JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

RESEARCH ARTICLE

A Comparative Study of Regulatory Guidelines, Digital Pharmacovigilance, and Software as a Medical Device across High- and Low-to-Middle-Income Countries

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Publication history: Received on 6th February 2026; Revised on 17th March 2026; Accepted on 18th March 2026

Article DOI: 10.69613/mdb50d20

Abstract: The rapid integration of artificial intelligence within pharmaceutical public health provides significant opportunities for optimizing therapeutic outcomes, yet it introduces profound regulatory, ethical, and systemic vulnerabilities. Deployment of AI can range from digital pharmacovigilance utilizing machine learning to scan electronic medical records and social media for adverse drug reactions and machine learning-driven drug discovery, where algorithms accelerate lead compound identification. Despite these technological strides, global governance remains structurally fragmented between high-income countries and low- and middle-income countries. High-income jurisdictions deploy mature, legally enforceable norms leveraging Software as a Medical Device classifications pioneered by the European Medicines Agency and the United States Food and Drug Administration. On the other hand, low- and middle-income countries encounter severe implementation barriers, primarily driven by the absence of specialized digital health sub-units within national pharmaceutical regulatory authorities, fragmented digital registries, and restricted technical capacity to audit predictive models. This disparity threatens to deepen global health inequalities, leaving developing healthcare systems susceptible to unvalidated therapeutic algorithms and biased diagnostic software. Mitigating these governance asymmetries requires a shift from aspirational ethical declarations to localized, risk-based legislative frameworks. Establishing dedicated digital health divisions within national medicines boards, standardizing local health data registries, and leveraging regional regulatory coalitions represent essential interventions to secure equitable, safe, and transparent algorithmic applications. Sustainable international cooperation must prioritize technical capacity transfer to prevent the colonization of digital health infrastructure and to ensure that algorithmic innovations serve diverse population demographics equitably.

Keywords: Artificial Intelligence; Pharmaceutical Public Health; Digital Pharmacovigilance; Software as a Medical Device; Low- and Middle-Income Countries.

1. Introduction

Artificial intelligence (AI) is redefining the public health, transforming population-level interventions from reactive epidemiological responses to predictive, precision-driven computational models [1]. Within pharmaceutical public health, the integration of AI algorithms has become a disruptive force, reforming traditional paradigms of therapeutic development, clinical evaluation, and post-market safety monitoring [2]. Public health systems increasingly rely on deep learning, natural language processing, and advanced predictive analytics to handle the massive volumes of biomolecular, clinical, and observational data generated across the pharmaceutical life cycle [3]. These computational tools offer unprecedented capabilities to accelerate therapeutic pipelines, optimize resource deployment, and manage population-scale health outcomes with elevated accuracy [4].

Despite these developments, the rapid clinical translation of AI poses significant governance, regulatory, and safety challenges. Traditional pharmaceutical regulations are designed for static, physical entities, such as small-molecule chemicals and biological therapeutics [5]. Conversely, clinical AI models are inherently dynamic, adaptive, and frequently non-transparent, presenting unique challenges regarding algorithmic bias, transparency, and clinical accountability [6]. The utilization of biased datasets in model training risks propagating historical systemic inequities, while the "black-box" nature of deep neural networks complicates clinical verification

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and risk stratification [7]. These issues are particularly acute in high-stakes pharmaceutical applications, such as the automated detection of adverse drug reactions (ADRs) and the optimization of clinical trials, where algorithmic failures can result in widespread population harm. A primary tension in current policy spaces is the structural asymmetry in AI governance across different income settings. High-income countries (HICs) have rapidly established sophisticated, legally binding regulatory protocols [8]. These frameworks utilize Software as a Medical Device (SaMD) classifications to subject clinical software to rigorous validation, post-market surveillance, and computational auditing [9]. On the contrary, low- and middle-income countries (LMICs) encounter substantial obstacles, including fragmented legislative structures, a severe shortage of technical regulatory expertise, and inadequate digital health infrastructure [10]. The absence of specialized digital health divisions within national pharmaceutical regulatory authorities in LMICs leads to a regulatory vacuum, where clinical algorithms are deployed without empirical validation or localized safety oversight [11].

Although international bodies, such as the World Health Organization (WHO), the Organisation for Economic Co-operation and Development (OECD), and UNESCO, have articulated normative guidance on trustworthy AI, these frameworks are primarily aspirational [12]. There is a critical shortage of comparative policy research analyzing how these global standards are operationalized across divergent socioeconomic contexts [13]. Most existing policy assessments are restricted to descriptive analyses of single-country initiatives, failing to dissect the structural pathologies that impede effective enforcement in resource-constrained environments [14]. A rigorous, comparative policy analysis is therefore required to identify the legal, technical, and institutional mismatches between HICs and LMICs, and to construct context-specific policy strategies that ensure safe, equitable, and accountable algorithmic integration. This work aims to evaluate AI governance structures in pharmaceutical public health across selected HICs and LMICs

2. AI in Pharmaceutical Public Health

2.1. Software as a Medical Device (SaMD) and Clinical Classifications

The regulation of clinical software has shifted from generalized digital health oversight to formalized Software as a Medical Device (SaMD) frameworks [15]. As defined by the International Medical Device Regulators Forum (IMDRF), SaMD is software intended to be used for one or more medical purposes that performs these purposes without being part of a hardware medical device [16]. This definition encompasses clinical decision support systems, predictive diagnostic models, and algorithms used to monitor patient safety or therapeutic compliance. The IMDRF risk-categorization framework classifies SaMD based on two primary dimensions: the state of the healthcare situation (critical, serious, or non-serious) and the significance of the information provided by the SaMD to the healthcare decision (treating/diagnosing, driving clinical management, or informing clinical management) [17].

