RESEARCH PAPER

AI in Pharmacovigilance: Addressing Regulatory Challenges and Global Harmonization

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Received: 6th May, 2026; Revised: 23th May 2026; Accepted: 27th Jun, 2026; Available Online: 09th July, 2026

ABSTRACT

Artificial intelligence (AI) and machine learning have shown great promise in the field of pharmacovigilance and have the potential to completely change the way adverse drug reactions (ADRs) are identified and reported. However, the use of AI in the regulation of drugs is still in its infancy, with varying degrees of adoption and implementation by different drug regulatory authorities around the world. Pharmacovigilance plays a critical role in the monitoring of ADRs and ensuring drug safety. The current methods used are slow and irregular, while AI, with its ability to automate and analyze, improves the efficiency and accuracy of managing increasing data complexity. This paper discusses the use of AI in pharmacovigilance, with emphasis on the latest technological advancements and the challenges of implementing AI in real-world applications. It also discusses the use of realworld data sources, such as electronic health records (EHRs), voluntary and passive surveillance systems, and data from social media sites. By combining multiple data sources with advanced analytics, the ability to identify safety signals can be improved, making it possible to move from a reactive to a proactive approach to monitoring. The paper discusses how the lack of consistent regulatory policies by drug regulatory authorities such as the FDA, EMA, and PMDA makes it difficult to implement AI in drug safety surveillance around the world. It also discusses the critical ethical issues of algorithmic bias and the need for standardized model validation. The current state of evidence suggests that a global strategy is required for the optimal use of AI in monitoring drug safety. Review of regional strategies and new technologies indicates that the governance framework needs to be strengthened, capacity developed in less developed regions, and collaboration between regulators and industry increased. This would ensure that systems are standardized globally and that AI is used to improve medicine safety.

KEYWORD: Artificial Intelligence, Pharmacovigilance, Adverse Drug Reactions, Regulatory Harmonization, Electronic Health Records

How to cite this article: Karade RJ, Balakshe PV, Velhal AB, Jadhav PD, Botare AB. AI in Pharmacovigilance: Addressing Regulatory Challenges and Global Harmonization. Int J Drug Deliv Technol. 2026;16(66s):1410-1425. DOI: 10.25258/ijddt.16.66s.151

1. INTRODUCTION

1.1 Historical Evolution of Pharmacovigilance

For the past thirty years or so, The WHO defines an ADRs as "a noxious and unintended response to a drug that occurs at normal doses. "One However, this definition is ambiguous because it uses the word "noxious," which the Oxford English Dictionary defines ADRs as "injurious, hurtful, harmful." Does it, for instance, encompass all negative reactions, regardless of how slight? The existing state of monitoring technology would be defeated by such inclusivity[1] . With the aim of monitoring r the safety of pharmaceutical products, passive surveillance and self-reporting of spontaneous adverse events by consumers and healthcare providers (HCPs) after a medication is administered are typically used. ADRs are reported to the National PV Centre via a variety of reporting techniques, including the cohort event monitoring system and the spontaneous report monitoring system (also called stimulated, enhanced, and targeted). These techniques are important for determining the quantitative features of drug safety, identifying high-exposure groups and

special risk factors, and differentiating ADRs associated with specific medications and in a patient cohort. One of the earliest techniques for reporting ADRs is the cohort event monitoring (CME) system. Targeted spontaneous reporting (TSR) is a novel PV system technique that unifies results from traditional safety monitoring systems[2].

The commonly used PV system known as the "voluntary" reporting system is called the spontaneous reporting system (SR). Reporters must be informed and inspired to document and submit their observations in order for spontaneous reporting to occur. All community members and practicing healthcare professionals should get training to raise awareness of the reporting culture on what, where, when, how, and to whom ADRs should be reported. In order to address the limits of spontaneous reporting, particularly underreporting, further training will be provided[3]. Because they record suspected AEs and (ADRs) from actual clinical use, frequently before concerns are fully apparent in clinical trials, SRS continue to be the foundation of post-marketing pharmacovigilance globally. Nevertheless, SRS data are infamously challenging to employ for quick and precise signal recognition, despite their importance for public health. In addition to significant underreporting and reporting biases influenced by media attention, regulatory warnings, and disparities in healthcare access, reports sometimes contain missing fields, duplication, inconsistent language, and varied clinical description[4].

PV has undergone a radical change in the last few years due to the use of automated databases and electronic health records (EHRs). Electronic platforms allow for the collection of data in real time, quicker investigation, and the consolidation of data from multiple sources, as opposed to paperbased systems. By combining vast amounts of patient data from various healthcare settings, this change has made it possible to detect signals more robustly, improving the overall sensitivity and specificity of pharmacovigilance efforts. Proactive risk management has become increasingly important in tandem with these technological advancements. Instead of concentrating only on post-marketing surveillance, regulatory agencies and healthcare groups increasingly promote ongoing drug monitoring throughout their life cycle [5].

