in the same year, highlighting fragmentation.
23. **Reliance and recognition review (2024)** analysed global initiatives on regulatory reliance, showing that regulatory authorities are increasingly accepting trusted agency decisions to streamline approvals in resource-limited settings.
24. **MHRA International Recognition Framework (2023)** reported how the UK's MHRA established recognition routes using approvals from several regulators (Australia, Canada, EU, US) to support streamlined decision-making post-Brexit.
25. **FDA ANDA deficiency patterns (2025)** highlighted that method validation and labelling issues are top sources of regulatory filing deficiencies across major regions, highlighting areas where harmonized guidance could improve efficiency.
26. **Comparative European–US drug approval processes (2016)** discussed regulatory system differences, with the FDA's centralized approach contrasted with the EU's multi-national system, emphasizing structural fragmentation despite harmonization guidelines.
27. **Parallel regulatory decision concordance (2023)** noted high concordance in regulatory decisions across Swissmedic, EMA, and FDA for oncology and non-oncology products, yet differences in acceptance rates point to procedural divergence in risk tolerance.
28. **Regulatory milestones comparison (2013–2023)** showed that FDA generally approves a higher number of novel drugs earlier than EMA, reflecting divergent regulatory priorities and review flexibility.
29. **ASEAN harmonization critique (2019)** reported that although ASEAN nations have adopted common technical dossiers, national regulatory variances still impede truly unified approval processes for generics in the region.
30. **Regulatory reliance models (2022)** identified that shared review programs such as Project Orbis and ASEAN joint assessments promote global collaboration but still require national authorization, capturing both convergence and fragmentation.
31. **ICH's role in harmonization** has been widely documented by the FDA and other authorities to reduce redundant clinical studies and align scientific requirements across member regions, aiding global regulatory efficiency.
32. **Regulatory science and innovation (2021)** found that digital regulatory submission platforms such as eCTD improve data consistency but regional differences in electronic system acceptance still challenge global filings.
33. **Bioequivalence divergence impacts (2025)** emphasises that differing procedures to demonstrate bioequivalence across regulatory regions continue to delay multi-jurisdictional generic approvals.
34. **Clinical trial harmonization challenges (2025)** detailed by global regulatory frameworks show that varying clinical endpoint requirements and genetic diversity guidelines affect simultaneous global trial acceptance.
35. **Regulatory harmonization benefits (2025)** reported that harmonized dossier structures such as CTD and eCTD raise submission efficiency but complete procedural uniformity is yet to be achieved globally.

36. **Policy review of reliance pathways (2024)** demonstrates that reliance on trusted authorities can accelerate approvals in low-capacity regulatory environments, promoting convergence.
37. **Global regulatory strategy (2023)** suggests that collaborative scientific clusters and bilateral meetings between regulators help reduce localized technical divergences.
38. **Multi-agency regulatory dialogues (2023)** reveal that collaborative efforts such as the International Generic Drug Regulators Pilot (IGDRP) aim to create shared scientific positions to ease dual or multiple submissions.
39. **Post-market divergence studies (2024)** illustrate that regional differences in pharmacovigilance reporting and risk management plans create fragmentation, even when initial approvals align scientifically.
40. **Comparative regulatory review (2025)** underscores that structural differences in national policies—such as exclusivity and patent linkage—impact timing and strategies of generic market entries.

4. SELECTION OF REGULATORY REGIONS (US, EU, ASEAN, AUSTRALIA, CANADA, RUSSIA)



Figure 2: Global distribution of selected regulatory regions

In this study, global regulatory harmonization and fragmentation in drug approvals are being investigated.

- Considering that it is not feasible to study every country's regulations in detail, representative regions were selected that reflect diverse regulatory models, levels of development, and harmonization practices.
- The chosen regions include below Regulatory bodies, allowing for a comprehensive comparison of regulatory expectations, submission requirements, and post-approval processes.
 1. **United States (FDA)** - Highly structured, centralized system.
 2. **European Union (EMA)** - Multi-national framework with centralized, decentralized, and mutual recognition procedures.
 3. **ASEAN countries** - Regional harmonization initiative, but with national differences.
 4. **Australia (TGA)** - Mix of independent and reliance-based regulations.
 5. **Canada (Health Canada)** - Independent authority with reliance on international assessments.
 6. **Russia** - Emerging market with local adaptations of international guidelines.

This selection ensures that both advanced and emerging regulatory systems are represented, providing practical insights for global generic drug development.

4.1 Selection of Regulatory Jurisdictions

The selection of regulatory jurisdictions is a crucial step in understanding the global landscape of generic drug approvals. This study focuses on six representative regulatory authorities that collectively capture diverse regulatory models, levels of development, and harmonization practices.

4.1.2 United States (FDA) - Highly Structured, Centralized System

The United States Food and Drug Administration (FDA) is one of the most widely recognized and structured regulatory authorities globally, overseeing the approval, regulation, and post-marketing surveillance of pharmaceuticals. The FDA operates a centralized system, meaning that all new drug and generic applications are reviewed under standardized processes, which ensures consistency, scientific rigor, and public health protection. For generic drugs, the FDA requires applicants to submit an Abbreviated New Drug Application (ANDA) that demonstrates bioequivalence to the reference product.

A key feature of the FDA's regulatory system is its emphasis on bioequivalence, quality assurance, labelling compliance, and post-approval changes. These components are crucial to ensuring that generic drugs perform in the same manner as their innovator counterparts while maintaining safety and efficacy. The FDA's stringent

requirements also include comprehensive Chemistry, Manufacturing, and Controls (CMC) documentation, clinical pharmacology data, and risk assessment measures.

4.1.2.1 Key Features of FDA Generic Drug Regulation:

Centralized Review:

All ANDAs are reviewed by the Office of Generic Drugs (OGD), ensuring uniformity in evaluation.

Bioequivalence Studies:

Generics must demonstrate that pharmacokinetic parameters (C_{max}, AUC) fall within 80–125% of the reference product.

Labelling and Packaging Compliance:

FDA mandates strict adherence to labelling requirements, including drug facts, indications, dosage, and safety information.

Post-Approval Change Management:

Any changes to manufacturing process, site, or formulation require supplement submissions (e.g., CBE, PAS).

Risk-Based Classification:

The FDA classifies submissions based on potential patient risk to prioritize review.

Feature	Requirement	Purpose/Impact
Application Type	ANDA	Demonstrates bioequivalence to reference product
Bioequivalence Range	80–125%	Ensures therapeutic equivalence
Labelling	Detailed compliance	Patient safety and clarity
Post-Approval Changes	CBE, PAS submissions	Maintains quality during lifecycle
Review Timeline	~10–12 months (standard)	Provides predictable approval schedule
Risk Assessment	Low, Moderate, High	Prioritizes review based on patient safety

Table 4.1: Summary of Key FDA Generic Drug Requirements

- The United States Food and Drug Administration (FDA) serves as a benchmark for global regulatory standards, with many countries referencing FDA guidelines for regulatory alignment or reliance frameworks.

4.1.2.2 FDA Guidelines for Regulatory Alignment or Reliance Frameworks:

❖ Global Benchmark:

The FDA is widely recognized as a reference authority, and its guidelines are often used by other countries to shape or update their regulatory systems.

❖ Regulatory Reliance:

Several countries, including Mexico, Brazil, and parts of the Middle East, rely on FDA approvals or assessments when evaluating new or generic medicines, reducing duplication of effort.

❖ Harmonization of Standards:

FDA guidelines promote alignment in safety, efficacy, and quality requirements, contributing to international regulatory convergence.

❖ Risk-Based, Science-Driven Approach:

The FDA's focus on scientific evidence and risk management encourages other regulatory authorities to adopt similar strategies in their evaluation processes.

❖ Facilitation of Efficiency:

By referencing FDA assessments, countries can streamline their approval processes, accelerating patient access to high-quality medicines.

❖ Capacity Building:

FDA guidelines serve as educational and operational models, helping emerging regulatory agencies strengthen their review and inspection capabilities.

- The FDA's regulatory system is characterized by a centralized, risk-based, and scientifically driven approach, ensuring that approved generic medicines meet stringent standards of safety, efficacy, and quality.
- Examination of the FDA model provides researchers with valuable insights into how a highly structured, centralized authority effectively balances regulatory efficiency with patient safety.
- Furthermore, understanding this framework can inform strategies for regulatory harmonization across multiple jurisdictions, highlighting best practices that may be adapted or adopted internationally.

4.1.2.3 FDA as a Reference Authority in Global Regulatory Reliance

- The U.S. Food and Drug Administration (FDA) is widely recognized as a stringent regulatory authority and serves as a reference model for many national drug regulatory agencies worldwide. Several countries adopt regulatory reliance or alignment frameworks, wherein FDA approvals, scientific assessments, inspection reports, or regulatory decisions are used to support, abridge, or expedite their own national approval processes.
- This approach helps reduce duplication of regulatory effort, optimizes limited regulatory resources, and accelerates patient access to safe, effective, and high-quality medicines. Regulatory reliance on FDA decisions does not imply automatic approval; rather, national authorities retain sovereignty while leveraging FDA's scientific evaluations as part of a risk-based decision-making process. Such practices align with the World Health Organization's (WHO) principles of Good Reliance Practices (GRP) and contribute significantly to international regulatory harmonization.