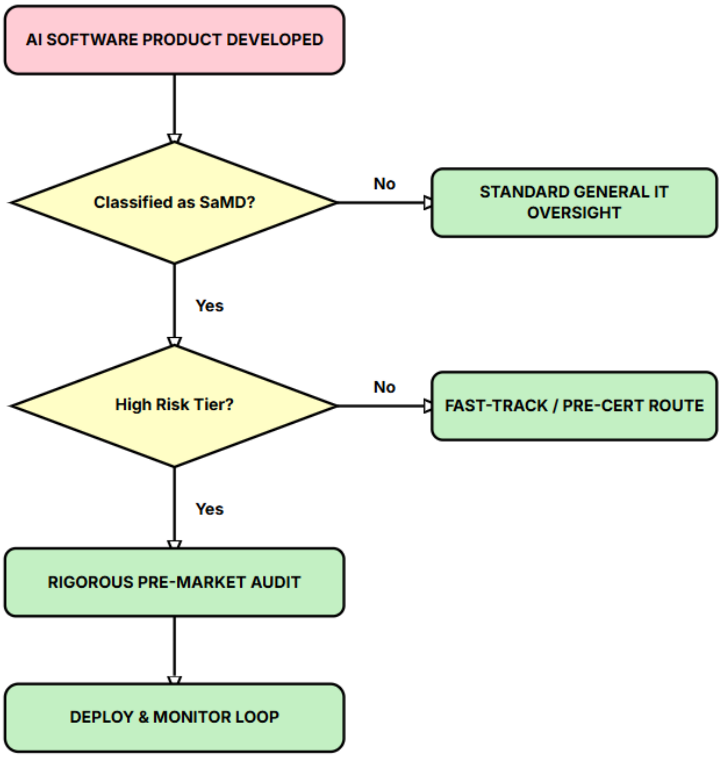

Figure 1. Regulatory Lifecycle and Risk-Stratification for Software as a Medical Device (SaMD)

In high-income jurisdictions, national regulatory bodies have codified these principles into hard law. The United States Food and Drug Administration (FDA) regulates SaMD through its Center for Devices and Radiological Health (CDRH), classifying applications into Class I (low risk), Class II (moderate risk), and Class III (high risk) [18]. Recognizing that traditional, static pre-market clearance pathways are ill-suited for iterative, self-learning machine learning algorithms, the FDA initiated the Software Pre-Certification (Pre-Cert) Program. This regulatory innovation shifts focus from individual product clearance to an organizational assessment, evaluating the developer's robust design, software development, and post-market tracking capabilities [19].

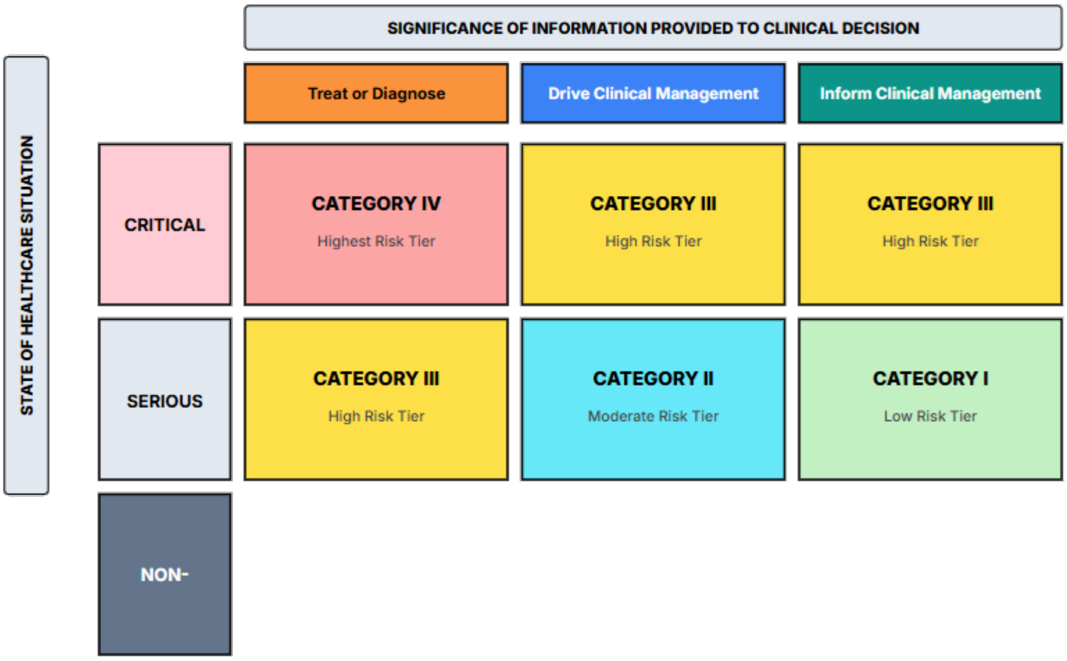

Figure 2. Software as a Medical Device (SaMD) Risk Categorization Matrix

Table 1. Global Reference Policies and Operational Limitations

Policy	Issuing Body & Year	Primary Scope & Focus Areas	Functional Mechanism	Core Limitations in Pharmaceutical Public Health
Guidance on the Ethics and Governance of AI for Health	World Health Organization (WHO), 2021	Autonomy, safety, transparency, explainability, equity, and sustainability in healthcare.	Soft Law / Normative Guidance	Lacks statutory authority to enforce compliance; provides no specific technical parameters for auditing neural networks or clinical trial software.
Principles on Artificial Intelligence	OECD, 2019	Trustworthy AI, inclusive growth, human values, transparency, and accountability.	Soft Law / Multi-sectoral Policy Directives	Non-health-specific; lacks structural frameworks for dynamic medical software or molecular drug discovery validation.
Recommendation on the Ethics of Artificial Intelligence	UNESCO, 2021	Human rights, social justice, non-discrimination, and data governance.	Global Ethical Basis / Soft Law	Primarily aspirational; provides no operational protocols for national medicines boards or clinical validation.
EU Artificial Intelligence Act	European Union, 2024	Risk-based regulation categorizing AI systems into distinct risk tiers.	Hard Law / Legally Enforceable Regulation	Highly resource-intensive; places massive administrative and compliance burdens on localized or lower-resource developers.

Similarly, the European Medicines Agency (EMA) and the European Commission enforce SaMD regulations through the Medical Device Regulation (MDR 2017/745) and the In Vitro Diagnostic Regulation (IVDR 2017/746) [20]. Under Rule 11 of the MDR, software intended to provide information used to take decisions with diagnosis or therapeutic purposes is classified as Class IIa, IIb, or Class III, depending on the severity of the clinical scenario [21]. This classification effectively elevates almost all AI-driven clinical software out of the low-risk Class I category, mandating rigorous, independent assessment by Conformity Assessment Bodies (Notified Bodies) before clinical deployment.

