REVIEW ARTICLE

Smart Safety: Automating Pharmacovigilance for Unmatched Drug Safety and Compliance

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Abstract

Pharmacovigilance (PV) is the science that is dedicated to the safe and effective use of drugs by recognizing, assessing, comprehending, and preventing adverse drug reactions (ADRs) as well as other drug-associated issues. Its overall mission is to provide patient safety and population health by continually monitoring the safety of drugs throughout the lifecycle of a product. To accomplish this, PV depends on a number of important methods. These include post-marketing surveillance, spontaneous reporting systems for ADRs and signal detection using data mining and statistical tools, and implementation of risk management plans as dictated by the regulatory authorities. The field involves publicizing well communications of safety information to healthcare providers, patients, and regulatory governments. Technological advancements such as electronic health records, artificial intelligence, and real-time safety databases have all helped to greatly improve the ability to identify and analyze safety signals in a more efficient manner. Findings of PV activities have led to important improvements in drug safety. Historical events, namely the thalidomide tragedy of the 1960s, strongly imposed the need for monitoring of drugs in a systematic and well-organized "government." Today, phantom of example, PV has played a major role in the updating of safety labels, in the identification of rare or long-term side effects, in informing regulatory decisions, and even rarely, in leading to the withdrawal from the market of unsafe medications. In conclusion, PV is a critical and evolving field that is important in keeping the balance between the benefits and risks of pharmaceutical products. Proactive stakeholder engagement and continuous collaboration, technological integration, and runtime are still helping build its capacity to protect public health in an increasingly complicated therapeutic world.

Key words: Artificial intelligence, automation, drug safety, pharmacovigilance, signal detection

INTRODUCTION

Pharmacovigilance (PV) has evolved into an informative practice not only because PV can guarantee the safe utilization of medicines but also to safeguard the health status of the population. Historically, some of the most important PV activities such as reporting adverse events (AE), evaluation of group cases, and reporting to regulators have been very manual. This commonly brings about slow reaction and high probability of involving human glitches. The inadequacy of these traditional modes is getting more and more obvious nowadays, with the speed of pharmaceutical innovation increasing, and with regulation getting even more complicated.[1] The way the market is now, there needs to be more intelligent, more precise, and scalable solutions. The emergence of high technologies adds to a bright opportunity of replacing inflexible, manual processes with smart and automated ones. It is one of the most dramatic changes in PV since it was only a reactive and disparate model to a proactive and streamlined method of worldwide consistent protection of drugs. The Food and Drug Administration (FDA), the European Medicines Agency (EMA), and other national regulatory bodies have existed and set standard operating procedures and rules for the execution of PV operations. The range of PV domain-facing activities is comprehensively

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Received: 20-05-2026
Revised: 18-06-2026
Accepted: 27-06-2026

outlined in Table 1, which illustrates the key functions and operational areas within the PV system.[2]

These requirements force pharmaceutical companies to collect and evaluate information on AEs, develop safety plans, and submit safety information within the stipulated time. PV is an important regulatory tool empowered with the monopoly task of protecting the public from effects that may arise from medicinal products. They entail post-marketing surveillance (PMS), signal detection, risk communication, and post-marketing risk-benefit assessment on products. This is crucial for ensuring the safety of the drugs existing in the market and the trust that the patients and health care practitioners have in the pharmaceutical system. Thus, there is a need for a more active and accommodating approach to the use of real-world evidence, patient-reported outcomes, and big data in PV. The field progresses, and regulators continue to adapt their frameworks to address new matters such as biologics, biosimilars, and advanced therapy medicinal products safety evaluation.[3]

FACTORS AND REPORTS ON ADVERSE DRUG REACTION (ADR)

Conventionally, PV was more focused on identifying ADRs, which means the unfavorable effects of drugs. In fully developed PV systems, including those of industrialized countries, reports do not only encompass ADRs but also other types of PV.

- Unexpected lack of effectiveness
- Defects in quality
- Drug misuse
- Errors in medication administration
- Social interactions with conventional and medicinal plants
- Poisoning incidents

Adverse drug events (ADEs) may be caused by variations in the quality of the products, misuse, and even other factors yet to be identified.[4] The other evidence of extended focus is the additional information indicated in the definition of PV in the European Union, which involves medication errors. In essence, three primary factors contribute to ADEs: Failure to have product quality, wastage, and unidentified products as depicted in Figure 1.

They can broaden the scope of drug-related matters and enhance the analysis and control of safety concerns. Reporting of ADEs is relevant to the cause of enhancing medication safety and promoting the welfare of patients. Any HCP, including doctors, nurses, pharmacists, or others, can report ADEs through the national PV center, the regulatory authority, or the respective pharma company.[5] ADEs can also be reported by the patient to the doctor or through

Table 1: PV domain-facing tasks and the knowledge and skill sets required to facilitate them