Region	Country / Regulatory System	Nature of FDA Reliance / Alignment
North America	United States	FDA is the primary regulatory authority
Latin America	Argentina	Abridged review based on FDA approval
	Colombia	Reliance on FDA/EMA approvals
	Mexico	Reference authority for expedited pathways
	Brazil	Uses FDA as one of several trusted authorities
	Peru	Abbreviated approval using FDA decisions
	Chile	Reference-based regulatory evaluation
	Ecuador	Recognition of FDA approvals
	Panama	Relies on FDA-approved products
	Paraguay	Uses FDA as a reference authority
	Uruguay	Accelerated pathways using FDA data
Caribbean	CARICOM States (15 countries)	Caribbean Regulatory System relies on FDA approvals
Asia	India	FDA approvals used for regulatory reliance and exports
	Singapore	FDA used as a reference authority
	Malaysia	Abridged pathways referencing FDA
	Thailand	FDA approval supports expedited review
	Sri Lanka	Reference authority for drug registration
	Bangladesh	Relies on FDA approvals for selected products
	Pakistan	FDA used as a reference regulator
	Vietnam	FDA considered a trusted regulatory authority
Africa	Taiwan	Reliance on FDA scientific assessment
	Kenya	Formal cooperation and reliance on FDA decisions
	Ghana	Uses FDA as reference for selected medicines
Middle East	Nigeria	FDA recognized as a stringent authority
	Saudi Arabia	FDA approvals support fast-track registration
	United Arab Emirates	FDA used as reference authority
	Jordan	Reliance-based regulatory review
Developed Regulators (Collaboration)	Bahrain	FDA approvals accepted for abridged review
	United Kingdom (MHRA)	Uses FDA data via international recognition
	Canada (Health Canada)	FDA used as reference authority
	Australia (TGA)	FDA included in trusted regulators list
	Japan (PMDA)	Scientific collaboration with FDA

Table 4.2: Countries Using FDA as a Reference or Reliance Authority

4.1.2.4 Integration of FDA Reliance with WHO, ICH, and PIC/S Frameworks

- Global pharmaceutical regulation increasingly emphasizes regulatory convergence, reliance, and harmonization to ensure timely access to safe, effective, and high-quality medicines. In this context, the

U.S. Food and Drug Administration (FDA) functions as a stringent regulatory authority (SRA) and plays a pivotal role within international regulatory networks coordinated by the World Health Organization (WHO), the International Council for Harmonisation (ICH), and the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

- The WHO promotes regulatory reliance through its *Good Reliance Practices (GRP)*, encouraging national regulatory authorities to leverage assessments and inspections conducted by trusted reference agencies such as the FDA. WHO explicitly recognizes FDA as a reference authority for medicine registration, inspection outcomes, and prequalification-related activities, particularly in low- and middle-income countries.
- The ICH provides the technical foundation for harmonization by developing globally accepted guidelines on quality (Q), safety (S), efficacy (E), and multidisciplinary (M) topics. FDA is a founding and leading member of ICH, and its regulatory decisions are firmly grounded in ICH guidelines. Consequently, when countries rely on FDA approvals, they indirectly adopt ICH-aligned scientific standards, thereby facilitating convergence across multiple jurisdictions.
- The Pharmaceutical Inspection Co-operation Scheme (PIC/S) complements FDA's regulatory role by focusing on Good Manufacturing Practice (GMP) harmonization and inspection reliance. FDA is an active PIC/S participating authority, and FDA GMP inspection reports are frequently used by PIC/S member countries to reduce duplication of inspections and strengthen supply-chain oversight. This linkage ensures consistent manufacturing quality standards worldwide.
- Collectively, the alignment of FDA with WHO reliance principles, ICH technical guidelines, and PIC/S inspection frameworks creates a robust, multilayered regulatory ecosystem. Studying this integrated model provides critical insights for researchers into how science-based regulation, inspection convergence, and reliance mechanisms can be leveraged to advance global regulatory harmonization while maintaining patient safety.

Organization / Framework	Role in Global Regulation	Linkage with FDA	Research Significance
FDA (USA)	Stringent Regulatory Authority	Central authority; conducts scientific review, approval, and inspections	Benchmark for safety, efficacy, and quality
WHO	Global public health & regulatory guidance	Recognizes FDA as reference authority; promotes reliance via GRP	Supports access, capacity building, and convergence
ICH	Harmonization of technical guidelines	FDA is founding member; FDA approvals are ICH-based	Ensures global consistency in quality, safety, efficacy
PIC/S	GMP inspection harmonization	FDA is a participating authority; inspection reliance	Prevents duplication; strengthens GMP compliance

Table 4.3: FDA Reliance and Its Linkage with WHO, ICH, and PIC/S

Region	Countries / Systems	Frameworks Involved
Latin America	Mexico, Brazil, Argentina, Colombia, Peru, Chile	FDA + WHO GRP + ICH
Asia	India, Singapore, Malaysia, Thailand, Sri Lanka, Taiwan	FDA + ICH + WHO
Africa	Kenya, Ghana, Nigeria	FDA + WHO reliance
Middle East	Saudi Arabia, UAE, Jordan, Bahrain	FDA + ICH
Caribbean	CARICOM States	FDA + WHO
Developed Regulators	UK (MHRA), Canada, Australia, Japan	FDA + ICH + PIC/S

Table 4.4: Countries Using FDA Reliance within WHO-ICH-PIC/S Framework

The FDA operates as a cornerstone of global pharmaceutical regulation, with its decisions integrated into international frameworks led by WHO, ICH, and PIC/S. Through Good Reliance Practices, ICH harmonized

guidelines, and GMP inspection cooperation, many countries utilize FDA assessments to strengthen regulatory efficiency while maintaining high standards of safety, efficacy, and quality. This interconnected regulatory ecosystem provides a practical model for achieving global regulatory harmonization.

4.1.2.5 Challenges and Future Directions of the U.S. FDA

a) Challenges

- The FDA, as a centralized regulatory authority, is widely regarded as a global benchmark for drug approval; however, it faces several ongoing challenges. One major limitation is the increasing complexity of pharmaceutical products, including biologics, complex generics, and combination therapies, which require more sophisticated scientific evaluation.
- Resource constraints and high submission volumes can lead to extended review timelines, particularly for generics and post-approval changes.
- Rapidly evolving technology and digital health innovations pose challenges for regulatory adaptation, including real-time monitoring, software as a medical device, and novel drug delivery systems.
- While the FDA's risk-based framework is robust, integration of real-world evidence and post-marketing safety data remains complex due to decentralized reporting and fragmented health data systems.

b) Future Directions

- The FDA continues to focus on advanced regulatory science, leveraging modelling, simulation, and real-world evidence to improve evaluation efficiency and predict patient outcomes.
- Expansion of international collaboration and reliance initiatives aims to reduce duplication of inspections, clinical trial assessments, and quality reviews in partnership with other stringent regulatory authorities.
- Adoption of electronic submissions and AI-assisted review tools is expected to streamline application processing and post-marketing surveillance.
- Strengthening post-marketing safety monitoring through integrated data systems and predictive pharmacovigilance will enhance patient protection while maintaining timely market access.
- The FDA's centralized, science-driven, and risk-based regulatory model remains a global standard. Its future lies in adaptive regulatory strategies, international collaboration, and digital integration, ensuring both efficient drug approvals and sustained patient safety.

4.1.3 European Union (EMA) – Harmonized, Multi-State Regulatory System

- The European Medicines Agency (EMA) represents one of the most comprehensive and harmonized pharmaceutical regulatory systems globally, coordinating the scientific evaluation, authorization, supervision, and pharmacovigilance of medicinal products across the European Union (EU) and the European Economic Area (EEA). Unlike the centralized national regulatory model of the United States Food and Drug Administration (FDA), the EMA operates through a network-based, multi-state regulatory framework, involving the European Commission and the national competent authorities of EU Member States.
- For generic medicines, the EMA facilitates approvals through multiple regulatory pathways, including the Centralized Procedure, Decentralized Procedure (DCP), Mutual Recognition Procedure (MRP), and National Procedures. Applicants must demonstrate bioequivalence to an EU-authorized reference medicinal product, ensuring comparable safety, efficacy, and quality.
- A defining strength of the EMA system is its emphasis on harmonization across Member States, supported by common scientific standards, coordinated regulatory procedures, and shared pharmacovigilance systems. Generic medicine approvals under the EMA framework are based on rigorous evaluation of quality (CMC) documentation, bioequivalence data, labelling harmonization, and lifecycle management strategies.

4.1.3.1 Key Features of EMA Generic Drug Regulation

- **Harmonized Review System:**
Generic applications are evaluated through coordinated EU regulatory procedures, ensuring consistency across Member States.
- **Bioequivalence Studies:**
Generics must demonstrate bioequivalence with pharmacokinetic parameters (AUC and C_{max}) within the accepted 80–125% range.
- **Quality and CMC Requirements:**
Comprehensive Chemistry, Manufacturing, and Controls (CMC) documentation is required to ensure GMP compliance and product quality.
- **Labelling Harmonization:**
Summary of Product Characteristics (SmPC), Patient Information Leaflets (PIL), and package labelling must be harmonized across the EU.
- **Post-Approval Lifecycle Management:**
Variations to approved products are managed via Type IA, IB, and II variations, ensuring continued quality and safety.

➤ **Risk-Based Scientific Assessment:**

EMA applies a science-driven, benefit–risk evaluation approach, particularly for complex generics and narrow therapeutic index drugs.

Feature	Requirement	Purpose / Impact
Application Routes	Centralized, DCP, MRP	EU-wide or multi-state approval
Bioequivalence Range	80–125%	Ensures therapeutic equivalence
Quality Documentation	Comprehensive CMC	Ensures GMP compliance
Labelling	SmPC, PIL harmonization	Patient safety and consistency
Post-Approval Changes	Type IA, IB, II variations	Lifecycle quality control
Review Timeline	~210 active review days	Predictable regulatory pathway

Table 4.5: Summary of Key EMA Generic Drug Requirements

4.1.3.2 EMA Guidelines for Regulatory Alignment or Reliance Frameworks

➤ **Global Reference Authority:**

The EMA is widely recognized as a stringent regulatory authority, and its scientific opinions and approvals are frequently used as benchmarks worldwide.

➤ **Regulatory Reliance:**

Several non-EU countries rely on EMA approvals, European Public Assessment Reports (EPARs), and inspection outcomes to support or expedite national marketing authorization decisions.

➤ **Harmonization of Standards:**

EMA guidelines are closely aligned with International Council for Harmonisation (ICH) standards, promoting convergence in quality, safety, and efficacy requirements.

➤ **Risk-Based, Science-Driven Evaluation:**

EMA employs a robust benefit–risk assessment framework supported by multidisciplinary scientific expertise.

➤ **Facilitation of Regulatory Efficiency:**

Reliance on EMA assessments enables countries to reduce duplication of regulatory work and shorten approval timelines.

➤ **Capacity Building:**

EMA scientific outputs serve as reference tools for emerging regulatory agencies seeking to strengthen evaluation and inspection capabilities.

Note:

- The EMA regulatory framework ensures that generic medicines meet uniform standards of quality, safety, and efficacy across multiple jurisdictions.
- Study of the EMA system provides valuable insights into how harmonized multi-country regulation can be achieved without compromising scientific rigor.