1.2 The AI Revolution in Drug Safety

The use of artificial intelligence (AI) in pharmacovigilance (PV) has grown dramatically, with the potential to increase the speed and precision of adverse event identification[58]. The shift has been fuelled by the growing complexity of post-market surveillance and drug development, particularly the enormous amount of data, the intricacy of drug-drug interactions, and patient variability.[7]

The inception of data mining techniques for signal detection in SRS during the early 2000s signified the commencement of AI use in pharmacovigilance (PV). More complex AI applications in PV were made possible by groundbreaking techniques such as the MGPS and the BCPNN methodology. Since then, AI has been used in a number of PV applications, such as signal detection, automated case processing, and real-world evidence analysis[8,10]. Pharmacy has a fore most promising applications of artificial intelligence, which is becoming more widely acknowledged as a revolutionary force in healthcare. Drug development, formulation, clinical practice, pharmacovigilance, and regulatory affairs are just a few of the many activities that fall within the broad category of pharmacy. These disciplines are all dataintensive and require sophisticated computational support for their intricate decision-making processes. AI, which includes machine learning (ML), natural language processing (NLP), and deep learning, provides innovative ways to maximize productivity, enhance patient outcomes, and quicken the pace of pharmaceutical innovation[11].

For medicine and biologics development companies, navigating the complicated ethical and regulatory landscape of AI and ML technologies in GMP and GCP is essential. It is crucial to keep up with changing legislation, such as the US's sectorbased approach and the EU's AI Act. Equally crucial is educating and teaching the public and healthcare professionals on the advantages and dangers of artificial intelligence. For responsible AI development, ethical concepts like accountability, transparency, and fairness are crucial. The FDA and CTTI collaborated to convene a workshop on AI in medication and living product development in August 2024. To highlight AI's revolutionary potential in expediting clinical trials, optimizing drug discovery, and enhancing patient outcomes, a panel of regulatory and industry professionals came together[13].

AI-based predictive models can foresee negative medication reactions and drug-drug interactions, allowing for better drug safety assessment and proactive risk management[14]. Real-time and predictive pharmacovigilance systems are supported by AI technologies like natural language processing and deep learning, which enable automatic ADR identification from sizable heterogeneous datasets[15].

1.3 Clinical and Public Health Significance

The process of monitoring marketed pharmaceuticals for ADRs following clinical trials is known as post-marketing surveillance (PMS). PMS studies are regarded as phase IV studies because most medications may not be able to enter the market without clearing phase III clinical trials[16]. The most frequent ADRs in vemurafenib's clinical phase I-III trials were arthralgia, rashes,

fatigue, hair loss, squamous-cell carcinoma, light sensitivity, nausea, and diarrhoea, all of which were controllable in a clinical trial. Toxic reactions necessitated dose change for 38% of individuals[17]. ADRs were projected to be the fifth most common cause of hospital fatalities in the EU, accounting for nearly 5% of hospital admissions. The annual number of deaths was estimated to reach 1,97,000, and the public cost of ADRs was 79 billion euros. following an evaluation of the EU. Schemes for reporting spontaneous adverse reactions have been created to alert people about unanticipated adverse effects. Early detection and assessment of possible safety signals are made possible by Eudra-Vigilance[18].

1.4 Scope and Objectives

Pharmacovigilance (PV) is one of the numerous sad occurrences that have shaped modern drug development structures and procedures over the course of a century. The essential pharmacovigilance functions include benefit-risk management, signal management, and case management are discussed in this overview. It also covers the wide range of safety-related tasks that a modern pharmaceutical business needs to be ready to handle, the majority of which are probably located in a department tasked with PV duties. Medical device safety concerns, the complexities of combination products, and companion diagnostics are not included in this evaluation. [19] AI and big data integration into pharmacovigilance has the potential to revolutionize the field by resolving numerous issues brought on by the demand for realtime drug safety monitoring and the growing complexity of data. To effectively utilize these technologies to enhance data quality, increase model openness, and guarantee that regulatory frameworks are established, however, continued efforts are needed. The future of pharmacovigilance can be more effective, precise, and thorough with ongoing developments in AI and machine learning, which will ultimately improve rational drug use throughout healthcare systems[20].

2. CURRENT AI TECHNOLOGIES IN PHARMACOVIGILANCE

2.1 AI/ML Methodologies in Signal Detection

The ability of ML and AI to anticipate and prevent ADRs has been demonstrated numerous drug development and discovery domains. These techniques have been used in pharmacovigilance to identify ADR signals linked to particular drugs[9,10]. For instance, ML approaches have been included into pharmacovigilance databases such as the FDA Adverse Event Reporting System (FAERS) to eliminate human data processing and more effectively discover drug-event connections[21]. A comparison of several ML techniques showed how successful ML is in drug discovery. In a different study, a model that analysed trends in discharge summaries using real-world clinical ADR data was used to predict 311 ADRs, 231 of which were verified. Most ADRs were unnoticed at the time because the main way to find them was through spontaneous reporting. Notwithstanding this drawback, the model was able to identify ADRs and differentiate them from other ADEs [22].

The rapid creation of new predictive models has been fuelled by advancements in NLP models, the availability of more thorough and standardized training data, the possibility of cost savings, and the pressing need for increased pharmacovigilance efficiency[23].Adverse medication reactions can be extracted from social media data and unstructured clinical narratives using Natural Language Processing algorithms. In order to create and test novel machine-learning natural language processing (NLP) approaches that can interpret unstructured data (such as clinical notes, social media comments, and scientific literature) and find pertinent facts for further analysis, annotated corpora are required[24] .