Table 2. Software as a Medical Device (SaMD) Classification

Jurisdiction / Agency	**Regulatory Statutory Basis**	**Software Classification Tiers**	**Pre-Market Evaluation Mechanisms**	**Post-Market Tracking Mandates**
United States (FDA / CDRH)	Food, Drug, and Cosmetic Act; Medical Device Amendments	Class I (Low Risk), Class II (Moderate Risk), Class III (High Risk)	Traditional 510(k) clearance, De Novo pathways, and Pre-Market Approval (PMA); supplemented by the Software Pre-Certification Program.	Real-world performance monitoring, mandatory medical device reporting for adverse software events, and algorithmic version tracking.
European Union (EMA / European Commission)	Medical Device Regulation (MDR 2017/745)	Class I, Class IIa, Class IIb, Class III (Rule 11 elevates almost all diagnostic/therapeutic AI to Class IIa or higher)	Independent conformity assessments executed by designated Notified Bodies; verification of technical documentation and clinical safety.	Post-Market Surveillance (PMS) plans, Periodic Safety Update Reports (PSUR), and mandatory registration in the EUDAMED database.
Canada (Health Canada)	Food and Drugs Act; Medical Device Regulations	Class I (Lowest) to Class IV (Highest) based on modified IMDRF risk-categorization matrices	Licensing pathways that allow for dynamic, iterative machine learning adjustments under pre-authorized re-training protocols.	Active post-market surveillance, mandatory problem reporting for software drift, and continuous validation logging.

2.2. Pharmaceutical AI-Driven Drug Discovery

The application of AI in the preclinical and clinical phases of drug development introduces distinct governance requirements that diverge from traditional chemical and biological testing protocols [22]. In preclinical drug discovery, machine learning models are deployed for high-throughput screening of lead compounds, de novo molecular design, predictive absorption, distribution, metabolism, excretion, and toxicity (ADMET) modeling, and target identification [23]. The primary governance challenge in this domain is the validation of predictive toxicology models. Traditional regulatory pathways rely on standardized, empirical in vitro and in vivo assays. When deep learning models replace these physical tests, regulators require transparency regarding the training data, the model's biological plausibility, and the mathematical validation of its predictive boundaries to prevent safety failures in phase-I clinical trials [24].

In the clinical trial phase, algorithmic systems are deployed to optimize trial design, automate patient recruitment, monitor patient retention, and manage real-time physiological data [25]. AI tools analyze electronic medical records (EMRs) and genetic registries to identify eligible cohorts, accelerating enrollment. Additionally, algorithms are increasingly used to construct "synthetic control arms" by modeling historical patient data, reducing the need for physical control groups [26].

These applications require strict regulatory oversight to protect human subjects and preserve trial integrity. Regulators must monitor the potential for algorithmic selection bias, which can systematically exclude marginalized demographics from trials, thereby compromising the external validity of efficacy and safety data. The use of adaptive algorithmic protocols, where the trial parameters dynamically adjust based on real-time data analysis, requires pre-specified regulatory protocols to ensure that statistical power and patient safety are not compromised.

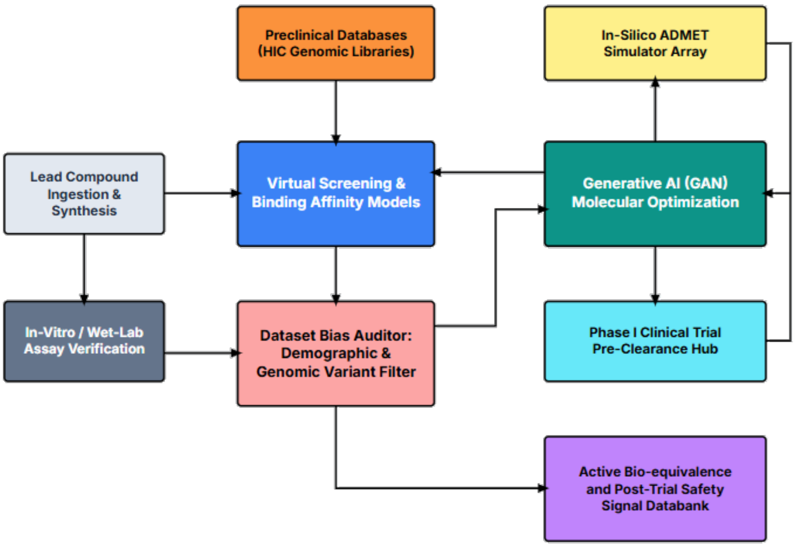

Figure 3. Computational Preclinical Drug Discovery Pipeline and Toxicology

2.3. Global Multi-Sectoral Guidance vs. Hard Law

Global multi-sectoral organizations have established a foundation of normative principles to guide AI development, yet these frameworks exhibit significant functional limitations when applied to pharmaceutical public health [27]. The World Health Organization (WHO) Guidance on the Ethics and Governance of Artificial Intelligence for Health articulates six core principles: protecting autonomy, promoting human well-being and safety, ensuring transparency and explainability, fostering responsibility and accountability, ensuring inclusiveness and equity, and promoting responsive and sustainable AI [12]. While highly influential in establishing ethical standards, the WHO framework is non-binding, lacking the statutory power to enforce compliance or penalize regulatory violations.

Similarly, the OECD AI Principles and the UNESCO Recommendations on the Ethics of Artificial Intelligence provide high-level, multi-sectoral paradigms emphasizing human rights, non-discrimination, and international collaboration [28]. However, these international platforms operate primarily as instruments of soft law. They lack specific technical parameters for clinical software verification, leaving a significant gap between abstract ethical consensus and the enforceable, risk-stratified legislative frameworks required to govern pharmaceutical public health [29]. Consequently, while HICs utilize these global principles as foundational values to build enforceable domestic legislation, LMICs often adopt them merely as aspirational declarations, resulting in a disconnected policy landscape without practical clinical utility.

3. Methodology

3.1. Study Design

This investigation utilizes a qualitative comparative policy analysis, employing a framework-based approach to systematically evaluate and contrast AI governance models in pharmaceutical public health across different socioeconomic settings. This methodological design facilitates a structured evaluation of policy design, statutory authority, and institutional implementation capacities.

3.2. Country Selection and Purposive Sampling

A purposive sampling strategy was implemented to select seven jurisdictions representing distinct socioeconomic profiles, technological infrastructures, and regulatory histories:

- **High-Income Countries (HICs):** The United Kingdom, the European Union (evaluated at the regional policy level), and Canada. These jurisdictions represent mature, highly integrated legal structures with established clinical software classification pathways.
- **Low- and Middle-Income Countries (LMICs):** India, Nigeria, Kenya, and South Africa. These countries represent dynamic, evolving digital health ecosystems experiencing rapid technological integration alongside distinct institutional and infrastructural challenges.