4.1.3.3 EMA as a Reference Authority in Global Regulatory Reliance

- The European Medicines Agency functions as a major reference authority within global regulatory reliance frameworks. Many national regulatory authorities use EMA marketing authorizations, EPARs, GMP inspection outcomes, and scientific assessments to inform or abridge their own approval processes.
- Regulatory reliance on EMA decisions aligns with the World Health Organization (WHO) Good Reliance Practices (GRP) and allows countries to optimize regulatory resources while retaining national decision-making authority. This approach supports faster access to high-quality medicines without compromising public health protection.

Region	Country / Regulatory System	Nature of EMA Reliance / Alignment
European Union	EU/EEA Member States	Centralized and harmonized EMA approvals
Latin America	Brazil, Chile, Colombia, Peru	EMA used as reference authority
Asia	Singapore, Malaysia, Thailand	EMA approvals support expedited review
Africa	South Africa, Ghana	EMA reliance for selected medicines
Middle East	Saudi Arabia, UAE, Jordan	EMA approvals recognized
Developed Regulators	Australia (TGA), Canada	EMA considered trusted authority

Table 4.6: Countries Using EMA as a Reference or Reliance Authority

4.1.3.4 EMA Scientific Committees and Their Role

- The EMA operates through specialized scientific committees that ensure transparent, consistent, and high-quality regulatory decision-making.

- The Committee for Medicinal Products for Human Use (CHMP) is responsible for evaluating marketing authorization applications, including generic medicines. The Pharmacovigilance Risk Assessment Committee (PRAC) oversees post-marketing safety and risk management, while other committees support specific regulatory domains.
- For generic medicines, the CHMP plays a central role in evaluating bioequivalence data, quality documentation, and overall benefit–risk balance. This committee-based system enables integration of scientific expertise from multiple Member States and strengthens regulatory harmonization.

4.1.3.5 Post-Marketing Surveillance and Pharmacovigilance

- Post-authorization safety monitoring is a core component of the EMA regulatory framework. Pharmacovigilance activities are coordinated through Surveillance, a centralized EU database for adverse drug reaction reporting. Marketing authorization holders are required to submit Periodic Safety Update Reports (PSURs) and implement Risk Management Plans (RMPs) where applicable.
- This coordinated pharmacovigilance system enables early detection of safety signals and consistent regulatory action across EU Member States, ensuring ongoing protection of public health.

4.1.3.6 Integration of EMA with WHO, ICH, and PIC/S Frameworks

- Global pharmaceutical regulation increasingly emphasizes regulatory convergence and reliance.
- In this context, the EMA operates within an integrated regulatory ecosystem supported by the World Health Organization (WHO), the International Council for Harmonisation (ICH), and the Pharmaceutical Inspection Co-operation Scheme (PIC/S).
- WHO recognizes EMA as a reference authority under Good Reliance Practices, particularly for regulatory strengthening initiatives. EMA is a founding member of ICH, ensuring that its regulatory decisions are fully aligned with internationally harmonized scientific standards. Furthermore, EMA works closely with PIC/S through EU national inspectorates, enabling reliance on GMP inspection outcomes and reducing duplication of inspections.

Organization / Framework	Role in Global Regulation	Linkage with EMA	Research Significance
EMA (EU)	Regional regulatory authority	Coordinates EU scientific reviews	Harmonized multi-country regulation
WHO	Global regulatory guidance	Recognizes EMA for reliance (GRP)	Supports access and convergence
ICH	Technical harmonization	EMA is founding member	Scientific consistency
PIC/S	GMP inspection harmonization	EU inspectorates participate	Inspection reliance

Table 4.7: EMA Reliance and Its Linkage with WHO, ICH, and PIC/S

- Table 4.7 highlights the EMA’s integration with global regulatory frameworks. EMA coordinates harmonized scientific reviews across the EU, is recognized by WHO under Good Reliance Practices, aligns its decisions with ICH technical standards, and supports GMP inspection reliance through PIC/S. Together, these linkages promote regulatory convergence, efficiency, and consistent assurance of medicine quality and patient safety.

Region	Countries / Systems	Frameworks Involved
EU/EEA	All Member States	EMA + ICH + PIC/S
Latin America	Brazil, Chile, Colombia	EMA + WHO + ICH
Asia	Singapore, Malaysia, Thailand	EMA + ICH
Africa	South Africa, Ghana	EMA + WHO
Middle East	Saudi Arabia, UAE	EMA + ICH

Table 4.8: Countries Using EMA Reliance within WHO–ICH–PIC/S Framework

- The European Medicines Agency represents a highly harmonized regulatory model that integrates scientific rigor with multinational cooperation. Through alignment with WHO Good Reliance Practices, ICH technical guidelines, and PIC/S inspection frameworks, the EMA serves as a robust reference authority for regulatory reliance worldwide. Together with the FDA, the EMA exemplifies complementary regulatory models that support global harmonization while ensuring patient safety and product quality.

4.1.3.7 Challenges and Future Directions of EMA

a) Challenges

- Despite being a highly harmonized multi-state regulatory system, EMA faces challenges inherent to coordinating across 27 EU Member States. Differences in national implementation, resource allocation, and legal frameworks can occasionally result in variable timelines for product assessment and approval.

- EMA's centralized procedures for certain products, while efficient, may struggle to accommodate rapidly emerging complex generics and advanced therapies without additional specialized scientific capacity.
- Ensuring consistent post-marketing surveillance across all Member States remains challenging due to differences in national pharmacovigilance infrastructure and reporting practices.
- The integration of EMA activities with global reliance frameworks (WHO, PIC/S, ICH) requires ongoing coordination, trust-building, and alignment of technical standards, particularly for emerging markets.

b) Future Directions

- EMA is expected to enhance scientific capacity and specialized expertise, particularly for complex generics, biosimilars, and advanced therapies.
- Expansion of work-sharing initiatives and reliance models with non-EU regulators will reduce duplication of effort and accelerate patient access globally.
- Greater digitalization of submissions, inspections, and pharmacovigilance reporting will improve efficiency, transparency, and real-time regulatory decision-making.
- Harmonization of post-marketing safety monitoring and data sharing across Member States will strengthen coordinated pharmacovigilance and risk management.
- EMA's multi-state, harmonized, and science-driven regulatory model provides a robust platform for regional and global convergence. Its future lies in enhanced collaboration, digital integration, and proactive scientific capacity building, ensuring both efficient approvals and high standards of patient safety.

4.1.4 Association of Southeast Asian Nations (ASEAN) – Regional Harmonization through Regulatory Convergence

- The Association of Southeast Asian Nations (ASEAN) represents a unique regional approach to pharmaceutical regulation, characterized by regulatory convergence rather than full centralization. Unlike the centralized authority of the FDA or the harmonized multi-state framework of the EMA, ASEAN operates through national regulatory authorities (NRAs) of its ten Member States, coordinated under a common harmonization framework.
- ASEAN pharmaceutical regulation is guided by the ASEAN Consultative Committee for Standards and Quality – Pharmaceutical Product Working Group (ACCSQ-PPWG), which aims to reduce technical barriers to trade while ensuring the safety, efficacy, and quality of medicinal products across the region. Each Member State retains sovereign regulatory authority, but adopts regionally harmonized technical requirements.
- For generic medicines, ASEAN countries follow common principles for bioequivalence, quality (CMC) documentation, GMP compliance, and labelling, as defined in the ASEAN Common Technical Dossier (ACTD) and ASEAN Common Technical Requirements (ACTR). This harmonized framework facilitates simultaneous or sequential submissions across multiple ASEAN markets and supports faster access to affordable generic medicines.

4.1.4.1 Key Features of ASEAN Generic Drug Regulation

- **Harmonized Technical Dossier (ACTD):** Generic drug applications are submitted using the ASEAN Common Technical Dossier, structured to align with ICH CTD principles while remaining adaptable to regional regulatory capacity.
- **Bioequivalence Requirements:** Generics must demonstrate bioequivalence with an approved reference product, typically accepting pharmacokinetic parameters (AUC and C_{max}) within the 80–125% equivalence range.
- **Quality and GMP Compliance:** Manufacturers are required to submit comprehensive CMC data and demonstrate compliance with WHO GMP or PIC/S-aligned GMP standards, depending on national requirements.
- **National Review with Regional Alignment:** Although approvals are granted at the national level, regulatory assessments are guided by harmonized ASEAN technical standards, promoting consistency across Member States.
- **Post-Approval Change Management:** Variations to approved products follow nationally implemented but regionally aligned procedures, enabling lifecycle management without re-submission of full dossiers.

Feature	Requirement	Purpose / Impact
Application Format	ACTD	Harmonized dossier submission
Bioequivalence Range	80–125%	Ensures therapeutic equivalence
Quality Documentation	CMC + GMP compliance	Product quality assurance
Regulatory Authority	National NRAs	Sovereign decision-making
Post-Approval Changes	National variations	Lifecycle control
Review Timeline	Country-dependent	Flexible regulatory pathway

Table 4.9: Summary of Key ASEAN Generic Drug Requirements

4.1.4.2 ASEAN Guidelines for Regulatory Alignment and Reliance

- **Regional Harmonization Model:**
ASEAN promotes harmonization through mutual understanding of technical standards rather than centralized authorization, enabling gradual regulatory convergence among Member States.
- **Regulatory Reliance and Abridged Reviews:**
Several ASEAN countries apply reliance or abridged review pathways, particularly for generic medicines approved by stringent regulatory authorities such as the EMA, FDA, or WHO-prequalified products.
- **Alignment with International Standards:**
ASEAN technical guidelines are progressively aligned with ICH, WHO, and PIC/S standards, supporting global regulatory convergence.
- **Risk-Based Evaluation:**
National regulators apply risk-based scientific assessment, allowing regulatory resources to focus on higher-risk products such as complex generics and biologics.
- **Capacity Strengthening:**
ASEAN harmonization initiatives support regulatory capacity building in less mature agencies through shared guidelines, training programs, and regional cooperation.

Note:

ASEAN harmonization enhances regulatory efficiency while respecting national sovereignty. The ASEAN model demonstrates how regional convergence can improve medicine access without full regulatory centralization.