Table 1. AI/ML Technologies Used in Signal Detection

Technology	Data Source	Applica tion	Key Advant a ge
Machine Learning (RF, SVM)	FAERS, VigiBase	ADR detectio n and signal predictio n	High accuracy
Natural Language Processing	Clinical notes, social media	Mining adverse event informat ion	Handles unstruct ured data
Deep Learning	EHR, large datasets	Pattern recogniti on	Detects complex relations hips
Disproporti o nality + AI	Spontan eous reports	Signal detectio n	Establis h ed PV method
Federated Learning	Multiinstituti o n datasets	Privacypreserv i ng analysis	Data security

Figure 1. AI Technologies in Pharmacovigilance Workflow

2.2 Applications Across the Drug Lifecycle

To maintain the safety of already available medications, pharmacovigilance is a crucial continuous duty of all drug manufacturers, healthcare professionals, and drug therapy consumers. Throughout a drug's lifecycle, from clinical development to usage in clinical practice, pertinent safety signals are recorded using the methods outlined in this study[25]. Artificial intelligence integration and the efficient use of automated tools have recently begun to aid in the global integration of data. Additionally, it is anticipated to lower overall costs and significantly streamline the pharmacovigilance process. The pharmacovigilance procedure during phased clinical trials and post-marketing surveillance are covered in detail in this review[26].To make information readily available and clinically applicable, preclinical and premarketing study designs must be enhanced. Suitable sample size, duration, co-morbid conditions, quantity of concomitant drugs, intra- and inter-subject variability, and pharmaceuticals with a comparatively limited therapeutic index, certain atrisk populations, and clinical outcomes should all be considered in studies. Certain phase IV studies (and/or active pharmacovigilance studies) should be mandated to track and quantitatively evaluate their clinical impact following premarketing development in circumstances when there may be a high risk of significant adverse events[27].The sponsor is required to keep the IND up to date during clinical development by submitting yearly reports that summarize the program's progress, safety reports that detail serious adverse events and other important safety information, and amendments that describe new protocols, protocol changes, or updates to previously submitted data[26].

Researching rare ADRs, ADRs with a long latency, and ADRs in specific populations requires careful medication monitoring during the post-marketing era. There are two types of descriptive studies: intense monitoring and spontaneous reporting [29]. Due to the scarcity of newly discovered drugs in India and the minimal introduction of novel medications in the past, there was no impetus to establish a robust pharmacovigilance system for detecting adverse drug reactions of marketed goods. Companies and regulatory bodies used the experience from the markets where the drug was used for a number of years prior to its release in India to evaluate the safety parameters and implement remedial measures, like the drug's withdrawal or prohibition[30].

Nearly 20-30% of ADR have been reported as associated with DDIs, of which 1-2% are lifethreatening while a considerable percentage (nearly 70%) are clinically relevant ADR, needing intervention. DDIs can result in toxicity or treatment failure through both pharmacological and pharmacokinetic mechanisms [31]. Drug metabolism causes a number of DDIs, most of which involve CYP450 isoenzyme inhibition or induction [32].

2.3 Data Sources and Integration

Artificial Intelligence (AI) applied to real-world data (RWD), such as Electronic Healthcare Records (EHR), has been recognized as a potentially advantageous technology framework for the pharmacovigilance (PV) domain. Numerous applications of AI methodologies on Real-World Data (RWD) exist; nevertheless, the majority of studies concentrate on unstructured RWD, specifically employing Natural Language

Processing (NLP) across diverse data sources such as clinical notes, social media, and blogs[33]. The phrase "Real-world data" (RWD) denotes data gathered beyond the regulated context of clinical studies, including (EHRs), patient registries, insurance claim databases, and e-Prescription systems[34]. There is an increasing interest in utilizing real-world data for pharmacovigilance signal management to enhance the speed and efficiency of post-marketing surveillance. AI is recognized as a potentially significant technological advancement that can aid decision-making in healthcare owing to its capacity to efficiently analyse large datasets to extract valuable information. Artificial Intelligence can be used to identify patterns and correlations in large datasets (real-world data) that may be difficult to analyze using traditional statistical analysis methods due to the complexity and volume of the data[35,36]. Artificial Intelligence has been widely researched as it can be applied in the healthcare industry, including personalized medicine, and has produced encouraging results; however, it is still not fully utilized in the healthcare industry. In the pharmacovigilance field, AI can improve different aspects, such as the identification of patient subgroups that could be more vulnerable to certain adverse drug reactions, thus improving the goal of personalized drug safety management[37].

The foundation of conventional pharmacovigilance is voluntary reporting. National agencies and healthcare providers put forward reports of suspected ADRs to centralized databases. Prominent instances encompass the U.S. FDA (FAERS) and the

WHO Programme for International Drug Monitoring's VigiBase. These systems record suspected ADRs for a diverse array of pharmaceuticals, biologics, and vaccines. For example, FAERS encompasses both ADRs and medication errors reported in the United States. The WHO VigiBase compiles reports from more than 160 nations, representing almost 99% of the global population. By mid-2023, VigiBase housed more than 35 million reports (World Health Organization, 2023)[38]. The quantity of Individual Case Safety Reports documented by the US Food and Drug Administration. The Adverse Event Reporting System (FAERS) has had a threefold increase over the past decade (2011–2021), with a comparable trend observed in Europe (i.e., EudraVigilance)[39]. Real-world evidence is currently impacting the conduct of clinical studies and the interpretation of their results by providing insights into medication usage outcomes across diverse populations. This pharmacovigilance approach provides a holistic perspective of drug performance in conditions that may not be easily replicated in research settings. Real-world evidence (RWE) has demonstrated significant utility in pharmacovigilance reporting, surpassing the limitations of conventional randomized controlled trials (RCTs)[40].