3.3. Data Sources and Search Strategy

The qualitative dataset was constructed through a systematic search of official, publicly accessible repositories, spanning documents published up to 2026. Data sources included:

- National AI strategies and digital economy roadmaps.
- Digital health policies, pharmaceutical regulations, and medical device guidelines.
- Statutory acts, legislative bills, and clinical trial regulations.
- Formal policy publications from the WHO, OECD, and the European Commission.

3.4. Inclusion and Exclusion Criteria

Documents were evaluated against strict selection criteria.

3.4.1. Inclusion Criteria

- Official policy documents, statutory frameworks, national strategies, or legislative bills addressing AI governance.
- Direct or indirect applicability to pharmaceutical public health, digital pharmacovigilance, medical devices, clinical trials, or drug regulation.
- Enacted or endorsed by national governments, regional coalitions, or recognized international organizations.
- Published in English or available as official translated texts.

3.4.2. Exclusion Criteria

- Technical research manuscripts focusing solely on algorithmic design without policy, regulatory, or ethical considerations.
- Commercial whitepapers, opinion pieces, editorials, or non-peer-reviewed commentaries.
- Generalized AI strategies lacking clear applicability to the healthcare, pharmaceutical, or medical device sectors.
- Superseded policy documents that have been replaced by updated legislative frameworks.

3.5. Analytical Coding

Extracted policy documents were analyzed using a predefined, matrix-based coding framework adapted from global pharmaceutical and digital health standards. Data were coded across six operational domains:

3.5.1. Regulatory Maturity and SaMD Integration

The presence of legally binding statutes, risk-stratified classifications for clinical software, and specialized validation pathways.

3.5.2. Preclinical and Clinical Trial Oversight

Rules governing computational drug discovery, preclinical validation, and algorithmic trial optimization.

3.5.3. Data Governance and Interoperability

Statutory protections for patient data privacy, standardized health data exchanges, and rules for training-set compilation.

3.5.4. Institutional and Enforcement Capacity

The existence of dedicated technical regulatory sub-units, computational auditing infrastructure, and specialized human capital.

3.5.5. Post-Market Surveillance and Digital Pharmacovigilance

Guidelines for real-time safety tracking, active signal detection, and monitoring adverse drug events.

3.5.6. Equity, Representation, and Bias Mitigation

Enforceable mandates to identify and eliminate algorithmic bias, ensuring diverse demographic representation in training datasets.

A thematic analysis was performed on the coded data, comparing the operationalized reality of these domains across the selected jurisdictions to identify structural gaps and implementation barriers.

4. Results

4.1. High-Income Countries

4.1.1. United Kingdom

The United Kingdom has established an integrated regulatory ecosystem for clinical AI, coordinated by the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA manages this transition through the Software and AI as a Medical Device Change Programme, which provides clear regulatory pathways for digital therapeutics and diagnostic algorithms [30]. This initiative aligns closely with the UK's post-Brexit life sciences strategy, seeking to establish a flexible yet rigorous regulatory environment.

A primary pillar of this system is the integration of the MHRA's regulatory oversight with the National Health Service (NHS) AI Lab. The NHS AI Lab facilitates the safe evaluation and ethical deployment of AI technologies within the public health system, acting as an intermediary that tests software in real-world clinical environments before widespread adoption.

For digital pharmacovigilance, the UK relies on the Yellow Card Scheme, which is increasingly enhanced by natural language processing (NLP) algorithms to scan electronic health records and detect early signals of adverse drug events [31]. This integrated clinical-regulatory pipeline ensures that software tools are subjected to continuous post-market surveillance under structured, legally enforceable standards.

4.1.2. European Union

The European Union represents the most formalized, risk-based legislative model globally, anchored by the enactment of the EU Artificial Intelligence Act [20]. The AI Act classifies AI systems based on their potential to cause harm, designating medical software including algorithmic diagnostic systems and AI-driven clinical decision support tools as "high-risk." This designation subjects developers to stringent pre-market conformity assessments, detailed technical documentation mandates, and mandatory human oversight protocols.

To complement this regulatory structure, the EU is implementing the European Health Data Space (EHDS), which standardizes health data exchanges and provides a secure framework for the primary and secondary use of health data across member states [32].

In the pharmaceutical sector, the European Medicines Regulatory Network, led by the EMA, executes a joint AI workplan. This strategy provides concrete guidance on the use of machine learning in the pharmaceutical product lifecycle, from preclinical target validation to automated signal detection in European pharmacovigilance databases. This centralized, highly coordinated approach ensures that software products are audited by designated Notified Bodies before securing market entry.

4.1.3. Canada

Canada utilizes a structured, policy-integrated model overseen by Health Canada's Digital Health Division. Health Canada regulates clinical AI under the Food and Drugs Act as a subset of Medical Device Regulations, using a risk-stratified classification system that mirrors the IMDRF framework [33]. To address the challenges of adaptive, self-learning algorithms, Health Canada has established pre-market authorization pathways that allow for iterative software updates, provided the developer conforms to pre-authorized "re-training" protocols and continuous post-market surveillance.

At the legislative level, Canada has advanced the Artificial Intelligence and Data Act (AIDA), introduced as part of Bill C-27 [34]. AIDA establishes a legal framework to govern "high-impact" AI systems, mandating that developers implement robust risk-mitigation strategies, maintain detailed algorithmic logs, and provide public-facing transparency reports.

This legislative framework is supported by Canada's provincial health authorities, which collaborate to develop provincial health data repositories, ensuring that digital pharmacovigilance tools can access standardized, high-quality clinical data for active safety monitoring.

4.2. Low- and Middle-Income Countries

4.2.1. India

India presents a complex, rapidly evolving digital health landscape characterized by high technological innovation alongside fragmented regulatory structures [10]. The government's primary policy direction is outlined in the National Strategy for Artificial Intelligence, developed by NITI Aayog, which promotes "AI for All" and identifies healthcare as a key focus area [35]. This is supported by the Ayushman Bharat Digital Mission (ABDM), which seeks to establish a national digital health infrastructure by standardizing digital registries, creating unique health accounts, and building federated health data exchanges.