4.1.4.3 ASEAN as a Reliance Platform for Emerging Regulatory Systems

- ASEAN regulatory systems increasingly function within global regulatory reliance frameworks, particularly for generic medicines. National authorities often reference approvals, assessment reports, and GMP inspections conducted by stringent regulatory authorities (SRAs).
- This approach aligns with WHO Good Reliance Practices (GRP) and enables ASEAN regulators to optimize limited resources while maintaining responsibility for final authorization decisions.

Region	Country / Authority	Nature of Reliance
ASEAN	Singapore (HSA)	Reference + abridged review
	Malaysia (NPRA)	Reliance on EMA/FDA/WHO
	Thailand (FDA Thailand)	Abridged review pathways
	Indonesia (BPOM)	Partial reliance
	Philippines (FDA PH)	WHO & SRA reliance
	Vietnam (DAV)	Gradual convergence

Table 4.10: Regulatory Reliance Practices in ASEAN Countries

4.1.4.4 ASEAN Regulatory Bodies and Coordination Mechanisms

- Regulatory oversight in ASEAN is coordinated through ACCSQ-PPWG, which develops harmonized technical guidelines, promotes mutual trust, and facilitates regulatory dialogue among Member States.
- Unlike the EMA's centralized committee system, ASEAN relies on consensus-based coordination, enabling flexibility while progressively strengthening harmonization.
- Advanced regulators such as Singapore HSA and Malaysia NPRA often serve as regional reference points, supporting regulatory strengthening initiatives.

4.1.4.5 Post-Marketing Surveillance and Pharmacovigilance in ASEAN

- Pharmacovigilance systems in ASEAN are primarily managed at the national level, with increasing regional collaboration for signal detection, safety communication, and regulatory action.
- Marketing authorization holders are required to submit Periodic Safety Update Reports (PSURs) and implement Risk Management Plans (RMPs) where applicable.
- ASEAN Member States collaborate with WHO Programme for International Drug Monitoring (PIDM), enhancing regional pharmacovigilance capacity.

4.1.4.6 Integration of ASEAN with WHO, ICH, and PIC/S Frameworks

- ASEAN pharmaceutical regulation operates within a broader global regulatory ecosystem, supported by WHO, ICH, and PIC/S.
- Several ASEAN countries are ICH observers or members and PIC/S participating authorities, enabling reliance on internationally accepted GMP inspection outcomes

Organization / Framework	Role	Linkage with ASEAN	Research Significance
WHO	Global guidance	Technical & reliance support	Access to medicines
ICH	Harmonization	Progressive alignment	Scientific consistency
PIC/S	GMP convergence	Inspection reliance	Quality assurance
ACCSQ-PPWG	Regional coordination	ASEAN harmonization	Regulatory convergence

Table 4.11: ASEAN Integration with Global Regulatory Frameworks

- The ASEAN regulatory framework represents a pragmatic, convergence-based harmonization model, balancing national regulatory autonomy with regional cooperation. While lacking centralized authorization like the EMA, ASEAN has achieved substantial alignment in technical standards, dossier requirements, and reliance practices.
- Together with the FDA and EMA, the ASEAN model highlights an alternative pathway toward global regulatory harmonization one that emphasizes flexibility, capacity building, and reliance, particularly suited for regions with diverse regulatory maturity levels.

4.1.4.7 Challenges and Future Directions of ASEAN Regulatory Harmonization

a) Challenges

- Despite notable progress in regulatory convergence, ASEAN pharmaceutical harmonization faces several structural and operational challenges. One of the primary limitations is the heterogeneity in regulatory capacity and maturity among ASEAN Member States. While countries such as Singapore and Malaysia possess well-established regulatory systems, others continue to strengthen review expertise, inspection infrastructure, and pharmacovigilance capabilities.
- Absence of a centralized regulatory authority remains a key constraint. Unlike the EMA, ASEAN approvals are granted at the national level, resulting in variability in review timelines, administrative requirements, and decision-making processes, even when common technical standards are applied.
- Differences in national legal frameworks and languages necessitate country-specific adaptations for product registration, labelling, and post-approval changes, increasing regulatory complexity for manufacturers.
- Limited formal work-sharing mechanisms and partial implementation of reliance pathways further restrict the efficiency gains expected from regional harmonization.

b) Future Directions

- The future of ASEAN pharmaceutical regulation is expected to move toward deeper regulatory convergence through structured reliance and work-sharing models, while preserving national sovereignty in final decision-making.
- Expanded adoption of WHO Good Reliance Practices (GRP) and increased recognition of approvals and inspection outcomes from stringent regulatory authorities (SRAs) will likely reduce duplication of regulatory assessments.
- Greater alignment with ICH guidelines, wider participation in PIC/S, and progressive transition to electronic Common Technical Dossier (eCTD) systems are anticipated to enhance scientific consistency and regulatory efficiency.
- Strengthening regional pharmacovigilance cooperation, including data sharing and joint signal detection, will improve post-marketing safety oversight across ASEAN.
- Collectively, these developments position ASEAN as an evolving harmonization model, offering a flexible and scalable regulatory framework that complements the centralized FDA system and the harmonized multi-state EMA model.

ASEAN's regulatory future lies in balanced convergence leveraging reliance, harmonization, and capacity building to ensure timely access to high-quality generic medicines while maintaining robust public health protection.

4.1.5 Australia (TGA) - Centralized National Regulatory Authority

- The Therapeutic Goods Administration (TGA) serves as Australia's centralized regulatory authority for medicines, medical devices, and other therapeutic products. Unlike the regional convergence model of ASEAN or the multi-state harmonized system of the EMA, the TGA operates under a nationally centralized, science-driven regulatory framework, ensuring compliance with high standards of safety, quality, and efficacy across all marketed products.
- The TGA regulates generic medicines through structured application processes, including the standard pathway, abridged review, and priority review schemes, requiring demonstration of bioequivalence to an approved reference product. Regulatory assessment emphasizes comprehensive evaluation of CMC documentation, GMP compliance, labelling, and post-approval lifecycle management.

- A defining feature of the TGA system is its alignment with international regulatory standards (ICH, WHO, PIC/S), enabling Australia to participate actively in global regulatory harmonization while maintaining national sovereignty.

4.1.5.1 Key Features of TGA Generic Drug Regulation

Structured Review Pathways:

Generic medicines are evaluated through standard, abridged, or priority pathways, ensuring timely and scientifically rigorous assessment.

Bioequivalence Requirements:

Pharmacokinetic parameters (AUC and Cmax) must fall within the accepted 80–125% range relative to the reference product.

Quality and GMP Compliance:

Comprehensive Chemistry, Manufacturing, and Controls (CMC) documentation is required. Manufacturers must comply with TGA standards or internationally recognized GMP frameworks (WHO/PIC/S).

Labelling and Packaging:

Consistent labelling in accordance with TGA-approved formats ensures patient safety and regulatory compliance.

Post-Approval Change Management:

Variations to approved products are managed through formal change notification or approval processes to maintain lifecycle quality.

Feature	Requirement	Purpose / Impact
Application Pathways	Standard / Abridged / Priority	Efficient, risk-based review
Bioequivalence Range	80–125%	Therapeutic equivalence
Quality Documentation	Comprehensive CMC + GMP	Product quality assurance
Regulatory Authority	TGA (national)	Centralized decision-making
Post-Approval Changes	TGA variation processes	Lifecycle quality control
Review Timeline	Standard: ~255 days	Predictable regulatory pathway

Table 4.12: Summary of Key TGA Generic Drug Requirements

4.1.5.2 TGA Guidelines for Regulatory Alignment and Reliance

International Reference Model:

TGA frequently relies on assessments, GMP inspections, and approvals from stringent regulatory authorities (FDA, EMA, WHO-prequalified products) to facilitate abridged reviews.

Alignment with International Standards:

TGA guidelines are harmonized with ICH, WHO, and PIC/S standards, promoting global scientific consistency and regulatory convergence.

Risk-Based Assessment:

The TGA applies a risk-based evaluation, prioritizing higher-risk products such as complex generics, biologics, and narrow therapeutic index drugs.

Capacity Building and Collaboration:

TGA engages in international regulatory training, work-sharing programs, and collaborative reviews to strengthen both domestic and global regulatory systems.

4.1.5.3 TGA as a Reliance Platform for Global and Regional Regulation

TGA approvals often serve as reference points for regional regulators in the Asia-Pacific and other emerging regulatory systems. Abridged or reliance pathways enable faster access to medicines while reducing duplication of effort.

Region	Country / Regulatory Authority	Nature of Reliance
Asia-Pacific	Singapore (HSA), Malaysia (NPRA)	Recognition of TGA approvals and inspections
Global	WHO-prequalified products	Facilitates abridged review
Developed Regulators	FDA, EMA	Reference for complex generics and biosimilars

Table 4.13: TGA Reliance Practices and Regional Linkages

4.1.5.4 Post-Marketing Surveillance and Pharmacovigilance

TGA maintains a centralized national pharmacovigilance system, including adverse event reporting, Periodic Safety Update Reports (PSURs), and Risk Management Plans (RMPs).

Integration with global pharmacovigilance networks, including WHO Programme for International Drug Monitoring (PIDM), ensures early signal detection and consistent regulatory action.

Organization / Framework	Role	Linkage with TGA	Research Significance
WHO	Global guidance	TGA follows GRP and WHO-prequalified product guidelines	Facilitates access and reliance
ICH	Technical harmonization	TGA is a member, aligns regulatory decisions	Ensures scientific consistency
PIC/S	GMP inspection harmonization	TGA inspections recognized internationally	Supports quality assurance

4.1.5.5 Integration of TGA with WHO, ICH, and PIC/S Frameworks

4.1.5.7 Challenges and Future Directions of the TGA

a) Challenges

- Despite its centralized and rigorous regulatory framework, TGA faces challenges in balancing timely access with scientific rigor, particularly for complex generics, biologics, and advanced therapies.
- Increasing workload and resource constraints can impact review timelines, especially for post-approval variations and priority products.
- The rapid evolution of pharmaceutical technologies, digital health products, and novel drug delivery systems requires ongoing updates to guidelines and regulatory expertise.
- Geographical and demographic diversity of Australia can complicate real-world pharmacovigilance and rapid safety monitoring.

b) Future Directions

- TGA is progressively implementing reliance pathways and collaborative reviews, leveraging approvals, assessments, and inspections from FDA, EMA, and WHO-prequalified products to streamline regulatory processes.
- Digitalization of submissions (eCTD), inspection reporting, and pharmacovigilance systems is expected to improve efficiency, transparency, and real-time regulatory decision-making.
- Expansion of risk-based assessment frameworks and work-sharing initiatives will allow TGA to prioritize higher-risk products while maintaining robust safety oversight.
- Greater alignment with international standards and harmonization initiatives (ICH, PIC/S, ASEAN collaborations) will strengthen regulatory convergence globally and regionally.
- TGA represents a centralized, science-driven regulatory authority with strong international recognition. Its future lies in digital integration, reliance models, risk-based evaluation, and global harmonization, ensuring efficient approvals while maintaining high standards of patient safety and product quality.