Activities focused on Domains	Acquired knowledge and proficiency	
	Focused on content	**Focused on process**
	Subject matter authorities	**Experts in operations**
Essential PV Specialties		
Case handling	Medical and Analytical	Project oversight database management
Signal processing	Medical System analysis, Social media and TSA	Data management, social media
Risk-benefit coordination	Risk: ideas, evaluation, and discourse	Risk: Project management and communication
Other disciplines involving the PV domain		
Animal Pharmacology	Animal Pharmacology: PK/PD characteristics, adverse event profiles	Project management
Clinical Pharmacology	PK/PD characteristics and adverse event patterns in human physiology	Project management
Regulatory/labeling	International regulatory frameworks, risk distribution, and bargaining	Rules and risk disclosure
Clinical trails	Consent, IRB, DMC, and trial design in bioethics	
Manufacturing	Production procedure; FMEA; SPC; security; quality	
Database management	Artificial Intelligence and Software	
Epidemiology/biostatistics	Quantitative techniques, such as analytics	
Medical affairs	Interaction	

PV: Pharmacovigilance, PK/PD: Pharmacokinetics, SPC: Statistical process controls, TSA: Time series analysis

the reporting systems that the regulatory agencies create. ADEs can be reported through electronic means using the technology-based tools and mobile applications provided for use, as depicted in Figure 2.

When recording ADEs, it is necessary to provide detailed information on the patient and the concerned medication, including databases on the AE occurrence, medication, or pre-existing medical condition. ADE reports should be submitted on time to make a fast determination and conform to the regulatory period for serious or unintended ADEs. General healthcare practitioners, patients, and other stakeholders are involved in the constant medication safety assessment via ADE reporting to improve healthcare services and the best patient care.[6]

PROCESS OF PV

According to current understanding, PV may be described as a large process of identifying, measuring, and assessing the risk of drugs and medical products during the pre-marketing approval stage up to post-marketing evaluations. The tasks of reviewing, evaluating, and monitoring ADRs and any other complications relating to drug intake are assigned by the agency. Derived initially from collecting surveillance data from spontaneous reporting systems (SRSs), clinical trial data, and electronic medical records, the core objective of PV is the identification of safety signals. Through this process, the signals undergo extensive evaluation to determine clinical relevance and risk, which may be accompanied by further investigation and more objective risk calculation.[7] Subsequently, adequate risk management strategies are developed, which could translate to altering the labels or implementing risk-reducing measures as depicted in Figure 3.

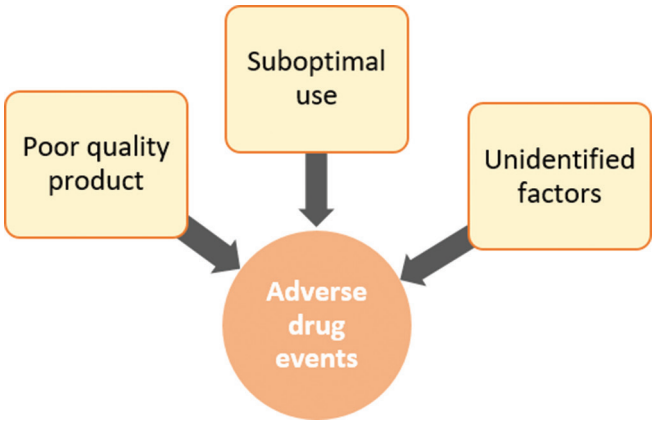

Figure 1: Possible factors resulting in adverse drug events

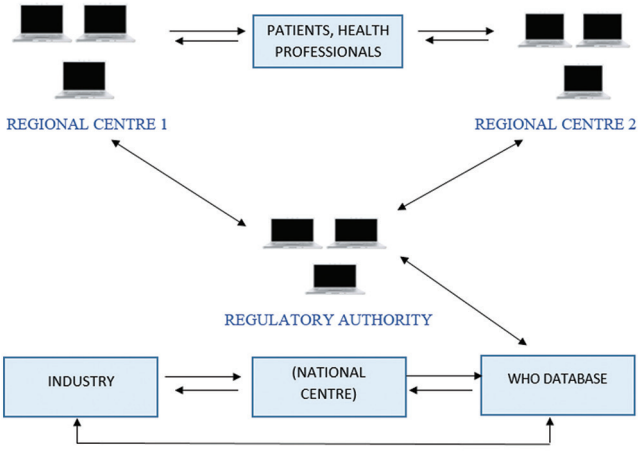

Figure 2: Flow of reports on adverse drug reactions and their feedback

In this process, the dissemination and reporting of safety data are paramount in informing healthcare practitioners, institutional stakeholders, and the public. PV is a branch of science that analyses risks associated with medications and applies strictly regulated methods to reduce the possible adverse effects and provide the population with quality medications and adequate treatment.[8]

PV METHODS

Overall, approaches to PV may be subdivided into passive monitoring, active monitoring, and observational studies, and novel ways of data analysis methodologies which have distinct roles in drug safety surveillance. The most common design of standard PV which is a form of passive monitoring is the SRS. According to this system, the medical staff, the patient, and the pharmaceutical firms report potential ADRs directly to the national or international regulatory authorities. Those most prominent are the FDA AE Reporting System (FAERS) that is managed by FDA, EudraVigilance that is managed by the EMA, and the WHO VigiBase. Even though SRS has the advantage in that it is able to identify rare or unforeseen ADRs, it is under-reporting and does not quantify the denominator data, which diminishes its ability to estimate incidence rates or causality.