Table 3. Cross-Jurisdictional Policy and Operational Maturity Matrix

Jurisdiction	SaMD Integration & Regulatory Maturity	Preclinical & Trial Optimization Rules	Data Governance & Interoperability	Dedicated Institutional Capacity	Post-Market Pharmacovigilance Systems	Bias Mitigation & Representation Mandates
United Kingdom	Advanced (MHRA Change Programme)	Structured (Clinical trials software frameworks)	High (GDPR-aligned, secure health data linkages)	High (MHRA partnered with NHS AI Lab)	Advanced (Active NLP integration in Yellow Card Scheme)	Moderate (Evolving guidelines on demographic equity)
European Union	Advanced (Legally binding risk tiers via EU AI Act)	Advanced (EMA joint pharmaceutical AI workplan)	Very High (Standardized via European Health Data Space)	Very High (Coordinated systems across Notified Bodies)	Advanced (Active, centralized European signal detection)	High (Strict, rights-based algorithmic bias audits)
Canada	Advanced (Health Canada SaMD rules & AIDA)	Structured (Food and Drugs Act updates)	High (Provincial health repositories & Bill C-27)	High (Health Canada Digital Health Division)	Structured (Provincial active monitoring registries)	Moderate (Transparency logs and equity reporting requirements)
India	Emerging (Basic medical device rules cover software)	Nascent (Preclinical rules lack ML parameters)	Moderate (Improving via ABDM data exchanges & DPDP Act)	Moderate (Growing technical expertise but uncoordinated)	Fragmented (Passive spontaneous reporting remains dominant)	Low (Language and demographic bias rules are non-binding)
Nigeria	Nascent (Aspirational national AI strategy roadmaps)	Absent (No software rules within drug discovery)	Low (Fragmented EHR databases; NDPA limits)	Low (NAFDAC lacks any dedicated software unit)	Passive (Paper-based reporting; severe underreporting)	Absent (No statutory protocols for dataset diversity)
Kenya	Emerging (Digital Health Act establishes basic framework)	Absent (No rules for machine learning in drug design)	Moderate (Data Protection Act active but limited EHR use)	Low (Pharmacy & Poisons Board lacks tech infrastructure)	Passive (No automated surveillance mechanisms)	Absent (No regulatory mechanisms to audit software bias)
South Africa	Emerging (SAHPRA software rules aligned to IMDRF)	Nascent (Preclinical validation pathways lack clarity)	Moderate (Strong privacy via POPIA; unequal EHR systems)	Moderate (Improving capacity but limited by drug backlogs)	Passive (Uneven private vs. public sector data capacity)	Low (Awareness of representation bias but unevenly applied)

However, India's pharmaceutical regulatory body, the Central Drugs Standard Control Organisation (CDSCO), lacks a dedicated, statutory medical device pathway specifically designed to evaluate SaMD or predictive drug discovery models [36]. The Medical Devices Rules, while updated to cover software, do not provide detailed technical parameters for auditing neural networks or managing adaptive clinical software.

Consequently, while India's technological sector possesses advanced software development capabilities, the domestic deployment of pharmaceutical AI remains largely unregulated, relying on generalized IT standards rather than clinically validated, software-specific enforcement protocols.

4.2.2. Nigeria

Nigeria represents an emerging digital health ecosystem with significant policy-practice gaps [11]. The regulatory landscape is governed by the National Information Technology Development Agency (NITDA) and the National Agency for Food and Drug Administration and Control (NAFDAC). While NITDA has spearheaded the development of the National Artificial Intelligence Strategy, this document remains a high-level roadmap with limited integration into the clinical drug regulatory space. NAFDAC, the statutory authority responsible for regulating pharmaceuticals and medical devices, lacks specialized sub-units to evaluate digital health technologies, software as a medical device, or AI-driven pharmacovigilance tools [37].

Data privacy is nominally protected under the Nigeria Data Protection Act (NDPA), but the implementation of this statute within public hospitals and pharmaceutical registries is limited.

Most public health facilities utilize fragmented, non-interoperable electronic health record systems or paper-based records. This lack of standardized digital registries prevents the deployment of automated digital pharmacovigilance systems, leaving NAFDAC reliant on passive, paper-based spontaneous ADR reporting, which suffers from severe underreporting and data quality limitations.

4.2.3. Kenya

Kenya, often recognized as a regional leader in digital innovation within sub-Saharan Africa, has made progressive strides in digital health legislation [38]. The government enacted the Digital Health Act, which establishes the Digital Health Agency and outlines a clear mandate to build an integrated national digital health ecosystem. This legislation is designed to standardize health information systems, secure patient data privacy under the Data Protection Act, and facilitate telehealth services.

However, the practical application of these rules within the pharmaceutical sector, governed by the Pharmacy and Poisons Board (PPB), remains constrained. The PPB lacks the technical infrastructure and specialized personnel required to validate medical software or assess the safety of clinical algorithms.

Although the national digital health policy advocates for the integration of telemedicine and mobile health applications, there is a major regulatory gap concerning the classification and verification of SaMD. This leaves the Kenyan pharmaceutical market vulnerable to unvalidated diagnostic and therapeutic software, as the PPB has not yet established a dedicated sub-unit to audit algorithmic safety or regulate machine learning applications in drug distribution.

4.2.4. South Africa

South Africa possesses a relatively mature regulatory structure in the region, managed by the South African Health Products Regulatory Authority (SAHPRA) and the National Department of Health [14]. SAHPRA regulates medical devices under the Medicines and Related Substances Act, and has increasingly moved to incorporate software guidelines that align with international IMDRF standards. This regulatory oversight is supported by a strong legal framework for data privacy established under the Protection of Personal Information Act (POPIA), which strictly regulates the processing of personal health information [39]. Despite these legislative advantages, SAHPRA faces significant capacity constraints when executing technical audits of clinical AI software.

The authority has struggled to cope with the backlog of traditional drug registrations, leaving limited resource allocation for the complex, time-consuming evaluation of machine learning models. The public healthcare system remains deeply divided, with highly advanced private hospital groups deploying sophisticated clinical decision support systems, while the under-resourced public sector lacks the digital infrastructure required to implement basic automated pharmacovigilance tools.

5. Discussion

5.1. Normative Proclamations vs. Enforceable Execution

The comparative analysis reveals a profound gap between the articulation of global ethical principles and the actual enforcement of clinical regulations [13]. At international levels, there is broad agreement on the ethical requirements for AI in health, focusing on values such as transparency, explainability, justice, and human oversight. However, when these principles are translated into national policy, a significant division emerges. HICs have successfully moved from abstract ethics to enforceable laws by integrating these values directly into their medical device and pharmaceutical licensing regulations. In these jurisdictions, "transparency" is operationalized as a mandatory technical file containing validation data, and "explainability" is enforced as a statutory requirement for algorithmic logs and user-interface disclosures.