4.1.6 Russia - Emerging Market with Local Adaptations of International Guidelines

- Russia represents a growing pharmaceutical regulatory market characterized by national regulatory oversight with adaptations of international standards. The Ministry of Health of the Russian Federation (MoH), through its regulatory body Roszdravnadzor, serves as the central authority responsible for the registration, supervision, and safety monitoring of medicinal products, including generics.
- Unlike the fully centralized FDA model or the harmonized EMA system, Russia follows a nationalized regulatory approach while gradually incorporating ICH, WHO, and PIC/S guidelines into its legal and technical framework. For generic medicines, applications require demonstration of bioequivalence to a locally authorized reference product, along with compliance with Russian GMP, quality documentation, and labelling requirements.
- A defining feature of the Russian system is its emphasis on local adaptations: while global scientific standards are referenced, products must meet Russia-specific dossier requirements, local language labelling, and post-approval reporting obligations.

4.1.6.1 Key Features of Russian Generic Drug Regulation

Structured Review Process:

Generic applications are evaluated by Roszdravnadzor through a **national registration process**, with pathways for standard, expedited, or priority review, depending on the product type.

Bioequivalence Requirements:

Generics must demonstrate pharmacokinetic equivalence (AUC and C_{max}) within the accepted 80–125% range relative to a Russian reference product.

Quality and GMP Compliance:

Manufacturers must submit comprehensive CMC documentation and comply with Russian GMP standards, which are increasingly aligned with PIC/S and WHO frameworks.

Labelling and Packaging:

All product labelling must meet Russian language and local regulatory requirements, ensuring clarity for patients and healthcare professionals.

Post-Approval Change Management:

Changes to approved products require submission of notifications or variations to maintain lifecycle quality and regulatory compliance.

Feature	Requirement	Purpose / Impact
Application Pathways	Standard / Expedited / Priority	Efficient, risk-based review
Bioequivalence Range	80–125%	Ensures therapeutic equivalence
Quality Documentation	Comprehensive CMC + GMP	Product quality assurance
Regulatory Authority	Roszdraznadzor	National centralized decision-making
Post-Approval Changes	National variation process	Lifecycle quality control
Review Timeline	Standard: ~210–270 days	Predictable regulatory pathway

Table 4.15: Summary of Key Russian Generic Drug Requirements

4.1.6.2 Russian Guidelines for Regulatory Alignment and Reliance**Local Adaptation of International Standards:**

Russian guidelines increasingly reference ICH, WHO, and PIC/S standards, supporting alignment with global scientific requirements while incorporating national legal and technical specifications.

Risk-Based Assessment:

Roszdraznadzor applies risk-based evaluation, prioritizing higher-risk products, including complex generics and biologics.

Reliance and Reference Approaches:

Abridged or reliance review pathways exist for products already approved by stringent regulatory authorities (SRAs) such as FDA, EMA, or WHO-prequalified products, although national authorization remains mandatory.

Capacity Building and International Collaboration:

Russia participates in international training, bilateral cooperation, and scientific exchange programs to strengthen domestic regulatory expertise.

4.1.6.3 Russia as a Reliance Platform in Emerging Markets

Russian regulatory decisions are increasingly considered reference points for neighbouring CIS countries and regional markets. Reliance on SRA approvals and GMP inspections helps reduce duplication and improve regulatory efficiency.

Region	Country / Authority	Nature of Reliance
CIS & EAEU	Kazakhstan, Belarus, Armenia	Recognition of Russian approvals and inspections
Global	FDA, EMA, WHO-prequalified products	Facilitates abridged review and regulatory trust
Emerging Markets	Central Asia & Eastern Europe	Reference for generics and biosimilars

Table 4.16: Russian Reliance Practices and Regional Linkages

4.1.6.4 Post-Marketing Surveillance and Pharmacovigilance

- Roszdraznadzor maintains a national pharmacovigilance system, requiring adverse event reporting, periodic safety updates, and implementation of risk management plans (RMPs).
- Russia increasingly collaborates with WHO Programme for International Drug Monitoring (PIDM) and regional partners to enhance safety signal detection and coordinate post-marketing actions.

4.1.6.5 Integration of Russia with WHO, ICH, and PIC/S Frameworks

Organization / Framework	Role	Linkage with Russia	Research Significance
WHO	Global guidance	Technical support and Good Reliance Practices (GRP)	Facilitates safe access to medicines
ICH	Harmonization of technical standards	Russian regulations gradually aligned	Ensures scientific consistency
PIC/S	GMP inspection harmonization	PIC/S-aligned GMP increasingly adopted	Supports product quality assurance

Table 4.17: Russia Integration with Global Regulatory Frameworks

4.1.6.6 Integration of Russia with Global Regulatory Frameworks and International Cooperation

- Russia participates in global regulatory initiatives to align its national requirements with international standards while maintaining local adaptations.
- WHO Collaboration: Russia follows WHO Good Reliance Practices (GRP) and integrates WHO-prequalified product guidelines to enhance access to safe medicines.

- ICH Alignment: Russian regulatory guidelines are progressively harmonized with ICH standards, particularly for quality (Q), safety (S), and efficacy (E) requirements, supporting scientific consistency.
- PIC/S Engagement: Russian GMP regulations are increasingly aligned with PIC/S principles, enabling reliance on internationally recognized inspection outcomes and improving pharmaceutical quality assurance.
- Regional Cooperation: Through the Eurasian Economic Union (EAEU), Russia collaborates with neighbouring countries to share assessment expertise, harmonize dossiers, and facilitate mutual recognition of certain approvals.

Organization / Framework	Role	Linkage with Russia	Research Significance	Organization / Framework
WHO	Global guidance	Technical support, GRP, WHO-prequalified products	Facilitates safe access to medicines	WHO
ICH	Harmonization of technical standards	Progressive alignment with Russian regulations	Ensures scientific and regulatory consistency	ICH
PIC/S	GMP inspection harmonization	PIC/S-aligned GMP increasingly adopted	Supports product quality assurance	PIC/S
EAEU	Regional collaboration	Mutual recognition and harmonized assessment	Enhances regional regulatory convergence	EAEU

Table 4.17: Russia Integration with Global and Regional Regulatory Frameworks

4.1.6.7 Challenges and Future Directions of the Russian Regulatory System

a) Challenges

Regulatory heterogeneity:

Differences in expertise, infrastructure, and implementation timelines can slow approvals and create market variability.

Local legal and language requirements Increase administrative complexity, particularly for international manufacturer

Limited reliance mechanisms:

Although SRA reliance exists, final authorization is strictly national, potentially duplicating global assessments.

Rapid pharmaceutical innovation

(Biologics, advanced therapies) demands continuous updates to guidance, testing, and evaluation protocols.

b) Future Directions

Russia is expected to expand reliance pathways, collaborative reviews, and alignment with SRA approvals to streamline regulatory efficiency.

Ongoing harmonization with ICH, WHO, and PIC/S standards will enhance international credibility and support global integration.

Digitalization of submissions, inspections, and pharmacovigilance is anticipated to improve transparency, timeliness, and real-world monitoring.

Development of regional cooperation frameworks within EAEU will promote shared expertise and facilitate mutual recognition of approvals.

Russia exemplifies an emerging regulatory market with local adaptations of international guidelines. Its regulatory future lies in gradual alignment with global standards, adoption of reliance models, digitalization, and enhanced pharmacovigilance, ensuring access to high-quality generic medicines while maintaining national regulatory sovereignty.

5. COMPARATIVE ANALYSIS OF DRUG APPROVAL SYSTEMS

5.1 Introduction

- Drug approval systems across the world are founded on a shared scientific objective ensuring that medicines entering the market are safe, effective, and of acceptable quality. However, despite increasing global interaction and the adoption of international guidelines, regulatory approval processes continue to exhibit substantial variation.

- These differences arise from region-specific legal frameworks, administrative procedures, review philosophies, and degrees of reliance on external regulatory decisions.
- This chapter presents a comparative and analytical evaluation of drug approval systems across selected regulatory jurisdictions.
- The analysis focuses on four critical dimensions: approval pathways, data requirements, review timelines, and review models. Beyond descriptive comparison, the chapter assesses the degree of regulatory harmonization versus fragmentation, highlighting how these factors influence global drug development, approval efficiency, and patient access.

5.2 Comparative Analysis of Approval Pathways

Approval pathways define the regulatory routes through which pharmaceutical products obtain marketing authorization. Although all regulatory systems are grounded in the assessment of safety, efficacy, and quality, approval pathways differ significantly in structure, procedural flexibility, and decision-making authority. These differences reflect variations in legal frameworks, regulatory maturity, and policy priorities across regions.

Centralized approval pathways are characterized by a single national or regional authority responsible for regulatory decision-making. Such pathways offer high levels of procedural consistency and predictability, reducing uncertainty for applicants. Centralized systems facilitate uniform regulatory outcomes and are particularly effective in ensuring consistent public health standards across a defined jurisdiction. However, they may limit flexibility in addressing region-specific healthcare needs.

In contrast, multi-route approval frameworks provide applicants with multiple procedural options, such as centralized, decentralized, or national pathways. While this approach enhances strategic flexibility and supports broader market access, it introduces procedural complexity. Applicants must carefully select pathways based on commercial objectives, regulatory timelines, and administrative requirements. The coexistence of multiple pathways within a single regulatory system can result in variable approval outcomes and increased coordination challenges.

Some regulatory systems adopt nationally governed approval pathways that are technically aligned with international standards but legally independent. These systems often incorporate abridged or facilitated pathways for products already approved by trusted regulatory authorities. While such convergence-based models reduce duplication of scientific assessment, they retain national control over final authorization decisions, preserving regulatory sovereignty.