Pharmacovigilance investigates the revolutionary capacity of social networks in improving medication safety surveillance. These sophisticated methodologies offer instruments to address issues like data variability and bias, rendering social media a feasible adjunct to traditional PV approaches. General platforms such as Instagram, X, YouTube, Reddit, and Facebook facilitate extensive audience interaction, whereas health-oriented forums like WebMD and Q&A sites such as Quora (knowledge flat form) and Ask a Patient concentrate on medical discourse. Moreover, alternative platforms like the e-commerce site Amazon and several blogs provide user evaluations and conversations on pharmaceutical products, so augmenting the data reservoir for drug safety studies. These social media platforms collectively provide data that can enhance the understanding of patient experiences, drug effects, and healthcare trends[41].

2.4 Technological Advantages

Contemporary photovoltaic systems utilize binarylogic algorithms to facilitate safety data handling. Numerous and intricate emerging technologies are driving innovation in photovoltaic systems. Although the IT specialists who develop these technologies comprehend their mechanics, it is not always evident to the professionals endeavouring to apply them to the science and method of photovoltaic systems. Artificial intelligence has transformed signal detection[42,44]. Artificial intelligence has significantly enhanced our ability to detect signals. It employs machine learning algorithms to detect hidden patterns within large data sets. This means that tasks related to signal detection are now more efficient and accurate because computers can process data much faster than humans and detect patterns that human eyes may not be able to see. The BCPNN employed in the WHO VigiBase database has shown a 60% reduction in the time it takes to process cases by automatically detecting safety signals from AE reports. Similarly, deep learning algorithms can process millions of electronic health records to detect novel adverse drug reactions with high accuracy[43].

In the literature on signal identification, AI enhances and broadens conventional disproportionality analysis (e.g., PRR, ROR, and Bayesian approaches) by identifying nonlinear patterns and intricate connections. Pharmacovigilance (PV) is essential in recognizing and mitigating possible risks as pharmaceutical products evolve and patient safety remains a priority. As the complexity of drug safety data and the volume of ADRs reports escalate, conventional pharmacovigilance methods, which depend on clinical trials and manual processes, are proving insufficient. Recently, artificial intelligence and machine learning have emerged as transformative technologies across various industries, including pharmacovigilance[45].

3. REGULATORY LANDSCAPE AND GAPS

3.1 Current Regulatory Framework

The FDA advocates for innovative clinical trial designs utilizing real-world data analytics and digital health technologies. The FDA has observed a significant rise in regulatory submissions referencing the. Application of artificial intelligence and machine learning in recent years. In 2021, there will be over hundred submissions across all categories of pharmaceutical and biological products, including those related to AI/ML. These submissions encompass multiple phases of the drug development process and incorporate the applications of AI/ML across diverse therapeutic domains, including the formulation of novel pharmaceuticals and the optimization of clinical trials via endpoint evaluation and post-market safety surveillance[46].

In the pharmaceutical industry, AI models hasten the identification of drug candidates, optimize clinical trials, and enhance safety surveillance. The FDA and EMA are developing risk-based frameworks to ensure that AI systems adhere to principles of transparency, safety, and efficacy[47]. Unlike conventional analytical techniques, which follow well-defined ICH Q2(R1) validation guidelines, AI technologies do not have universally accepted standards for verification, validation, and management. While some regions, including the United States, Europe, and Japan, are exploring

AIenabled regulatory affairs practices, other regions are impeded by infrastructural, economic, or policyrelated limitations. This diversity engenders inconsistencies in worldwide advanced pharmaceutical analytics techniques, especially in domains such as stability-indicating UHPLC/UPLC procedures or AI-driven impurity prediction. This variance hinders the harmonization efforts in accordance with ICH principles[48].

ICH Guidelines (E2E, E2B, etc.) – Although not exclusive to AI, these establish fundamental principles for the management of safety data that AI systems must adhere to.

The World Health Organization's Good Pharmacovigilance Practices underscore the need of quality, reliability, and transparency in worldwide safety monitoring systems[49].

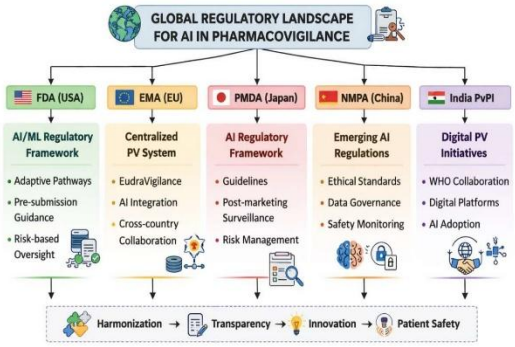

Figure 2: Global regulatory landscape for AIdriven pharmacovigilance.