In contrast, the policy environment in many LMICs is characterized by symbolic compliance [11]. National strategies in these countries frequently adopt the language of international frameworks, yet they lack the accompanying regulatory mechanisms to enforce these principles on the ground. Ethical concepts remain aspirational declarations because the statutory agencies responsible for licensing medical products lack the legal authority, technical mandates, and specialized standards required to evaluate software.

Consequently, without enforceable regulations, developers of commercial clinical AI tools can deploy unvalidated products under general information technology licenses, bypassing the rigorous clinical trials and safety reviews required for traditional pharmaceuticals.

5.2. LMIC Enforcement Deficit

To move beyond a descriptive policy analysis, it is necessary to identify the exact institutional and systemic factors that drive the weak enforcement of AI regulations in LMICs. This regulatory deficit is not merely a result of political inaction; rather, it is a structural pathology shaped by several key factors:

5.2.1. Absence of Dedicated Pharmaceutical Regulatory Sub-Units for Digital Health

National medicine boards in LMICs, including NAFDAC (Nigeria), CDSCO (India), SAHPRA (South Africa), and PPB (Kenya), were historically designed to evaluate small-molecule chemistry, pharmacokinetics, and biological assays [36]. Their organizational hierarchies are structured around laboratories, physical manufacturing plant inspections, and toxicology evaluations. These agencies lack dedicated, internal sub-units specifically mandated to regulate software, digital therapeutics, or computational chemistry. As a result, when a software application or a predictive AI model is submitted for regulatory approval, it is often assigned to general medical device units or IT departments that lack the clinical and technical expertise to conduct a rigorous safety review.

5.2.2. Human Capital Flight and Technical Asymmetry

There is a severe global imbalance in technical expertise. Evaluating an AI algorithm particularly an adaptive deep learning model requires specialized knowledge in data science, software engineering, bio-informatics, and clinical epidemiology [10]. Regulatory agencies in LMICs are rarely able to compete with the salary structures and career opportunities offered by the private technology sector or research institutions in HICs. This brain drain leaves national regulatory bodies in developing countries with a critical shortage of technical personnel capable of performing code audits, assessing training datasets for bias, or verifying model generalizability.

Table 4. Deconstructed Drivers of the LMIC Regulatory Enforcement Deficit

Institutional Pathology Pillar	Underlying Systemic Root Cause	Operational Impact on Pharmaceutical Safety	Proposed Strategic Solution
Structural Omission of Digital Sub-Units	National medicines boards are historically structured around biochemistry, traditional toxicology, and physical facility inspections.	AI applications and SaMD are routed to general medical device or IT units lacking clinical software expertise.	Establish specialized, internal Digital Health and Software Safety Units built via academic networks.
Asymmetric Human Capital Flight	Chronic public-sector underfunding prevents regulatory bodies from matching private technology sector compensation.	Severe shortage of personnel capable of performing code audits, testing neural networks, or assessing training sets for bias.	Create multi-disciplinary technical review boards leveraging university partnerships and shared regional experts.
Computational Sandbox Infrastructure Deficits	Regulatory authorities lack the secure digital environments needed to run testing datasets independently.	Evaluation of complex algorithms is reduced to a paper-based check of developer-submitted reports.	Develop shared regional digital sandboxes (e.g., via the African Medicines Agency) to pool infrastructure.
Statutory and Legislative Lag	Existing data protection laws are designed for broad commerce and lack healthcare-specific clauses.	Regulators lack a clear statutory basis to demand algorithmic logs, training-set data, or patient consent audits.	Enact targeted amendments to national drug laws defining SaMD risk tiers and developer transparency mandates.

5.2.3. Severe Computational and Financial Infrastructure Deficits

The technical audit of a machine learning model cannot be performed purely on paper. It requires computational infrastructure, including secure sandbox environments where regulators can run testing datasets against the developer's model to evaluate performance, accuracy, and bias [37]. Regulatory agencies in LMICs face chronic underfunding and are rarely equipped with these digital resources. Consequently, their evaluation of software is reduced to a passive paper-check of developer-submitted reports, with no independent empirical verification of the algorithm's actual performance or clinical safety.

5.2.4. Statutory and Legislative Lag

While several LMICs have recently enacted generalized data protection laws, such as India's Digital Personal Data Protection (DPDP) Act or Nigeria's NDPA, these statutes are designed for broad commercial applications. They lack the specialized, healthcare-specific provisions required to govern clinical trial simulation, electronic patient consent for automated data mining, or real-time algorithmic adjustments in pharmaceutical distribution [39]. This legislative lag leaves regulatory agencies without a clear statutory basis to demand algorithmic transparency or enforce data-sharing compliance on private developers.

5.3. Digital Pharmacovigilance and Drug Discovery

5.3.1. Digital Pharmacovigilance Challenges in Low-Resource Settings

Digital pharmacovigilance uses machine learning, particularly NLP, to scan electronic health records, insurance claims, and social media platforms to detect real-time signals of adverse drug reactions [31].

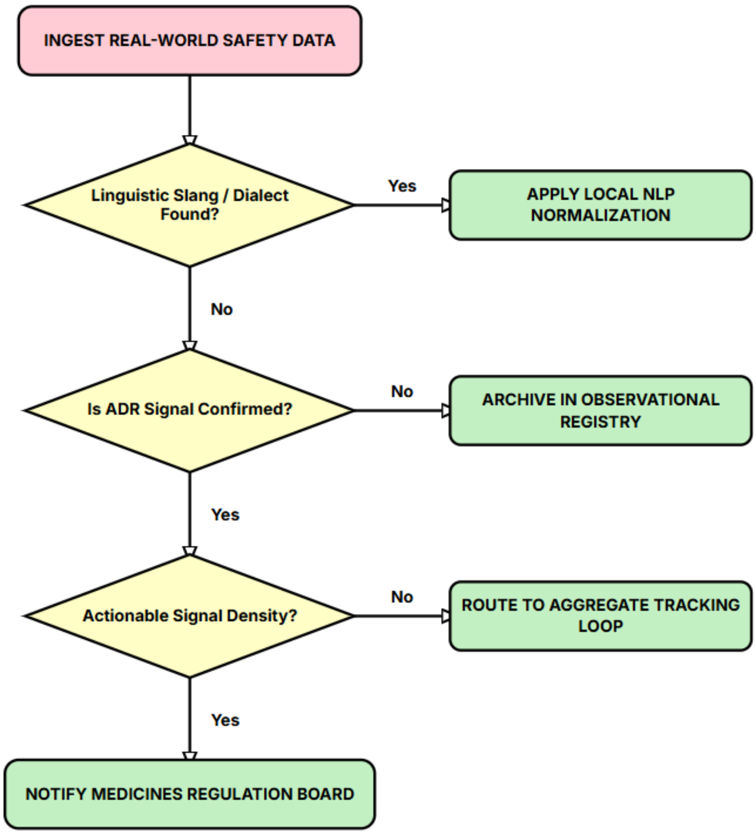

Figure 4. Automated Post-Market Digital Pharmacovigilance and Adverse Drug Reaction (ADR)