The drawback of the passive methods of reporting is overcome through applying active surveillance systems.[9] They encompass the proactive or voluntary collection of safety data of the targeted populations using well-specified procedures. As an example, cohort event monitoring is in compliance to the patients who take specific drugs and follow their progress over the years and observe when AEs are manifested. Moreover, the electronic health record (EHR) systems allow an opportunity to extract clinical information on a continuous and automatic basis, which allows receiving a real-time safety rating. The more common examples would be broad population-based ones like the U.S. Sentinel System and the UK Clinical Practice Research Data-link, where active surveillance is currently being deployed in the modern PV.

The other significant category of methods is the observational epidemiological studies, which will include

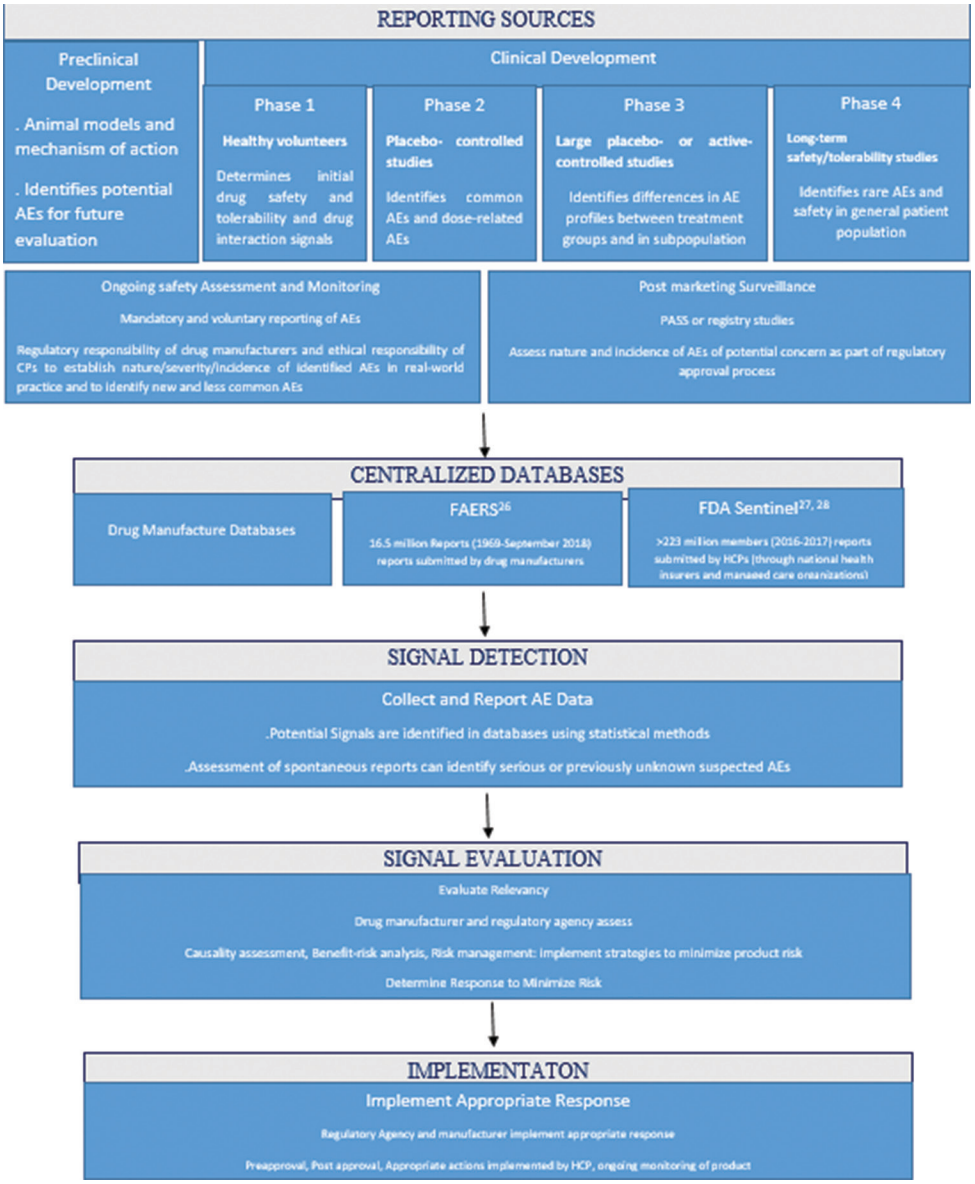

Figure 3: Pharmacovigilance process

cohort studies and case–control studies. Results of individuals who had been exposed to drugs are compared to those of the people who were not and this may be utilized to calculate relative risk and rates of incidence of a substance. Case–control studies, on their part, are the types of studies where the sufferers of a particular AE need to be ascertained and the history of the drug intake be compared to that of the non-sufferers. These kinds of studies are particularly helpful in validating safety signals and in determining risk factors where randomized controlled trials are impossible to conduct.[10]

Prescription event monitoring (PEM) is a hybrid trial, where patients taking new drugs available in the market are tracked by the data obtained within the health care practitioners. This is one of the most feasible methods in the very first phase of post-marketing and involves a practical understanding of ADRs in any real-life clinical practice.

PV with the emergence of big data also includes data mining and signal detection algorithms. Large safety databases could be analyzed with disproportionality analysis, Bayesian statistics, and machine learning (ML) algorithms to identify drug-event pairs that are greater than would be expected by chance. The techniques improve on the sensitivity and precision of detecting the signal and are becoming the standard in routine regulatory practice.