3.2 Identified Regulatory Gaps

The present condition of pharmacovigilance is consistently shaped by regulatory modifications, necessitating that future research monitor new proclamations and directives from FDA, MHRA, EMEA, HC international regulatory bodies. The problems and constraints associated with AI applications in photovoltaic systems will progress in tandem with improvements in AI technology[50]. AI tools are currently accessible to facilitate all essential tasks in signal control. Differences and inconsistencies in regulations and guidelines still exist in many areas. The results highlight the pressing need for continued international cooperation to standardize regulatory environments and facilitate the safe and ethical use of AI in pharmacovigilance. The regulatory and policy environment must change to facilitate the widespread use of AI in PV, including the creation of large public training data sets[51]. AI-driven healthcare technology frequently experiences a deficiency in standardized vocabulary and comprehension, resulting in ambiguity and regulatory postponements[52]. AI-driven pharmacovigilance instruments necessitate validation, transparency, and ongoing oversight to guarantee safety and regulatory compliance. Regulatory inconsistencies and variances endure throughout many locations[53,54].

Table 2. Regulatory Gaps and Proposed Solutions in AI-Driven Pharmacovigilance

Regulatory Gap	Description	Impact on Pharmacovigilance	Proposed Solution
Lack of standardized definitions for AI systems	Absence of clear classification of AI/ML tools used in pharmacovigilance	Difficulty in regulatory evaluation and approval of AI systems	Development of standardized terminology and classification frameworks through international regulatory bodies
Framework lag behind technological development	Regulatory policies evolve slower than rapidly advancing AI technologies	Delayed adoption of innovative pharmacovigilance tools	Implementation of adaptive and dynamic regulatory frameworks
Limited guidance for AI validation	Lack of globally accepted validation standards for AI algorithms	Inconsistent model evaluation and reliability concerns	Establishment of standardized validation protocols and benchmarking datasets
Transparency and explainability issues	Many AI systems function as “black box” models with limited interpretability	Reduced trust among regulators and healthcare professionals	Adoption of Explainable AI (XAI) approaches and mandatory transparency documentation
Data privacy and security regulations	Strict data protection laws (e.g., GDPR) limit access to healthcare datasets	Difficulty integrating large datasets for AI model training	Development of privacy-preserving technologies such as federated learning

Regional regulatory inconsistencies	Differences in requirements among regulatory authorities	Barriers to global implementation of AI pharmacovigilance systems	International harmonization through collaborative initiatives and global guidelines
Unclear accountability and liability frameworks	Ambiguity regarding responsibility for AI-generated safety decisions	Legal and ethical uncertainties	Clear governance structures defining roles of regulators, developers, and healthcare organizations

3.3 Governance and Oversight Challenges

Standardizing and carefully curating data from many sources, like as EHRs and social media, is essential for the effective application of AI/ML in pharmacovigilance. Another challenge is the level of transparency in many AI/ML models, particularly deep learning models. These models are capable of producing highly accurate predictions, but they may not always explain how they reached those predictions. This has contributed to concerns about the trustworthiness and credibility of decisions made by AI, particularly in highly regulated areas such as pharmacovigilance[55]. Another challenge is the need to meet regulatory requirements. Organizations such as the FDA and EMA are developing guidelines for the approval and regulation of AI/ML solutions in the healthcare sector. In order for AI pharmacovigilance to be widely accepted, these solutions must meet the criteria of accuracy, transparency, and patient safety[56]. Human intervention is required to confirm the AIproduced signals before any regulatory or medical choices are made. AI systems can integrate continuous learning that adjusts to new data stream[57].

3.4 Policy and Legal Considerations

The consistent and transparent performance of AI continues to pose a significant obstacle for regulatory acceptability. Artificial intelligence is evolving from experimental applications to standard se in pharmacovigilance systems[58]. Cloud-based data governance frameworks are essential infrastructure for contemporary pharmacovigilance systems. The incorporation of AI-driven analytics facilitates ongoing, real-time surveillance of pharmaceutical safety[59].

3.5 Case Studies: Regional Regulatory Responses

Artificial intelligence has rapidly evolved from experimental applications in pharmacovigilance to being considered for routine use. Ensuring AI's consistent and transparent performance remains a key challenge for regulatory acceptance[58].

- Utilization of AI and ML: Regulatory bodies (FDA, EMA) are endorsing AI for expedited identification of safety signals.
- Real-World Data and Real-World Evidence: are increasingly utilized in regulatory decisions, derived from electronic health records, mobile applications, and wearable devices.
- FDA Sentinel Initiative and EMA EudraVigilance: Actively surveilling millions of patients for adverse occurrences.
- Expansion of WHO VigiBase: Presently the largest global ADR database with enhanced international participation.
- India's PvPI: Enhancing ADR reporting and international cooperation[60].

Figure 3. Validation Framework for AI-Based Pharmacovigilance Systems

Table 3. Validation Requirements for AI in Pharmacovigilance

Use Case	Validation Method	Performance Metrics
ADR detection	Crossvalidation	Sensitivity, specificity
NLP case extraction	Expert annotation	Precision, recall
Signal detection	Benchmark comparison	AUC, signal rate

Causality assessment	Retrospective validation	Accuracy
Real-world evidence analysis	Prospective evaluation	Risk prediction accuracy

4. VALIDATION CHALLENGES AND REQUIREMENTS

4.1 Data Quality and Completeness Issues

The provocation in ADRs reporting, including underreporting, reporting bias, and complexities in causality evaluation, are thoroughly examined. Deficient or erroneous information affects signal detection and risk evaluation[61].Effective data management is crucial for pharmacovigilance to provide precise safety assessment. Quality standards must be enforced during the entry, processing, and storage of pharmacovigilance data[62].