This approach offers a powerful alternative to passive reporting systems, which suffer from severe underreporting in LMICs. However, deploying these digital tools in low-resource environments introduces major technical challenges:

- Linguistic and Dialectal Diversity: Social media data in LMICs is often written in localized dialects, mixed-language formats (e.g., Hinglish in India or Pidgin in Nigeria), and informal slang. Standard medical NLP models, trained on formal English clinical corpora from HICs, exhibit poor accuracy and high error rates when attempting to identify adverse event signals in these localized informal texts [40].

- Fragmented and Non-Interoperable EHR Systems: In many LMICs, electronic medical records are highly fragmented, using proprietary, non-interoperable software systems across different hospitals, or relying on hand-written physical charts. The absence of unified health data exchanges prevents the automated, system-wide extraction of patient safety data, rendering digital pharmacovigilance tools ineffective at a population scale.
- Inconsistent Medical Coding: The lack of standardized medical terminologies (such as MedDRA or ICD-11) in primary care clinics in LMICs means that diagnoses and symptoms are often entered as unstructured free text, making computational signal extraction highly unreliable.

5.3.2. Algorithmic Bias in Drug Discovery and Genomics

The use of AI in preclinical drug discovery relies heavily on massive genomic, proteomic, and clinical trial datasets to train predictive models of disease pathology and drug efficacy [23]. A critical, unresolved ethical risk is the geographic and demographic homogeneity of these training datasets. The vast majority of genomic and clinical registries used to train global drug-discovery algorithms are derived from populations of European ancestry in HICs [24].

This demographic imbalance has severe clinical consequences for LMICs. Pharmacogenomic profiles which dictate how different populations metabolize drugs vary significantly across ethnic groups. An AI-driven drug discovery model trained on Caucasian cohorts may design molecular structures or predict therapeutic dosages that are less effective or highly toxic when administered to patients in sub-Saharan Africa or South Asia [41].

Table 5. Technical Challenges in Digital Pharmacovigilance and Drug Discovery

Domain	**Core Technological Application**	**Primary Technical/Ethical Vulnerability**	**Consequence for Public Health**
Digital Pharmacovigilance	Natural Language Processing (NLP) mining of EMRs, clinical notes, and social media for real-time ADR signals.	Linguistic and Dialectal Diversity: Standard NLP models fail on mixed-language formats, local dialects, and informal slang.	Missing critical, localized adverse event signals; high rates of false negatives in post-market monitoring.
Digital Pharmacovigilance	Federated health data mining across clinical networks.	Fragmented EHR Architecture: Incompatible, proprietary electronic databases and paper-based clinical records in LMICs.	Total prevention of system-wide data collection; keeps safety tracking confined to isolated, passive reporting.
AI-Driven Drug Discovery	Deep learning architectures predicting molecular toxicity, binding affinity, and metabolic behavior (ADMET).	Demographic Homogeneity: Training datasets are almost exclusively derived from European-ancestry populations in HICs.	Discovery of molecular structures or therapeutic dosages that cause toxicity or exhibit reduced efficacy in non-European populations.
Clinical Trial Optimization	Machine learning models selecting patient cohorts and constructing synthetic control arms from historical EMRs.	Algorithmic Selection Bias: Predictive algorithms replicate systemic biases present in historical clinical data.	Systemic exclusion of marginalized demographics from clinical trials, undermining the external validity of drug evaluations.

Without local regulations mandating that drug-discovery algorithms prove safety on diverse, representative genetic datasets, LMICs risk importing therapeutic innovations that are biologically unsuitable for their populations, thereby entrenching global health inequities.

5.4. Strategic Policy Recommendations for Equitable Global Governance

To bridge these global divides and establish safe, accountable, and equitable pharmaceutical AI systems, the following five actionable policy interventions are proposed for implementation by 2030:

5.4.1. Establish Specialized Digital Health and Software Safety Units

National drug regulatory authorities in LMICs must undergo structural reorganization to create dedicated, internal sub-units specifically tasked with the oversight of Software as a Medical Device and algorithmic safety. Rather than attempting to train existing chemical-safety staff in advanced computer science, these agencies must establish collaborative networks with local academic institutions, computer science departments, and bio-informatics groups to bring in specialized technical experts. These specialized units should have the statutory authority to audit clinical code, evaluate model validation metrics, and approve clinical software before market entry.

5.4.2. Implement Graduated, Risk-Based Regulatory Pathways for SaMD

LMIC regulators should adopt a simplified, risk-stratified regulatory model based on the IMDRF framework, rather than attempting to enforce complex, resource-intensive legislative models like the EU AI Act. Software should be classified into clear, risk-based categories. Low-risk applications (e.g., basic medication adherence apps) should be fast-tracked through simple registration processes. Conversely, high-risk clinical software (e.g., algorithms driving diagnostic decisions or automated ADR detection) must be subject to rigorous validation, requiring developers to submit detailed technical logs, proof of model generalizability on local patient populations, and clear human-in-the-loop oversight plans.

5.4.3. Mandate Localized Validation and Representative Training Datasets

To eliminate algorithmic bias in both clinical diagnostic software and preclinical drug discovery, national regulatory bodies must establish legal mandates requiring developers to display their models' safety and efficacy on local, representative populations. If an AI tool is imported from an HIC, the developer must conduct localized validation trials on representative demographic cohorts within the importing country before securing clinical registration. This requirement must be paired with public-sector investments to build open-source, de-identified national genomic and clinical registries, providing high-quality, local training datasets for public-health research.