Recent pharmacogenomic methods also come in handy due to the ability to relate the drugs to a genetic profile. It is possible to gain at-risk populations at the early stage with the help of the strategies, and it may result in aspects such as personalized medicine and stratified strategies in the sphere of PV.

All these different methods of PV unite the dynamic holistic approach to drug safety surveillance. The recent development

of PV can probably be further enhanced by the incorporation of real-world data, advanced analytics, and patient-based tools, which could augment the efficiency, precision, and harmonization of PV over international borders.[11]

PV TOOLS AND DATABASES

The advanced digital solutions are increasingly aiding PV in ensuring that cases are properly processed effectively, signal identification is done quicker and that the same conforms to the global regulations. All this is generally divided into two categories: One of the data control and data analysis tools and another is a database for data storage and organization that holds data safety reports that are provided by several sources.

PV tools

It is possible to define PV tools as software platforms to facilitate managing case data, automated reporting, identifying safety signals, and submitting regulations. They enhance the PV workflows and make them more precise, quick, and uniform.

Oracle Argus safety

This is a widely used safety management system that is all rounded and they generate and receive ICSR and codes and reports on their regulations. It supports automation, tracking cases, MedDRA/WHO Drug harmonization, and international compliance.

Aries Global LifeSphere safety

A PV system based on a combination of AI and automation is an end-to-end safety case management cloud-based system. It offers triage services, case processing, signal identification, and reporting of these services to the health authorities.

Empirica signal

It is an Oracle product that enables the identification of advanced signals through the use of data mining algorithms and statistical techniques. It assists in determining the emerging safety issues, in the light of massive data, including SRSs.

PV-works

A case management, product coding, and preparation of regulatory report modules modular system addressing human and veterinary PV.

OpenVigil

Open-source PV search and visualization application which allows querying and visualization of publicly available safety data, including FAERS. It is typically employed in small-scale industry and research academic institutes.

PVNet

A web-based application that supports small to medium organizations and national agencies with the administration of PV process, such as AE reporting and compliance reporting.

VigiLyze

Uppsala Monitoring Centre (UMC) developed a data exploration/signal detector tool to be used in VigiBase. It also enables users to see trends, filter the reports, and find possible safety indicators with the help of a convenient dashboard.

WHO drug and MedDRA dictionaries

These coding dictionaries have important roles in the majority of the large PV tools. The standardization of the medicine events and reactions, along with the WHO drug that is being used to assist in standardizing the naming of drug identification, is acquired from MedDRA so as to promote reporting in the international marketplace.[12]

Databases of PV

PV databases are of the nature of repositories that accumulate AE reports of various entities such as the healthcare providers, regulatory bodies, or the pharmaceutical companies. Such databases are utilized in surveillance of safety signals, epidemiological investigations, and in informed decision-making in regulation.

European Union (EudraVigilance)

- Managed by: EMA
- Scope: Gathers and oversees reports of possible side effects to pharmaceuticals that are permitted inside the European Economic Area
- Features: Permits the study of individual case safety reports (ICSRs) and facilitates risk management, signal identification, and assessment tasks.

United States FAERS

The regulatory agent is the FDA of the U.S.

- Scope: It contains the data of ADRs and medication errors
- Characteristics: Free to everyone; helps in signal detection and regulatory decisions within the United States.

VigiBase (Global)

It is under the management of the UMC on behalf of the WHO

- Scope: The largest global ICSR database that is provided via the member states' reports
- Characteristics: It can encourage international collaboration, tracking of signals, and analysis of trends across nations.

Canada vigilance (health Canada)

- Scope: Witnesses the deplorable situations related to the health products that are sold in Canada
- Features: Enables mandatory and voluntary reporting by medical professionals, manufacturers, and consumers.

United Kingdom Yellow Card Scheme (United Kingdom)

- Controlled by: Medicines and Healthcare products Regulatory Agency
- Scope: It captures ADRs of drugs, immunizations, product formulations, natural and naturopathic products
- Features: It is publicly exposable and professional reporting and plays an important role in monitoring drug safety in the UK.

JADER Japan ADE report database

- Oversight: Pharmaceutical and Medical Devices Agency (PMDEA)
- Scope: The scope is on the negative events made in Japan
- Characteristics: It was used in Japan to conduct the national signal detection and regulatory review.

VigiFlow: UMC operated it

- Scope: It is a web-based computerized data management system, ICSR associated with a VigiBase
- The features: Only entering, validating, and submitting data into WHO were done using national centers.[13]

The comparison summary of the main advantages and limitations, as well as the application purposes of significant PV databases, is given in Table 2. This assists in visualizing their respective functions in the international surveillance of the safety of drugs and regulatory decision-making.[14]

DATA SOURCES FOR PMS

PMS is very relevant to observing the safety and effectiveness of a pharmaceutical product once it is in the market. Using these data sources, regulatory agencies, health care and insurance providers, and scientific researchers should be able to assess and mitigate the risks of harm that the drugs present and, in the same process, enhance patients' health and treatment outcomes, as depicted in Table 3.[15]