4.2 Algorithmic Bias and Equity Concerns

AI models are often trained on datasets that do not represent the diversity of real-world patient populations. Models may perform well for the majority group but poorly for minority or underrepresented populations. [58] AI systems may perpetuate social inequities or demonstrate biases such as those based on race or gender. Biases can occur before, during, or after the development of AI models[63]. Biased AI algorithms can result in certain patient populations not receiving appropriate care[64].

4.3 Model Validation Frameworks

AUC–ROC evaluates a model's capacity to differentiate between positive and negative instances. The majority of research presented AUC values for the internal validation through crossvalidation or train-test splits[65]. A minimal handful of studies presented external validation outcomes using separate datasets. External validation is essential to confirm model resilience across diverse patient populations. K-fold cross-validation was employed for training and internal validation during the initial prototyping of methodologies[66].

4.4 Explainability and Interpretability

Regulatory acceptance of AI systems depends on explainability, transparency, and auditability.

Methods such as SHAP and LIME are recommended to enhance interpretability of pharmacovigilance algorithms[67]. Many AI models are seen as a 'black box,' limiting their adoption in healthcare. Explainable AI provides confidence in predictions by explaining how the prediction is derived[68].

4.5 Causality Assessment in AI-Driven Systems

Most existing data sources and tasks for pharmacovigilance were not designed for causal inference[69]. Causality assessment scales serve as features in machine learning models that predict causality[70].Conventional instruments such as the Naranjo algorithm and Bayesian inference methodologies offer semi-quantitative or qualitative assistance. These methods are time-consuming, variable between evaluators, and depend on trained professionals' expertise[14].

4.6 Benchmarking and Performance Standards

The review investigates machine learning and deep learning methodologies for extracting adverse drug events from clinical benchmark datasets[71].Deep learning models outperformed machine learning models in several ADE extraction tasks[72]. Adverse drug reaction reports are typically evaluated manually by pharmacovigilance specialists to identify safety signals. Artificial intelligence could help support the work of pharmacovigilance experts by automatically coding reports[66].

5. SPECIFIC VALIDATION CONCERNS

5.1 Incomplete Data and Signal Detection

Insufficient data and biased analyses can profoundly impact the detection of medication safety signals. Pharmacovigilance analyses are vulnerable to bias when datasets lack completeness or representativeness[73].Disproportionality analysis is the predominant statistical method utilized to facilitate the identification of the safety signals. Small databases may raise the risk of failing to detect actual relationships in signal detection. Incomplete or inconsistent data may obscure actual safety trends. Poor-quality data could lead to a misunderstanding of drug safety signals[74].

5.2 Bias Amplification and Propagation

Practical implementation issues include reducing different biases and maintaining the performance of algorithms in a clear and transparent manner. AI has the potential to bring about a paradigm shift in drug safety surveillance, but it requires careful monitoring to avoid biased outcomes. Machine learning is being increasingly applied to pharmacovigilance for the automatic identification of adverse events, and the effectiveness of AI algorithms depends significantly on the quality of the training data[75].

5.3 Integration with Existing Pharmacovigilance Systems

Much of the data within spontaneous reporting systems and EHRs is not organized in a clean fashion or is missing, which hinders analysis and the conclusions we can make from the data. Using global data standards, in addition to AI-assisted data normalization, can improve the quality of data. Artificial intelligence has progressed from its beginnings in pharmacovigilance research to being considered mature and ready for application. However, implementing AI in applications is not without its difficulties, such as maintaining the

consistency of AI performance. AI provides scalable methods for identifying adverse drug reactions and automating the identification of ADRs within various data sets[6].

5.4 Continuous Monitoring and Model Drift

AI has greatly improved the field of pharmacovigilance by making the automation of signal detection, monitoring, and ADR reporting more efficient. The current predictive system is capable of predicting adverse drug reactions and possible interactions between drugs, which enables doctors to act proactively for the benefit of patients. AI has rapidly transitioned from experimental stages in pharmacovigilance to mainstream applications. Nevertheless, there are challenges associated with the implementation of AI, such as ensuring consistency in its performance. AI may degrade with time due to changes in data patterns[76].

6. GLOBAL HARMONIZATION STRATEGIES

6.1 Current State of Global Pharmacovigilance Systems

Pharmacovigilance is the science of drug safety, but it is now recognized as a new domain fuelled by the latest technology: digital health tools and AI. Large data from sources such as WHO VigiBase and the FDA Sentinel System reveal how we can enhance the detection of risk signals[77].The level of maturity and pharmacovigilance capability among African countries is not the same. Some African countries have exemplary pharmacovigilance systems, while others do not have fully functional pharmacovigilance systems[78].The World Health Organization has a pharmacovigilance database called VigiBase. VigiBase is the world pharmacovigilance database and the largest individual case safety report collection. VigiBase facilitates the identification of safety signals worldwide.[79].

6.2 Harmonization Challenges

Although both the U.S. and the E.U. employ robust regulatory frameworks, they differ significantly in their methodology. Addressing regulatory discrepancies is crucial to ensure product safety and global access[80].Initiatives to standardize the technical criteria for the registration of pharmaceuticals and biologics have yielded beneficial guidelines globally. Such efforts have not been extended to the regulatory review process or product labelling[81]. Global pharmacovigilance regulations are predominantly influenced by three principal regulatory entities: the FDA, EMA, and PMDA. Medication safety precautions are directly correlated with a nation's income level[82].