An emerging trend in approval pathways is the increasing use of reliance and recognition mechanisms. These pathways allow regulatory authorities to partially or fully rely on prior assessments conducted by established regulators. Reliance-based pathways improve efficiency, conserve regulatory resources, and accelerate access to medicines. Nevertheless, their implementation remains uneven due to legal constraints, differences in risk tolerance, and concerns regarding accountability.

Comparative Interpretation

The comparative evaluation of approval pathways reveals a regulatory landscape marked by structural diversity rather than uniformity. Centralized pathways promote efficiency and predictability, multi-route systems enhance flexibility but increase complexity, and convergence-based pathways offer partial harmonization without full unification. Despite shared scientific foundations, approval pathways remain shaped by national legal frameworks and regulatory philosophies.

This structural diversity underscores a key source of regulatory fragmentation. While international harmonization initiatives have aligned technical requirements, approval pathways continue to operate under distinct procedural and legal regimes. As a result, a single pharmaceutical product may navigate multiple regulatory routes before achieving global market access, reinforcing the challenge of achieving true global harmonization in drug approvals.

5.3 Comparative Analysis of Data Requirements

5.3.1 Clinical and Bioequivalence Data

All regulatory authorities require robust evidence demonstrating the safety, efficacy, or therapeutic equivalence of pharmaceutical products prior to granting marketing authorization. For generic medicines, bioequivalence (BE) studies have become the globally accepted scientific basis for approval, as they establish equivalence between the generic product and the reference listed drug. Most regulatory systems apply harmonized pharmacokinetic acceptance ranges commonly 80-125% for key parameters such as AUC and C_{max} reflecting convergence in scientific standards.

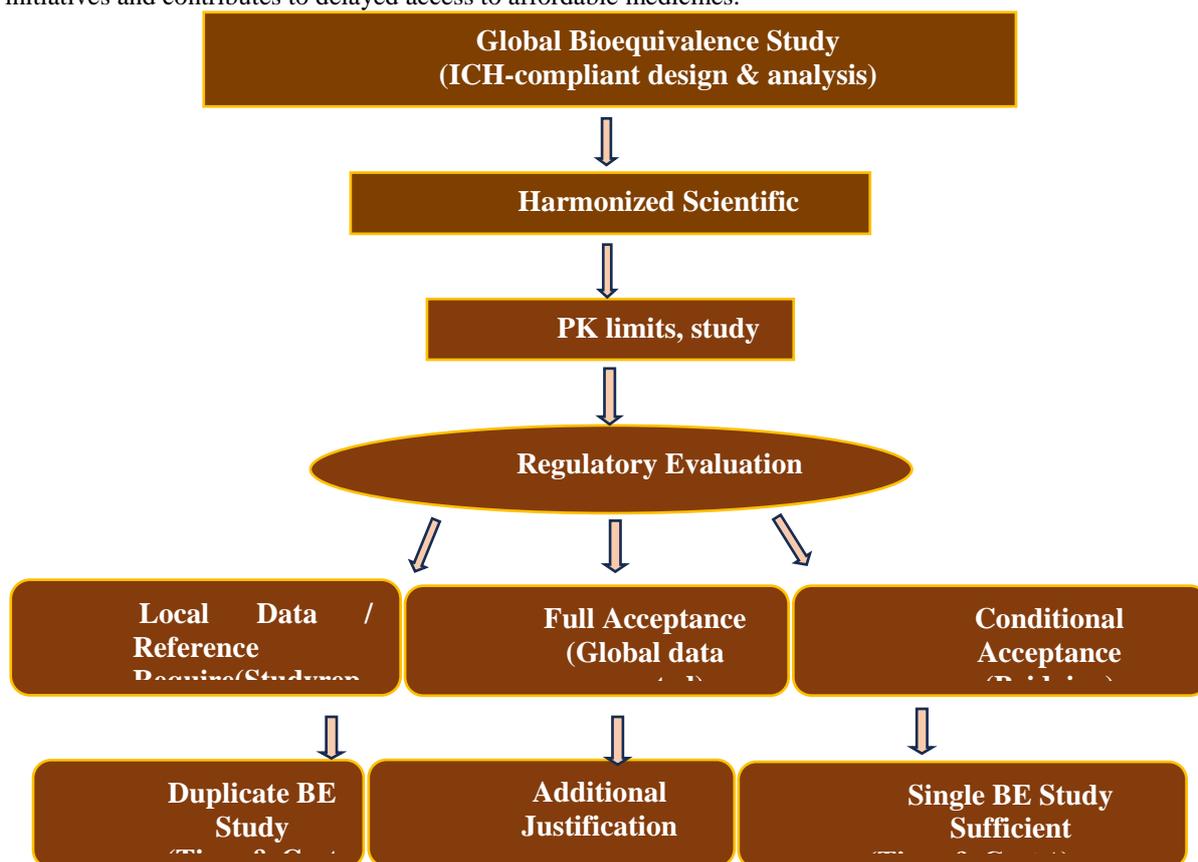
Despite this scientific alignment, significant regulatory divergence persists in the interpretation and acceptance of clinical and bioequivalence data. One of the major areas of variation is the acceptance of foreign-generated data. Some regulatory authorities accept global clinical and BE studies without additional requirements, provided that studies comply with international ethical and scientific standards. Other authorities impose supplementary conditions, including justification of population relevance, ethnic sensitivity analyses, or bridging studies.

A further source of fragmentation arises from reference product selection. While certain regulatory systems allow the use of internationally recognized reference products, others require comparison against a locally authorized reference product. This requirement often necessitates the repetition of BE studies even when the formulation, manufacturing process, and pharmacokinetic outcomes are scientifically comparable. Such duplication increases development costs and prolongs approval timelines without necessarily enhancing patient safety.

Population relevance is another critical factor influencing data requirements. Regulatory authorities may question whether pharmacokinetic data generated in one population can be directly extrapolated to another, particularly in regions where ethnic, dietary, or genetic differences are emphasized. Although international guidelines provide scientific justification for extrapolation in most cases, inconsistent regulatory acceptance continues to drive region-specific study requirements.

Analytical Interpretation

The comparative analysis demonstrates that harmonization of scientific criteria does not automatically translate into harmonization of regulatory practice. While bioequivalence standards are largely aligned, differences in data acceptance policies, reference product requirements, and population considerations lead to procedural duplication of studies. This fragmentation undermines the efficiency gains expected from global harmonization initiatives and contributes to delayed access to affordable medicines.



Flowchart 5: Flowchart of Global Drug Approval Harmonization and Fragmentation

5.3.2 Quality and Manufacturing Data

Quality-related data, including chemistry, manufacturing, and controls (CMC), are largely aligned with international guidelines. Nonetheless, regulatory fragmentation persists in the format of submissions, inspection reliance mechanisms, and lifecycle management of post-approval changes. Variations in documentation expectations and inspection acceptance continue to pose challenges for global submissions.

Analytical Interpretation

While scientific harmonization of data requirements has progressed significantly, procedural and administrative divergence remains a major contributor to regulatory fragmentation.

5.4 Comparative Analysis of Review Timelines

Regulatory review timelines directly influence global launch strategies and patient access to medicines. Although most authorities publish target review timelines, actual approval durations often vary due to procedural complexity, additional data requests, and administrative delays.

Regulatory Dimension	General Observation
Standard review period	Ranges from several months to over one year
Expedited pathways	Available in most systems but eligibility differs
Timeline predictability	Higher in centralized systems
Variability	Greater in nationally administered systems

Table 5.1: Comparative Review Timelines Across Regulatory Systems

Analytical Interpretation

Nominal similarities in review timelines mask significant real-world variability. Differences in procedural efficiency and reliance mechanisms contribute to staggered approvals, limiting synchronized global market entry.

5.5 Comparative Analysis of Review Models

Regulatory review models reflect how scientific and regulatory decisions are generated within approval systems.

5.5.1 Independent Review Models

These models rely primarily on internal regulatory expertise and emphasize national regulatory autonomy. Decision-making authority rests within a single regulatory body.

5.5.2 Committee-Based and Network Review Models

Committee-driven models draw on multidisciplinary expertise, often involving representatives from multiple jurisdictions. These models support harmonized regional decisions but may introduce additional coordination complexity.

5.5.3 Hybrid and Reliance-Based Models

Hybrid models combine independent scientific assessment with selective reliance on evaluations conducted by trusted foreign regulators. These models aim to improve efficiency while maintaining regulatory sovereignty.

Analytical Interpretation

The increasing adoption of reliance-based review models signals a shift toward regulatory convergence; however, uneven implementation limits their full harmonization potential.

5.6 Degree of Harmonization and Fragmentation

Regulatory Dimension	Degree of Harmonization
Scientific standards	High
Bioequivalence criteria	High
Quality guidelines	Moderate to High
Approval pathways	Low
Administrative procedures	Low
Reliance mechanisms	Moderate

Table 5.2: Degree of Regulatory Harmonization Across Key Dimensions

Interpretation

The degree of regulatory harmonization varies substantially across different dimensions of drug approval systems, reflecting uneven progress toward global regulatory convergence. Scientific standards exhibit a high level of harmonization, largely due to the widespread adoption of internationally accepted principles governing safety, efficacy, and risk–benefit evaluation. Regulatory authorities apply comparable scientific methodologies, enabling consistent interpretation of clinical and non-clinical data.

Bioequivalence criteria also demonstrate a high degree of harmonization, particularly in the context of generic drug approvals. The use of standardized pharmacokinetic parameters and universally accepted acceptance ranges has facilitated cross-regional consistency in evaluating therapeutic equivalence. This alignment has significantly reduced scientific uncertainty and duplication at the study design level.

Quality guidelines show a moderate to high level of harmonization. International standards governing manufacturing practices and quality systems are broadly adopted; however, differences remain in documentation formats, inspection practices, and post-approval lifecycle management. These procedural variations limit the realization of complete harmonization despite shared quality objectives.

In contrast, approval pathways exhibit a low degree of harmonization. Regulatory authorization routes are defined by national or regional legal frameworks, resulting in distinct procedural structures across jurisdictions. The absence of a globally unified approval pathway requires pharmaceutical products to undergo multiple regulatory processes, even when scientific data are equivalent.

Administrative procedures also display low harmonization. Variations in dossier submission formats, language requirements, review workflows, and regulatory fees create non-scientific barriers that significantly contribute to regulatory fragmentation and increase the complexity of global submissions.