Table 2: Comparison of pharmacovigilance databases

Databases	Advantages	Limitations	Use Cases
EudraVigilance	Centralized reporting system in the EU, Real-time signal detection, EMA compliance	Restricted full access to the public, requires EMA registration for advanced use.	PV compliance for EU/EEA markets, Risk management plan, Signal detection in Europe
FAERS	Robust U.S. data, the FDA Dashboard, can be analyzed publicly	Underreporting and duplicate entries may lack detailed clinical context	U.S. drug safety monitoring, Public signal research, Regulatory review in the FDA context
VigiBase	The biggest international ADR database, Potentiates global use of data, and allows prioritization of signals.	Access available on a UMC basis, Data de-identified and could be specified at a granularity level.	Detecting global signals, Comparative countries analysis, Support services of PV by member states of the WHO
Canada Vigilance	Applies to a broad line of items. Both voluntary and compulsory reports are accepted.	Unavailability of much public data, Less data than international databases	Domestic regulatory assessments in Canada, Post-market surveillance
Yellow Card Scheme	Considers both non-corporate and professional reports, covers immunization and products as well as equipment and herbs.	Restricted to UK data, may not be representative of Trends in the rest of the world.	Surveillance of vaccine and medicine safety in the UK, Public health safety communication
JADER	The local regulatory evaluation of Japanese-specific ADR information is based on data that supports local regulations.	Japanese language interface and access, Low contrast international.	National pharmacovigilance (Japan), National signal monitoring and regulatory response
VigiFlow	It allows standardized ICSR management, VigiBase integration, and an Easy-to-use interface.	Meta-analysis is used as a tool by national/regional centers only, not as an analysis tool in itself.	Use of VigiBase as a data reporting platform, National-level Case tracking, and Training on PV functions.

EU: European Union, EMA: European medicines agency, ICSR: Individual case safety report, UMC: Uppsala monitoring center, PV: Pharmacovigilance, EEA: European economic area

Table 3: Sources of data for ADR detection

Sources of data	Explanations	Benefits	Restrictions
Main sources of data			
Systems of spontaneous reporting (SRS)	Healthcare professionals or an individual like the patient reports adverse drug reactions (ADRs) to the regulatory authorities. After that, ADRs are easily accessible and documented for future analysis, investigation, or review.	A wide range of international people provided pertinent information. This platform, like FAERS, is available to the general public. The vast population-specific information gathered makes it a valuable resource for research and study.	Not all cases are reported. Due to inadequate data, incomplete data was received. Details provided. Certain facts are repeated because of comparable circumstances. Bias in ADR reporting arises from people placing the responsibility for adverse drug reactions (ADRs) on drugs rather than other factors, such as dietary adjustments or supplementation.
Digital health record	Information on inpatients is gathered via diagnostic and medication administration. Every event that occurs in the hospital for every patient, including missed medications, duplicate doses, and other activities, is noted and documented.	Since specific information is documented, including medication dose, test results, and diagnostic records, the information is accurate. Because patients vary in terms of their genetic origins, diets, and ethnicities, the information gathered about them is highly valuable for research and study.	Because hospitals can only accommodate a certain number of patients, the sample size is tiny. Because of the small patient population and brief hospital stays, the data may not be enough for ADR identification. Due to inconsistencies brought on by hospital staff mistakes, information is prone to prejudice.
Scientific writings	Scientific publications and peer-reviewed literature on adverse drug reactions. Data on adverse drug reactions is gathered from various research projects and examined.	Peer review is used to control the quality of information. Data gathered via research projects carried out by researchers leads to higher-quality data.	There are presumptions as well. Data is restricted to a small number of investigations. Data gathered from research may contain bias. Due to its small sample size, the research may not be enough to produce data with high accuracy regarding ADRs.
Social networks	Most social media content, including blogs, Twitter, and health-related forums, is authored by non-experts. People frequently use social media platforms to discuss health-related topics online.	The information is diverse and comes from several global demographic groupings. As more individuals share their healthcare experiences online, there is an abundance of content that may provide clinical practitioners with valuable insights.	Grammar and spelling mistakes, as well as colloquial language, need sophisticated linguistic processing. For instance, rather than referring to their state as “fatigue,” people frequently say that they are “flat out.” This makes understanding the data of ADRs more difficult. Due to the tendency of people not to provide every detail online, information is scarce.
Medical narratives	Books authored by medical specialists. They used their expertise and experiences to inform the writings they created.	A wide range of topics is covered in the literature, such as patient history, clinical circumstances, and therapy. Because it is based on the expertise and experience of healthcare experts, the literature is accurate.	The data may be skewed based on local documents. Their experiences and wisdom are the only sources of information. Moreover, only the local populace has access to information.

(Contd...)

Table 3: *(Continued)*

Sources of data	Explanations	Benefits	Restrictions
Principal sources of secondary data[16]			
Sider 4 Off-sides Two sides Meta ADEDB	Includes information on 1430 authorized medications, 5880 ADRs, and 140064 drug-ADR pairings. A database of medications, side effects, and indications compiled from Canada's Med Effect portal and FDA medicine labels. Includes off-label side effects of medications produced by FAERS and gathers information from physicians, patients, and pharmaceutical firms. It is a database of medication pairs' polypharmacy side effects that is produced by adverse event reporting systems. A thorough database of adverse drug events that includes all chemicals and ADEs, built using information obtained from SIDER 2, OFFSIDES, and the comparative toxicogenomics dataset (CTD). Concepts established in medical topic headings (MeSH) were tagged onto the merged data from these three databases.		The way that medicine labels are processed affects both accuracy and the quantity of negative effects. Not every ADE that takes place is recorded by systems for spontaneous reporting. It is necessary to notice, identify, and ascribe the drug's effects before reporting them. Thus, just as the restrictions of the OFF-SIDES data source preclude a clear interpretation of the findings, uneven reporting and covariate biases also do. There was no recruitment of ADE side-effect frequencies or placebo administration. There's a chance that some drug-ADE connections are false positives.