6.3 International Regulatory Frameworks and Initiatives

The guideline provides guidance on definitions and standards for the management and reporting of postapproval drug safety information. The original ICH E2D guideline was published in 2003 to establish an internationally standardized procedure for postapproval drug safety reporting. The revised Guideline ICH E2D(R1) provides updates on the definitions, standards, and regulatory guidance for the management and reporting of postapproval drug safety information with the aim to support appropriate safety surveillance of medicinal products based on the current practices and needs[83].

Regulatory frameworks are crucial to pharmacovigilance, guaranteeing drug safety via standardization, adherence, and monitoring. Global collaboration has increased, with harmonized guidelines and structured tools such as Risk Management Plans and PSURs enhancing consistency[84]. Differences in regulatory frameworks highlight the need for global harmonized pharmacovigilance practices. International collaboration among regulatory agencies plays a critical role in improving drug safety monitoring[85].

6.4 Technical Standardization Requirements

Much information in spontaneous reporting systems and EHRs is unstructured or incomplete, complicating analysis and limiting insights. Universal data standards… and AI-driven tools for data normalization can improve data quality[14]. MedDRA facilitates uniform encoding of medical terminology across various databases and platforms.

MedDRA includes cross-referencing capabilities, promoting interoperability between pharmacovigilance databases[86].Recommendations for the application of AI/ML in pharmaceutical GMP environments, delineates deficiencies and ambiguities, and suggests factors for forthcoming policy formulation. Emphasis is placed on understanding regulatory expectations across various agencies, including the US FDA, EMA, and MHRA[87].

6.5 Proposed Global Harmonization Pathway

Make the data more thorough and better quality Allow compatibility between regulators Support the automation of PV workflows Make it easier to find global signals Make it easier to use WHO-UMC tools like VigiFlow, VigiBase, and VigiLyze[88]. To get AI-driven pharmacovigilance to work the same way all over the world, regulatory authorities, healthcare organizations, and the pharmaceutical sector need to work together in phases.

In the short term (0–2 years), priority should be given to the development of risk-based regulatory oversight frameworks and consensus guidelines for

validation standards of AI models used in pharmacovigilance[89].

In the medium term (2–5 years), international collaboration should focus on building institutional capacity and strengthening global coordination mechanisms.

In the long term (more than 5 years), the ultimate objective is the establishment of a unified global pharmacovigilance platform integrating artificial intelligence technologies with international safety databases[14].

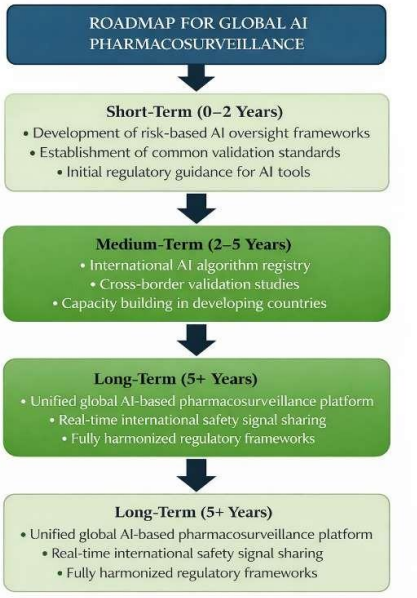

Figure 4. Global Harmonization Roadmap for AI-Driven Pharmacovigilance

6.6 Multi-Stakeholder Collaboration

The FDA has actively collaborated with the pharmaceutical sector on AI/ML via discussion papers, public seminars, and guidance publications. The 2019 discussion paper titled "Proposed Regulatory Framework for Modifications to AI/MLBased Software as a Medical Device (SaMD)" established the basis for a total product lifecycle (TPLC) methodology[87]. Pharmaceutical legislation creates a regulatory framework to ensure the safe and effective utilization of drugs. This framework requires national regulatory authorities to establish and maintain a PV system that delineates and enforces the regulatory responsibilities that essential stakeholders, including marketing authorization holders (MAHs), must fulfil. In past few years, national legislative bodies and national regulatory authorities globally have enacted substantial legislation and advice mandating the execution of pharmacovigilance activities. In nations where the NRA is a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), safety management protocols are typically aligned with ICH principles[90]. The consumption of pharmaceuticals in the private sector far exceeds that in the public sector. A 2014 government survey indicated that over 70% of illnesses were addressed in the private sector, encompassing clinics, hospitals, and charitable institutions, reflecting a four-percentage point rise over a decade[91].

6.7 Case Studies in Harmonization

EU Approach: Patients and HCPs in the European Economic Area (EEA) can submit reports on suspected ADRs to the relevant NCAs or MAHs. These findings are subsequently sent to EudraVigilance (EV), a centralized database that facilitates safety monitoring and the secure and effective utilization of pharmaceuticals inside the EU.

India's Experience: India's PvPI: Strengthening ADR reporting and global collaboration[60].

Emerging Markets: The rising markets represented by BRICS, where economic and healthcare factors are crucial in influencing the biosimilar environment. Navigating the regulatory landscape becomes imperative for biosimilar developers, and an overview of regulatory agencies within BRICS underscores the need for harmonized guidelines[92].