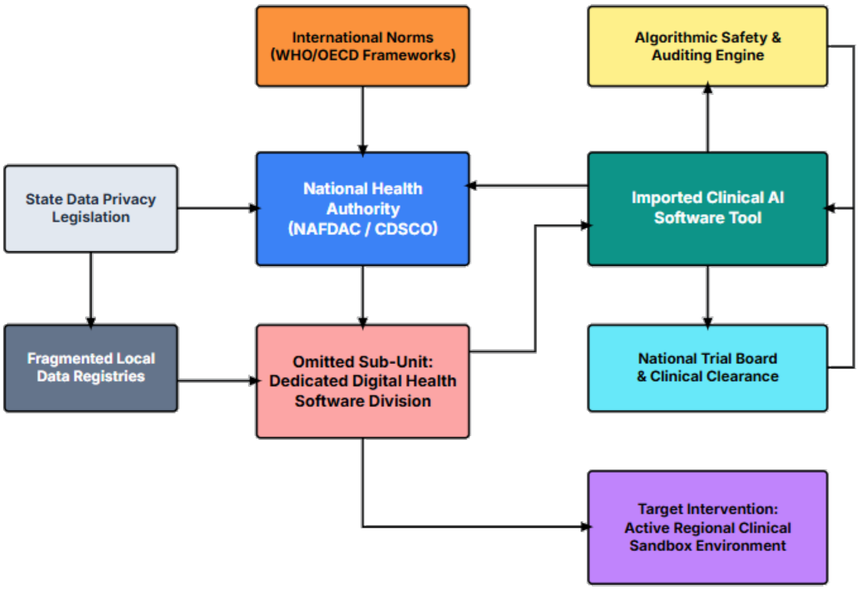

Figure 5. Systematic Diagnostic of the LMIC Regulatory Deficit and Institutional Process Flow

5.4.4. Regional Regulatory Alliances and Joint Sandboxes

Given the individual financial and computational constraints faced by many LMICs, countries should pool resources through regional regulatory coalitions. In Africa, the African Medicines Agency (AMA) can serve as a central platform to establish unified guidelines for SaMD and computational health technologies. Reducing the administrative and financial burden on individual national regulators by creating shared regional digital sandboxes, member states can collaboratively execute technical reviews and audit algorithms. This regional approach would also harmonize regulatory requirements, making it easier for local developers to scale safe innovations across borders.

5.4.5. Active, Algorithmic Post-Market Safety Surveillance

Regulators must transition from a static, pre-market clearance model to an active, life-cycle-based safety surveillance paradigm. Because machine learning models are dynamic and can degrade in performance over time (a phenomenon known as "algorithmic drift"), developers must be legally mandated to implement continuous, post-market monitoring systems. National drug registries should establish secure, automated data-sharing channels that allow approved digital pharmacovigilance tools to scan electronic health records and flag real-time safety signals, ensuring that any unforeseen adverse event is captured and evaluated rapidly.

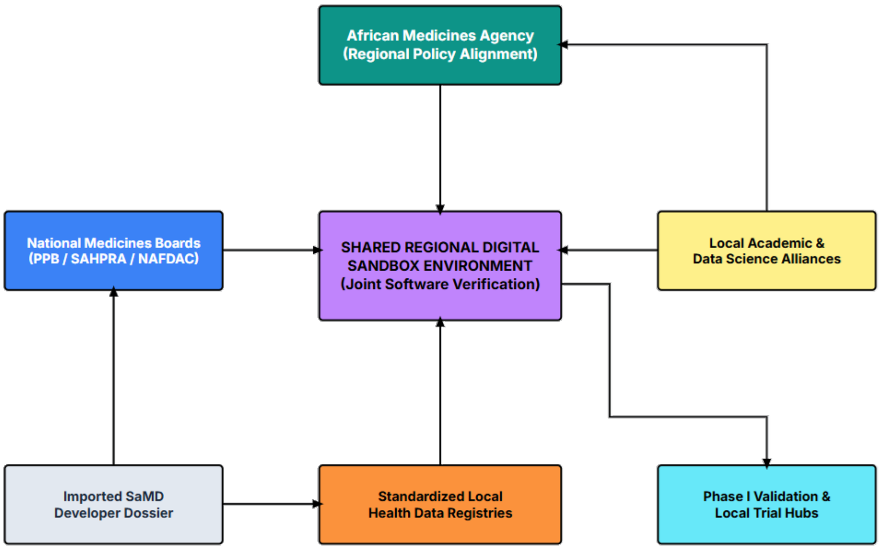

Figure 6. Collaborative Regional Governance and Technical Capacity Exchange Pipeline

5.5. Future Scope

The future of AI governance in pharmaceutical public health will depend on developing technical solutions that balance patient privacy with the need for robust, multi-center model validation [40]. A highly promising technical pathway is the integration of federated learning. This approach allows machine learning models to be trained across decentralized databases located in different hospitals or countries without physically transferring sensitive patient data. This decentralized design protects patient privacy, complies with national data sovereignty laws, and enables the validation of clinical algorithms on highly diverse population demographics. Additionally, future initiatives should prioritize the development of localized, open-source large language models optimized for regional dialects and medical terminology in LMICs. Researchers can construct highly accurate digital pharmacovigilance systems capable of detecting drug safety signals from informal patient communications by training models on diverse linguistic datasets.

International research collaborations must establish equitable data-sharing agreements that prevent the unilateral extraction of clinical and genetic data from developing nations, ensuring that LMICs remain active contributors to and beneficiaries of the global digital health revolution.

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6. Conclusion

This comparison study shows that the rapid integration of artificial intelligence within pharmaceutical public health has outpaced the development of global regulatory frameworks, resulting in a pronounced governance divide between high-income and low-to-middle-income countries. High-income countries have established sophisticated, legally enforceable regulatory structures utilizing Software as a Medical Device classifications to ensure clinical safety, algorithmic transparency, and post-market safety. On the other hand, low- and middle-income nations encounter a critical enforcement deficit, primarily driven by the absence of specialized digital health units within national medicine boards, a severe shortage of technical personnel, and fragmented digital health registries. This regulatory gap poses a substantial risk of exacerbating global health inequalities, exposing resource-constrained healthcare systems to unvalidated algorithms and biased diagnostic software that fails to account for local demographic and pharmacogenomic diversity. To secure an equitable and safe digital health transition, global health policies must move beyond non-binding ethical declarations toward actionable, risk-stratified legislative frameworks. Addressing these challenges requires strategic investments to build specialized regulatory capacity within national drug regulatory authorities, implement pragmatic SaMD classification pathways, and establish secure, standardized local health registries. Low- and middle-income countries can protect their populations from algorithmic harm while actively shaping digital health innovations to serve their unique healthcare needs by encouraging regional regulatory coalitions and mandating localized validation trials.

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