ADRs: Adverse drug reactions, CTD: Comparative toxicogenomics dataset, ADE: Adverse drug events, MeSH: Medical topic headings, FDA: Food and Drug Administration, FAERS: FDA adverse event reporting system, SRS: Spontaneous reporting systems

SRSs

The FAERS is an electronic database that keeps track of individual reports of drug mistakes and AEs that are submitted to the FDA. The National Vaccination AE Reporting System is a system designed to track vaccination safety in the United States. The European Union's system for reporting and tracking signals for possible post-marketing ADEs is called EudraVigilance, and it is run by the EMA.

EHRs

EHRs contain patient-level clinical information from the provider side and the hospital side and hence have benefits in the searches for AEs and the evaluation of the safety and effectiveness of a drug.

Claims databases

Claim databases get healthcare usage like diagnosis, treatment, and prescribed drugs and offer substantial real-world assets for PMS.

Patient registries

For instance, disease-specific or drug-specific registries where information on patients is captured over time, for assessments of disease and drug profiles over a certain period.

Pharmacoepidemiological studies

Cohort and case–control studies, as well as epidemiological research, are useful tools for comparing the effects of drug exposure on populations.

Clinical trials databases

Databases like ClinicalTrials.gov provide information on clinical trials involving post-marketing clinical trials that are required by ministries and agencies for regulation.

Social media and patient forums

Data obtained from other sources, such as social networks and patients' forums, can also reveal previously unrecognized

patients' outcomes and new AEs not included in the primary organizational system.

PEM

A system that collects data on prescriptions and associated AEs, often used in the UK.

Health surveys

National health surveys collect data on health behaviors, conditions, and treatment outcomes.

Literature and published case reports

Articles, case reports, and reviews published in medical and scientific journals provide information on AEs and drug effectiveness.

Pharmaceutical companies' safety databases

Proprietary databases are maintained by pharmaceutical companies to track AEs and other safety information related to their products.[17]

AUTOMATION IN PV

Artificial intelligence (AI)

AI finds applications in safety signal detection, detecting deviations in AE reporting, and predicting models of safety risks of drugs. Based on the concept of human decision-making by replicating the process, AI systems will allow the large volumes of data distributed across a multitude of different sources, including EHRs, social media, and clinical trials, to be analyzed in a smaller amount of time, leading to better PV results and faster signal discovery.

ML

The algorithms, in particular, the algorithms of supervised and unsupervised learning, can also constantly learn with the inflow of additional data. It enables dynamic profiling of medications to be safe and have automatic identification of danger patterns. ML models also reduce false positives in signal detection and enhance classification and triage of cases.

Robotic process automation (RPA)

This is the process of using software robots to handle rule-based and repetitive tasks such as the reception of cases, the input of data and code, and filing of regulations and others. It significantly shortens the turnaround time, which leads to lower costs in terms of operation, and ensures the elimination of the possibility of any human error and adherence to regulatory enforcements such as EMA and FDA.

Natural language processing (NLP)

NLP converts unstructured text information to structured information, hence permitting automatic derivation of valuable information in medical texts, spontaneous reports, clinical stories, and so on. It manages multilingual processing that is critical in PV activity across the globe. NLP can also be used to accelerate the rate of MedDRA coding and narrative summarization.

The cognitive automation cognitive automation mimics the thinking of a human

Reasoning and situational choices are made by AI, NLP, and ML. It is especially effective in intelligent case triaging, where they are able to prioritize high-risk cases for faster examination and can leverage the efficiency rate in safety teams.[18]

Cloud computing

The PV cloud platforms possess a scalable data storage platform, data analysis, and collaboration capabilities. They permit the real-time sharing of data across geographically remotely located organizations, different contract research organizations, and regulatory authorities. Cloud services are also more adaptable, enabling the implementation of updates and integrations with other digital tools to be implemented faster.

Optical character recognition (OCR)

OCR is used to scan handwritten or scanned AE reports, laboratory notes, and PDFs and then turned into text-based information into a structured database which can be automatically extracted. This not only increases the traceability of data but also alleviates the impact of mistakes made by humans in the transcription process and increases regulatory compliance due to audit trails.

Big data analysis

The ever-growing volume and diversity of healthcare data can offer the opportunity of structuring and processing both organized and unorganized data and information that have different sources, including EHRs, patient registries, insurance claims, and wearable devices. It allows robust signal identification and hypothesis generation and facilitates decision-making based on data to improve decision-making in regulations.

One can find numerous automation approaches that are currently implemented in PV to enhance its effectiveness, precision, and regulation-compliancy. Table 4 shows an overview of the key properties and capabilities of these new technologies, its advantages, constraints, and its applicability.[19]

Signal detection approaches

Analysis of disproportionality

- Proportional reporting ratios (PRR): Compare the rate of a side effect associated with a drug to that of all medications
- Reporting odds ratio: Similar to PRR but uses odds ratios to assess the strength of the connection
- Bayesian confidence propagation neural network (BCPNN): The WHO-approved BCPNN computes the information component to identify signals
- Multi-item gamma Poisson Shrinker: Utilized by the FDA, it calculates the empirical Bayes geometric mean for signal detection.