7. FUTURE DIRECTIONS AND EMERGING TECHNOLOGIES

7.1 Advanced AI Methodologies

The incorporation of artificial intelligence (AI) in the modernization of pharmacovigilance (PV) has the potential to bring about a significant improvement in the collection and processing of data for both healthcare professionals and patients. With the use of machine learning (ML) and natural language processing (NLP), AI has the capability of processing data at a rate that is unprecedented, thereby increasing the efficiency of data analysis and effectiveness in adverse drug reaction (ADR) detection. Although there are limitations, the use of AI in combination with human intelligence has the potential to overcome these limitations. With the exponential rise of technology that has been witnessed in the last ten years, it is important that data-driven fields like PV make use of AI to enhance their capabilities[93].In addition, the use of blockchain technology provides a secure and immutable platform for the storage and distribution of pharmacovigilance information[94].The convergence of artificial intelligence technology with wearable bioelectronic devices is transforming digital healthcare by making it possible to provide proactive, personalized, and data-driven medical interventions. These sophisticated devices, with multimodal sensing capabilities and artificial intelligence-driven analytics, enable real-time monitoring of physiological and biochemical

processes such as cardiac functions, glucose levels, and biomarkers, thus making it possible to provide early disease diagnosis, chronic disease management, and precision therapeutics[95].

7.2 Real-World Evidence Generation

Social media sites, which are marked by the presence of real-time data, form a new channel for pharmacovigilance as they provide abundant usergenerated content on the use of medications, adverse drug events, and public attitudes. However, the unstructured format of social media content creates difficulties in the analysis of data. Artificial intelligence based on real-world data has been recognized as an appropriate technological paradigm for pharmacovigilance studies. Electronic health care records are the most common sources of real-world data[96].

7.3 Predictive and Preventive Pharmacovigilance

Real-time Risk Prediction: Generating individual risk scores for ADRs based on patient characteristics, dosage regimens, and comedications. Recent innovations include the use of transformer-based models like BERT, RoBERTa, and GPT variants fine-tuned for ADR classification, which have demonstrated state-of-the-art performance in various NLP benchmarks. [96] Utilizing machine learning and AI, pharmacovigilance may proactively monitor patient responses to drugs, detect safety signals, and adapt treatment strategies accordingly. Pharmacogenetics is a scientific discipline that explores how unique genetic variations in individuals significantly influence their responses to medications, as well as the potential for varying therapeutic effects and the occurrence of ADR, thereby guiding more personalized and effective medical treatments[97].

7.4 Regulatory Evolution and Adaptive Frameworks

The evolution of regulations mirrors the everchanging nature of this area, emphasizing the importance of adaptive licensing and collective action for global data standardization[58]. Regulators have begun adopting a more proactive and adaptive stance toward AI in pharmacovigilance[98]. Artificial intelligence is progressively used into pharmaceutical development and regulatory decision-making. Frameworks differ substantially in scope, terminology, and application[99]. Regulatory sandboxes are a form of regulatory experimentation. Governments employ sandboxes for temporary live testing of technological innovations[100].

7.5 Global Infrastructure Development

Artificial intelligence technologies can support pharmacovigilance activities in regions with limited human and financial resources. Automated pharmacovigilance systems may help address capacity limitations in developing countries[101]. Machine learning and natural language processing have enabled a shift from manual safety reporting toward semi-automated surveillance systems. Global pharmacovigilance ecosystems include FAERS, EudraVigilance, and VigiBase for international safety monitoring[28]. The WHO created the Uppsala Monitoring Centre (UMC) in Sweden as the global centre for ADR reporting. The centre oversees VigiBase, a global database for individual case safety reports submitted by national pharmacovigilance centres[55].

8. CONCLUSIONS AND RECOMMENDATIONS

In conclusion, pharmacovigilance has significantly evolved from its initial reactive post-marketing surveillance to a more complete, proactive, and worldwide methodology for monitoring medication safety. As pharmacovigilance advances, international collaboration, regulatory harmonization, and the incorporation of customized medicine will be essential for safeguarding patient safety and welfare. The incorporation of artificial intelligence (AI) into pharmacovigilance (PV) represents a major breakthrough in the postmarketing safety surveillance of drugs, allowing for a significant enhancement of data processing, signal detection, and risk analysis that was not possible with conventional approaches. Traditional pharmacovigilance has been limited by manual analysis, underreporting, reporting bias, and the rudimentary analytical capability of disproportionality statistics applied in spontaneous reporting schemes (SRS); these factors have impeded the timely detection of adverse drug reactions (ADRs) and the establishment of credible safety signals. Real-World Evidence (RWE) has come to be recognized globally as a vital adjunct to conventional pharmacovigilance systems, allowing for earlier, more precise, and more contextually relevant detection of ADRs. With the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and global authorities such as the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) increasingly incorporating RWE into their frameworks, India finds itself uniquely poised to capitalize on its large and diverse population base, the growing digital health infrastructure, and the evolving pharmacovigilance ecosystem to develop a next-generation drug safety surveillance system.

However, there are still significant regulatory gaps, especially with respect to the definition criteria and governance framework of AI-based pharmacovigilance systems. Moreover, concerns about data quality, bias, and the absence of welldefined validation approaches have been

persistent issues that have impacted the credibility of AI-based safety monitoring tools. Resolving these challenges via regulatory harmonization, enhanced data infrastructure, and international cooperation will be critical for the successful global use of AI in PV and for bolstering drug safety surveillance globally.

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