Reliance mechanisms demonstrate a moderate degree of harmonization. While reliance-based and recognition approaches are increasingly incorporated into regulatory frameworks, their scope, legal enforceability, and operational implementation differ among authorities. These inconsistencies limit the full potential of reliance as a tool for global regulatory convergence.

Synthesis

The comparative assessment indicates that scientific harmonization has progressed more extensively than procedural and legal harmonization. This imbalance has produced a regulatory environment in which technical requirements are largely aligned, yet approval processes remain fragmented due to jurisdiction-specific legal, administrative, and policy constraints. As a result, a single pharmaceutical product developed under harmonized scientific standards must still navigate multiple regulatory pathways before achieving global market access.

This pattern underscores a fundamental challenge in contemporary drug regulation: while international initiatives have successfully standardized scientific evaluation, achieving harmonization at the procedural and policy level remains constrained by regulatory sovereignty. Consequently, global drug approval systems continue to reflect a coexistence of convergence in science and fragmentation in practice.

5.7 Case-Based Analytical Illustration

A generic drug developed using a globally accepted bioequivalence protocol may satisfy scientific requirements across multiple regulatory systems. However, differences in reference product selection, dossier format, inspection reliance, and administrative procedures can result in staggered approvals across regions. This illustrates how one medicine may face multiple regulatory realities, reinforcing the practical consequences of regulatory fragmentation.

5.8 Implications for Global Drug Development

- Regulatory fragmentation increases:
- Development and compliance costs
- Submission complexity
- Time to market
- Inequity in patient access
- Conversely, increased harmonization and reliance mechanisms:
- Reduce duplication of studies
- Improve regulatory efficiency
- Accelerate access to affordable medicines
- For pharmaceutical developers, strategic regulatory planning has become as critical as scientific development.

5.9 Conclusion

This chapter provides a PhD-level comparative analysis of global drug approval systems, demonstrating that while scientific standards are increasingly harmonized, regulatory approval processes remain structurally fragmented. Differences in approval pathways, data interpretation, review timelines, and decision-making models continue to prevent the realization of a truly unified global drug approval system. These findings underscore the central paradox of modern regulation: one medicine governed by many rules. Addressing this fragmentation is essential for advancing regulatory efficiency and equitable global access to medicines.

6. GLOBAL HARMONIZATION INITIATIVES IN DRUG REGULATION

6.1 Introduction

Global pharmaceutical regulation has increasingly shifted toward harmonization and regulatory cooperation to address duplication of effort, inconsistent approval timelines, and barriers to timely patient access to medicines. Given the globalization of pharmaceutical development and supply chains, no single regulatory authority can function in isolation. This chapter critically examines major global harmonization initiatives specifically the International Council for Harmonisation (ICH), World Health Organization (WHO) reliance frameworks, and regional regulatory collaborations and evaluates their role in reducing regulatory fragmentation while respecting national sovereignty.

6.2 International Council for Harmonisation (ICH)

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) represents the most advanced global effort toward regulatory harmonization. Established to unify technical requirements across major pharmaceutical markets, ICH develops globally accepted guidelines covering quality (Q), safety (S), efficacy (E), and multidisciplinary (M) domains.

ICH guidelines have significantly reduced scientific variability in drug development and evaluation. Harmonized standards for stability testing, bioequivalence, validation, and clinical trial design allow pharmaceutical companies to generate a single global data package applicable across multiple jurisdictions.

However, ICH harmonization is primarily technical rather than procedural. While scientific requirements are aligned, regulatory decision-making, approval timelines, and legal authorization processes remain under national control. Consequently, ICH reduces duplication in data generation but does not eliminate regulatory fragmentation at the approval stage.

6.3 World Health Organization (WHO) and Regulatory Reliance

The World Health Organization plays a central role in promoting regulatory convergence, particularly in low- and middle-income countries. WHO's Good Reliance Practices (GRP) encourage national regulatory authorities to leverage the assessments, inspection outcomes, and approvals of trusted reference agencies.

WHO reliance mechanisms improve regulatory efficiency by reducing duplication of reviews and accelerating access to essential medicines. Unlike ICH, which focuses on harmonized standards, WHO reliance emphasizes regulatory trust, transparency, and capacity building.

Despite its advantages, WHO reliance remains voluntary and context-dependent. Legal limitations, concerns regarding accountability, and variability in regulatory maturity restrict uniform adoption. As a result, reliance often complements but does not replace national regulatory decision-making.

6.4 Regional Regulatory Collaborations

Regional harmonization initiatives represent an intermediate approach between global harmonization and national regulation. Examples include the European Medicines Agency (EMA), ASEAN regulatory convergence, the African Medicines Regulatory Harmonization (AMRH) initiative, and regional reliance frameworks in Latin America and the Middle East.

These collaborations enable work-sharing, mutual recognition, and reliance-based approvals while preserving national authority. Regional initiatives are particularly effective in addressing administrative inefficiencies and facilitating simultaneous market access.

However, differences in national legislation, language requirements, and institutional capacity continue to limit full procedural harmonization. As a result, regional collaborations reduce but do not eliminate regulatory fragmentation.

6.5 Comparative Impact of Global Harmonization Initiatives

When examined collectively, global harmonization initiatives demonstrate uneven progress across regulatory dimensions. Scientific alignment has advanced substantially, while administrative and legal harmonization remains limited.

Regulatory Dimension	Degree of Harmonization
Scientific standards	High
Bioequivalence criteria	High
Quality guidelines	Moderate to High
Approval pathways	Low
Administrative procedures	Low
Reliance mechanisms	Moderate

Table 6.1: Comparative Impact of Global Harmonization Initiatives

This imbalance has resulted in a regulatory environment that is scientifically interconnected yet procedurally fragmented.

6.6 Synthesis of Harmonization Efforts

The analysis demonstrates that harmonization initiatives have successfully aligned technical requirements but have not achieved uniformity in regulatory decision-making. National legal frameworks, political accountability, and public health priorities continue to shape approval outcomes independently.

Consequently, pharmaceutical developers face a paradoxical system in which global scientific evidence is evaluated repeatedly through distinct national processes. This reinforces the theme of “one medicine, many rules” that underpins this thesis.

6.7 Critical Gaps in Global Harmonization Initiatives

Despite significant progress, current harmonization initiatives exhibit notable structural limitations. Most efforts prioritize scientific alignment while under-addressing procedural, legal, and policy-level integration. National laws governing marketing authorization, liability, and post-approval oversight restrict the extent to which harmonized standards can be operationalized.

Reliance mechanisms further depend on regulatory trust and institutional capacity, which vary widely across jurisdictions. Inadequate legal provisions for reliance, concerns regarding accountability, and uneven access to regulatory expertise limit broader adoption. As a result, harmonization often exists in principle rather than in practice, sustaining regulatory fragmentation despite technical convergence.

6.8 Future Directions for Global Regulatory Harmonization

Future progress toward meaningful regulatory harmonization will likely depend on expanding reliance-based models supported by clear legal frameworks and mutual accountability mechanisms. Strengthening regulatory capacity in emerging markets will be essential to enable effective participation in reliance networks.

Digital regulatory platforms, harmonized electronic submissions, and shared pharmacovigilance databases may further reduce administrative fragmentation. Moving forward, harmonization initiatives must evolve beyond technical alignment to incorporate procedural integration while preserving national regulatory sovereignty and public health priorities.

6.9 Implications for Global Generic Drug Regulation and Policy

The findings of this chapter have important implications for global generic drug regulation and policy development. While scientific harmonization through ICH and reliance initiatives has substantially reduced duplication in data generation, the persistence of fragmented approval pathways continues to delay market entry

and increase regulatory burden for generic manufacturers. This fragmentation has direct consequences for medicine affordability, supply chain resilience, and equitable patient access.

From a policy perspective, the analysis highlights the need for regulators to move beyond guideline-level harmonization toward legally supported reliance and work-sharing mechanisms. Strengthening institutional trust, clarifying accountability frameworks, and enabling formal recognition of foreign regulatory decisions could significantly improve regulatory efficiency without compromising national sovereignty.

For global generic drug development, these findings underscore the importance of strategic regulatory planning, including the use of reference authority approvals and regionally aligned submissions. Ultimately, advancing harmonization at the procedural level will be critical to achieving the objectives of faster access, reduced development costs, and sustainable global supply of quality-assured generic medicines.

6.10 Summary

This chapter demonstrates that global harmonization initiatives through ICH, WHO reliance, and regional collaborations have substantially aligned scientific standards but have not eliminated procedural fragmentation. The persistence of national approval pathways underscores the complexity of achieving full harmonization in a legally sovereign global regulatory environment. These findings provide a critical foundation for the concluding chapter, which synthesizes challenges, policy implications, and future recommendations.

7. REGULATORY FRAGMENTATION: CHALLENGES AND IMPACT

7.1 Introduction

Despite significant progress in global regulatory harmonization, drug approval systems remain fragmented across jurisdictions. Regulatory fragmentation arises from differences in scientific interpretation, legal frameworks, administrative procedures, and policy priorities. This chapter critically evaluates the scientific, legal, economic, and public health impacts of regulatory fragmentation and demonstrates how these dimensions collectively affect drug development efficiency, market access, and global health outcomes. The analysis positions regulatory fragmentation as a systemic challenge rather than a purely technical limitation.

7.2 Scientific Challenges

Scientific fragmentation persists despite the availability of harmonized international guidelines due to divergent regulatory interpretations of clinical evidence, bioequivalence requirements, reference product selection, and acceptance of foreign-generated data. Requirements for locally conducted clinical or bioequivalence studies, particularly for generic and complex products, continue to generate unnecessary duplication of research efforts. In addition, regulatory variability in the evaluation of biosimilars, complex generics, and advanced drug delivery systems further exacerbates scientific uncertainty across jurisdictions.

Impact: Increased development complexity, delayed approvals, and reduced incentives for innovation, particularly in complex and value-added generic medicines.

7.3 Legal and Regulatory Challenges

Legal fragmentation reflects the sovereign nature of pharmaceutical regulation. National laws governing marketing authorization, intellectual property protection, data exclusivity, pharmacovigilance, and regulatory accountability differ substantially across countries. These legal differences restrict the extent to which regulatory authorities can formally rely on foreign regulatory decisions, even when scientific equivalence is established. Variability in post-approval regulatory obligations further complicates global lifecycle management of medicines.