Implementing ML and data mining

- Supervised learning: Trains algorithms using labeled datasets to identify patterns linked to drug reactions
- Unsupervised learning: Detects concealed patterns or groupings in data without predefined labels
- NLP: Extracts details from sources like clinical records or social media.

Statistical approaches utilized

- Time-to-event analysis: Evaluate the duration between drug exposure and the onset of a reaction
- Sequential analysis: Monitors data over time to detect emerging signals.[20]

ADR PREDICTION THROUGH ML

It is a complex task to predict ADRs for the consideration of improving drug safety and patient care by using ML algorithms. First, it involves acquiring data from various

Table 4: Hollywood of automation

Technique	Advantages	Limitations	Use Cases
Artificial intelligence (AI)	- Signal detection speed- Processes large and wide data sets- Improved predictive risk modeling	- Not portable in quality training data- Lack of transparency in decision-making (black box)	- Signal detection - Anomaly detection - Drug safety risk prediction.
Machine learning (ML)	- Train constantly on new information- Minimizes false positives- Automatically learns risk patterns	- Safe any data- Biases results in biased data	- Signal refining- Case classification and triage
Robotic process automation (RPA)	- Process automation- Repetitive rule-based- Human error- Compliant with regulatory standards	- Structured tasks	- Unstructured case decision-making
Natural language processing (NLP)	- Unstructured text- structured data- Accelerates MedicDRA coding- Allows multilingual processing	- unable to interpret context ambiguity	- Fine-tuning of true medical text
Cognitive automation	- Replicates human reasoning- Puts the high-risk first	Requires constant learning updates	- Intelligent triaging - Context-aware safety reviews
Cloud computing	- Provides real-time exchange of data-Scalable, affordable- Integration amongst stakeholders	- Multi-site access- Centralized deployment of PV system	- Data privacy and security issues.
Optical character recognition (OCR)	- Digitizes scanned/handwritten data- Increased traces of data-Minimizes transcription errors	- Limited interpretation of context	- Digitizing AE forms- Extraction of lab notes- Structuring scanned PDFs
Big data analysis	- Processes structured and unstructured data-Assists hypothesis generation-Real-time analytics	- Complexities in data harmonization	- Signal validation-Pattern discovery-Regulatory decision support

RPA: Robotic process automation, NLP: Natural language processing, OCR: Optical character recognition, ML: Machine learning, AI: Artificial intelligence, AE: Adverse event, PV: Pharmacovigilance

sources, including clinical trials, EHR, and AE reporting systems, for instance, the FAERS. The next step is a process of feature selection to recognize the significant predictors of ADR that are involved in their occurrence of ADRs. They include drug attributes such as chemical identity and pharmacokinetic profile, as well as client-related factors such as age, gender, and heredity. After this, a data cleaning mechanism is applied to delete or deal with missing values, outliers, and noise to clean the data set for analysis. Model selection is particularly critical here, whereby different ML algorithms undergo performance assessment of ADR predictability. Logistic regression, decision trees, random forests, and neural networks form the standard toolbox of models that are used in practice and are used in conjunction or ensembles to obtain their best combined performance.[21] After selecting a model, a labeled dataset is used to train the model effectively so that it captures some of the subtle relationships between features and instances of ADRs. It is also important to validate the result and involve testing aspects such as accuracy, precision, recall, and the area under the curve-ROC measurements using the testing dataset. Also, validation of the model in one dataset cannot be replaced by another, and it is crucial to make sure that the results will not be model-specific. Finally, model optimization, such as hyperparameter tuning, helps to refine the model for improved predictive performance, thus increasing the model's robustness in real-world settings. Last but not least, the trained model is deployed for ADR prediction in clinical settings, and at regular intervals, vigilant monitoring is done to check any shift or decline in the model performance. However, there exists the problem of the imbalanced data set, the origin from different data sources, and the need for interpretability of ML as a tool shows great potential for further improvement of ADR prediction that will, in turn, improve the safety of pharmaceutical interventions.[22]

CASE STUDY

Pfizer Intelligence PV Automation.

Partner/Platform: In-house AI platform that is combined with the COVAES reporting portal and automated workflows.

Background: The PV team of Pfizer had already learned to deal with an apparently immense number of AE reports (over 1,000 medicines and vaccines) in COVID-19 vaccine case. However, given the understanding that additional human resources are operating on an individual scale and that they cannot be restructured in the context of reuniting the PV costs, Pfizer has begun to address the operation of integrating its operations through the adoption of AI, RPA, and digital solutions. It entailed the consideration of over 120 process improvements, and the same number of process improvements were implemented in a given time period, i.e., 50. Hopefully, this will neutralize the tediousness of the intake and processing since this process will be automated, which will allow the safety professionals to pursue more resourceful clinical research.[23]

Pfizer introduced the following solution: Solution Implemented: Pfizer adopted a mixture of both in-house and collaborator-developed automation solutions:

- A reporting online portal system, which can be automated by Partners, whose multilingual functionality is available to the AEs, and which will be published, is called COVAES.

Agent LEO is an AI bot that has automatic data collection of voice-based AE information.