Impact: Legal constraints reinforce procedural duplication and limit the practical implementation of reliance-based regulatory frameworks.

7.4 Economic Impact

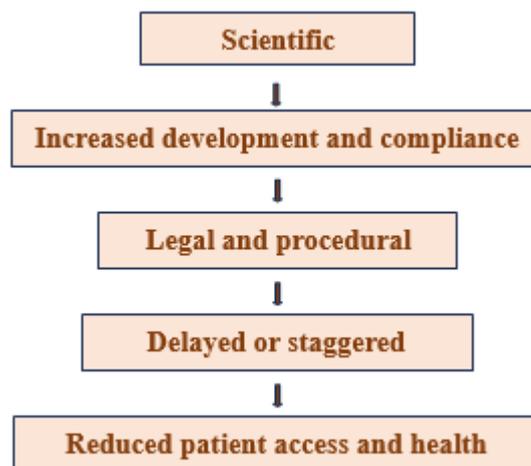
Regulatory fragmentation imposes significant economic burdens on pharmaceutical manufacturers due to multiple regulatory submissions, duplicated studies, and staggered approval timelines. For generic drug manufacturers, these additional costs reduce market participation and discourage entry into smaller or less harmonized markets. Fragmentation also results in inefficient allocation of regulatory resources, as authorities repeatedly conduct independent reviews of identical scientific data.

Impact: Increased medicine development costs, reduced competition, higher prices, and vulnerability of global supply chains.

7.5 Public Health Impact

The public health consequences of regulatory fragmentation are substantial. Delayed and inconsistent approval of medicines leads to unequal patient access across regions, even when products meet global safety and efficacy standards. In low- and middle-income countries, limited regulatory capacity combined with fragmented systems can significantly delay access to essential medicines. Fragmented pharmacovigilance systems also weaken global safety monitoring and reduce preparedness for public health emergencies.

Impact: Health inequities, delayed treatment availability, and compromised global health security.



Flowchart 6: Impact Pathway of Regulatory Fragmentation on Medicine Access

7.6 Integrated Nature of Regulatory Fragmentation

The impacts of regulatory fragmentation are interconnected across scientific, legal, economic, and public health domains. Scientific duplication increases economic burden; legal barriers restrict reliance; economic inefficiencies limit market participation; and public health outcomes are adversely affected. This interconnectedness demonstrates that regulatory fragmentation is a multidimensional and self-reinforcing phenomenon.

Regulatory Dimension	Key Sources of Fragmentation	Primary Impact on Drug Approval
Scientific	Divergent data interpretation, local study requirements, variable acceptance of foreign data	Duplication of studies, delayed approvals
Legal	National authorization laws, IP regimes, accountability frameworks	Limited reliance, procedural duplication
Economic	Multiple submissions, staggered approvals, compliance costs	Increased development cost, reduced competition
Public Health	Unequal regulatory capacity, fragmented pharmacovigilance	Delayed a

Table 7.1: Multidimensional Impact of Regulatory Fragmentation

7.7 Synthesis and Critical Perspective

The persistence of regulatory fragmentation highlights the structural limitations of current harmonization initiatives. While scientific standards have converged substantially through international guidelines, procedural and legal divergence continues to dominate regulatory practice. This sustains the paradox of globally developed medicines subjected to nationally fragmented approval systems, reinforcing the central thesis theme of “*one medicine, many rules.*” These observations are consistent across both highly regulated and emerging markets, indicating that regulatory fragmentation is a global structural challenge rather than a region-specific issue.

7.8 Implications of Regulatory Fragmentation for Global Drug Regulation

The multidimensional challenges identified in this chapter have important implications for the future of global drug regulation. Regulatory fragmentation not only affects individual approval outcomes but also shapes long-term regulatory behaviour, institutional priorities, and industry strategies. Persistent fragmentation discourages regulatory innovation, reinforces conservative decision-making, and limits the scalability of reliance-based and work-sharing models.

For pharmaceutical developers, particularly generic manufacturers, fragmentation influences market selection, submission sequencing, and investment decisions. Markets characterized by complex or non-aligned regulatory requirements may be deprioritized, resulting in delayed or limited medicine availability. From a regulatory perspective, fragmented systems reduce opportunities for capacity optimization, as authorities repeatedly allocate resources to duplicative scientific assessments.

At a systemic level, these implications highlight the need to reconsider how harmonization initiatives are operationalized. Scientific convergence alone is insufficient unless accompanied by procedural alignment, legal adaptability, and institutional trust. Understanding regulatory fragmentation as a structural governance issue rather than an isolated technical problem is therefore essential for achieving meaningful global convergence in drug approval systems.

Stakeholder	Consequences of Fragmentation
Regulatory Authorities	Duplication of reviews, inefficient use of resources
Pharmaceutical Industry	Increased costs, delayed market entry
Generic Manufacturers	Reduced incentives, limited market access
Patients	Delayed access, unequal availability of medicines
Public Health Systems	Reduced preparedness, supply vulnerabilities

Table 7.2: Consequences of Regulatory Fragmentation for Key Stakeholders

7.9 Conclusion

This chapter contributes to the thesis by systematically demonstrating that regulatory fragmentation extends beyond scientific divergence and is sustained by legal, economic, and public health factors that collectively limit the effectiveness of global harmonization initiatives. Despite advances in technical alignment, fragmented regulatory systems continue to impede efficient drug development and equitable patient access. Addressing these challenges will require coordinated reforms that integrate scientific harmonization with procedural, legal, and policy-level convergence. These findings provide a critical foundation for the final chapter, which presents overarching conclusions and strategic recommendations for reducing global regulatory fragmentation.

8. CONCLUSION AND RECOMMENDATIONS

8.1 Summary of Key Findings

This thesis examined the persistent tension between global regulatory harmonization and national regulatory autonomy in drug approval systems. Through comparative analysis of selected regulatory regions and evaluation of global harmonization initiatives, the study demonstrated that significant progress has been achieved in aligning scientific and technical standards for drug development. International guidelines have substantially reduced variability in quality, safety, and efficacy requirements.

However, the findings reveal that regulatory harmonization remains uneven. While scientific convergence is relatively advanced, procedural, legal, and administrative fragmentation continues to dominate regulatory practice. National sovereignty over marketing authorization, legal accountability, and public health decision-making has preserved divergent approval pathways, timelines, and post-approval obligations.

As a result, pharmaceutical developers face a regulatory landscape characterized by shared scientific foundations but fragmented operational execution. This imbalance reinforces the central thesis argument that modern pharmaceutical regulation operates within a paradox of globally developed medicines governed by nationally distinct rules. This study contributes to regulatory science by providing an integrated analytical framework that explains how scientific harmonization coexists with persistent legal and procedural fragmentation in global drug approval systems.

8.2 Policy Recommendations

8.2.1 Strengthening Reliance Mechanisms

Regulatory reliance represents one of the most practical and scalable pathways toward reducing regulatory fragmentation without undermining national sovereignty. Policymakers should establish clear legal frameworks that formally enable reliance on trusted reference authorities for scientific assessments, inspections, and approval decisions. Transparent criteria for selecting reference regulators, defined accountability mechanisms, and structured information-sharing platforms are essential for effective reliance implementation.

Expanding reliance-based pathways can reduce duplication of regulatory effort, accelerate approval timelines, and improve access to quality-assured medicines, particularly in resource-constrained settings.

8.2.2 Capacity Building for Regulatory Authorities

Sustainable harmonization requires strengthening regulatory capacity across jurisdictions. Investment in training, infrastructure, and digital regulatory systems is essential to support effective participation in harmonization and reliance initiatives. Capacity building should prioritize expertise in benefit–risk assessment, complex generics, biosimilars, and post-marketing surveillance.

International collaboration, joint reviews, and regulatory twinning programs can further enhance institutional competence while fostering trust among regulatory authorities. Strengthened regulatory capacity will improve the consistency and credibility of reliance-based regulatory decisions.

Recommendation	Objective	Expected Impact	Stakeholders
Strengthen reliance mechanisms	Reduce duplication, accelerate approvals	Faster patient access, lower costs	Regulators, Policymakers
Capacity building	Enhance institutional competence	Reliable and consistent regulatory decisions	Regulators, International Agencies
Integrate regulatory science in education	Develop skilled workforce	Better industry–regulator interaction, global readiness	Universities, Training Institutes
Promote digital platforms	Facilitate data sharing and pharmacovigilance	Reduce administrative fragmentation	Regulators, Industry

Table 8.1: Summarizing Recommendations

8.3 Implications for Pharmaceutical Education and Practice

The findings of this thesis have important implications for pharmaceutical education and professional practice. Pharmacy and pharmaceutical sciences curricula must increasingly integrate regulatory science, global regulatory systems, and harmonization frameworks to prepare graduates for complex, internationally connected regulatory environments.

For industry professionals, the study highlights the importance of strategic regulatory planning, early engagement with regulators, and understanding reliance-based pathways. Regulatory professionals must develop competencies that extend beyond national systems to encompass global regulatory intelligence, lifecycle management, and cross-jurisdictional coordination.

Regulatory professionals must also consider ethical dimensions of cross-border decisions, balancing expedited access with patient safety and equitable global distribution of medicines.

8.4 Future Research Directions

Future research should explore empirical assessment of reliance mechanisms by examining approval timelines, regulatory efficiency, and post-marketing safety outcomes across jurisdictions adopting reliance-based models. Comparative case studies of complex generics, biosimilars, and advanced drug delivery systems would provide valuable insights into areas where scientific harmonization remains limited.

Further investigation into digital regulatory platforms, shared pharmacovigilance systems, and real-world evidence integration may identify innovative solutions to procedural fragmentation. Research examining the legal and ethical dimensions of cross-border regulatory decision-making would also contribute to advancing global regulatory governance.

8.5 Conclusion

This thesis concludes that while global harmonization initiatives have successfully aligned scientific standards, regulatory fragmentation persists due to legal, procedural, and institutional constraints. Achieving meaningful convergence in drug approval systems will require a balanced approach that respects national autonomy while promoting reliance, trust, and regulatory cooperation. Addressing this balance is essential for improving regulatory efficiency, fostering pharmaceutical innovation, and ensuring equitable global access to safe and effective medicines.

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