- AI-enabled automation work processes to download, filter, and tag data that is downloaded in the regulatory space reports (e.g., EMA reports).

NLP-aided literature review devices to bring out the papers on which the mark was to be and determine the AE.

Human-in-the-loop governance structure, in which data were checked by safety professionals. Governance structure in which data safety was checked by professionals. It was fed into AI before the ultimate conclusion of a case was made.

Key outcomes

- Speed of case processing: Realized a reduction in manual intake and triage exceptionally at times, and due to this, is able to stand at a functional rate of processing cases with an exaggerated number
- Information protection of collection: Greater coverage of data through involving a patient in collecting data on AEs through portals and voice bot devices, thus getting more extensive and capturable in real-time
- Redundancy reduction: Redundancy was one such area that automation helped the safety analysts to find time to work on their job. More tasks such as signal detection, risk assessment, and case review
- Regulatory compliance: FDA and EMA certification has been done on the systems. Total trace and control possibilities within the regulatory powers. Human Management and Management:

Indeed, the automation realization achieved in some of the instances was always high but there were always some critical points that could be checked by a human. The safety doctors verified the AI output, and the clinic accuracy and decision-making reporting and risk analysis were overseen by a hybrid process that maintained an audit trail, regulatory compliance, and clinical decision-making in the processes of safety.[24,25]

Table 5: Problems with smart safety automation in pharmacovigilance

Challenge	Description
Data quality and consistency	The unfinished, unstructured, or discrepant data of and among the sources may undermine the detection of signals and the risk analysis.
Algorithm transparency	AI/ML systems tend to be black boxes and their decisions are hard to explain to the regulators.
Regulatory acceptance	Absence of international regulations on automation acts as a hindrance to its large-scale application.
Validation and audit readiness	Automated systems should adhere to GxP and should be able to be audited, further complicated by technical and operational requirements.
Ethical and privacy concerns	The managing of sensitive patient data poses privacy concerns and is particularly so when it comes to GDPR and HIPAA.[26]
System integration	Challenges in the integration of new automation devices with the old legacy systems and IT environment.
Human oversight	Complex safety signals still have to be evaluated through expert medical judgment, and this type of assessment cannot be completely substituted.
High implementation costs	Automation is expensive in terms of technology, training, and servicing.
Resistance to change	Adoption may be hindered by human resistance because of fear of being laid off or mistrust in automation.
Bias in AI/ML models	Algorithms can be biased by training data, which can provide inaccurate or unjust outputs.[27]

ML: Machine learning, AI: Artificial intelligence

ISSUES IN SMART SAFETY AUTOMATION OF PV

Table 5 identifies the key problems with the actualization of the automation of PV as part of the Smart Safety concept. These impediments are data quality and system integration, uncertainty over regulations, and ethics. These barriers are to be taken care of so as to ensure the effective and viable application of automation technologies in drug safety monitoring.

FUTURE DIRECTIONS

Smart safety in PV sphere will take subsequent evolutionary leaps in different ways. Among the primary areas will be the capacity to explain AI (XAI) to create transparency and increase confidence between regulatory organizations and medical practitioners. The common international regulation movement will demand harmonized instructions on how to use automated tools across regions. There will also be the introduction of advanced data platforms to enable sources of data, including EHRs, wearable devices, and social media to be combined without problems with structured and unstructured data. The real-time signal detection systems, with the aid of AI, will be capable of decreasing the number of days between the regulatory response to an event and its occurrence by a significant margin. Moreover, federated learning will be implemented, which will allow privacy-sensitive AI training at institutions. A system will also automate risk management plans, and therefore, they will be updated in real-time through constant updating of the live data on PV.[28] More cognitive automation will be applied, and therefore, the complex decision-making would be improved. Cloud-based platforms will encourage worldwide collaboration and expedited trade using information. Genomics and predictive analytics will provide patient-specific data on safety through personalized science which can also be called personalized PV. To fortify such developments, the personnel of the PV occupation will be required to undergo constant up-skilling in a bid to ensure efficient monitoring, search, and integration of automated processes.[29]

CONCLUSION

Because PV helps in monitoring the efficacy and safety of the pharmaceuticals, it is a very important aspect of health to the population. The paper has pointed out the complexity and dynamic nature of PV because of the challenging regulations imposed by various organizations such as the EMA and the FDA. The current developments in PV have included real-life data, patient-reported data, and voluminous data, which have enhanced the identification of ADRs. Signal detection methods and ML are major advancements in the research and prevention of ADRs, which can transform PV procedures. The potential for automation analysis has revealed the presence of enhancing the effectiveness and reliability of PV activities. In addition, regulatory intelligence guarantees that compliance and risk management are efficiently fulfilled in the pharmaceutical industry to provide a safer environment. The significance of the PV databases and PMS data sources can hardly be

overestimated in the sphere of protecting public health. Due to the further development of the sphere of PV, the implementation of technology and the use of regulatory intelligence will always be an essential part of the strategy to address the issues and maintain the confidence of patients and practitioners in the pharmaceutical system.

ACKNOWLEDGMENTS

The authors are thankful to Shri Vishnu College for providing the necessary facilities.

CLINICAL TRIAL NUMBER

Not applicable.

DATA AVAILABILITY

No datasets were generated or analyzed during the current study.

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Source of Support: Nil. **Conflicts of Interest:** None declared.