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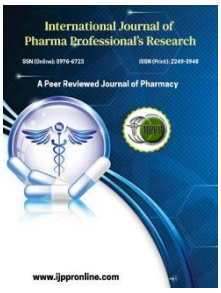

Automation in Pharmacovigilance

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Abstract: The term "pharmacovigilance," first proposed in the 1970s, has gradually gained traction to become one of the two common terms of art for the overall discipline, the other, older term being "drug safety." "World Health Organization (WHO)" as "the science and activities relating to the detection, assessment, understanding and prevention of drug-related problems". The information about suspect product is collected from healthcare providers and patients to detect and prevent abnormalities associated with it. Therefore, PV deals with adverse effects of drug, poly-pharmacy, paradoxical reactions, and severe adverse events. Automation in pharmacovigilance entails using cognitive technologies such as machine learning (ML) and advanced analytics to transform legacy data compilation processes and information gathering for regulatory approval. Automation technologies have strong potential to automate routine work and balance resource use across safety risk management and other pharmacovigilance activities. This article provides an overview of automation in pharmacovigilance.

1. Introduction

Drug safety monitoring identified as Pharmacovigilance (PV) is formally defined by the "World Health Organization (WHO)" as "the science and activities relating to the detection, assessment, understanding and prevention of drug-related problems". [1]All drugs can cause adverse effects and no drug is completely safe. [2] PV may be classified into two categories: preauthorization PV concerning the information adverse drug events accumulated from clinical trial settings (phase 0/I through phase III) [3]; and post-marketing/post-authorization PV concerning the safety information collected during the post-authorization life cycle. Data accumulated in the post approval stage and throughout a drug's market life shown in (Figure 1).

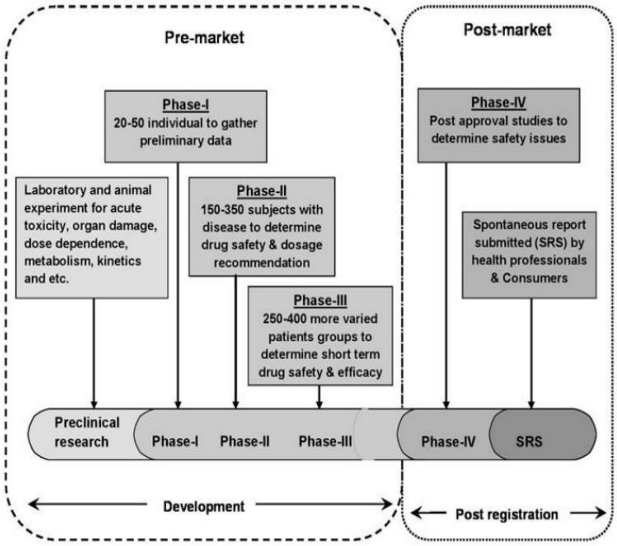


Figure 1: Pharmacovigilance at different stages of drug development

Even though pre-authorization clinical studies (i.e., RCTs) are deliberated as the lineament of explaining a drug's efficacy, they don't usually detect whole safety concerns of a certain drug before its use in the real world due to well-known limitations. Those limitations can be summarized in the restricted sample of trial participants involved in those studies compared to the total targeted population who may experience the drug whenever marketed, the limited interval of drug exposure per each study participant especially if the drug projected for chronic use, lack of possibly risky patient subpopulations who are usually omitted from clinical trials (e.g., patients with impaired organs, elderly patients, children, and childbearing woman who may be pregnant or lactating mother, patients on chemotherapy). [4] The main goal of pharmacovigilance is thus to promote the safe and effective use of health products, in particular by providing timely information about the safety of health products to patients, health-care professionals, and the public. Pharmacovigilance is therefore an activity contributing to the protection of patients and maintaining public health. [5] Pharmacovigilance involves more than spontaneous reporting, and is more than just evaluating marketed medications. It has grown from a minor component of drug control to a major activity and expanded its scope to encompass the assistance for patient safety during clinical trials by ensuring adequate informed consent and institutional review boards (ethical committees); development of a safety profile for proper use of a new molecular entity and appropriate communication of that information to a range of relevant stakeholders; selection of the first safe dose for use in humans based on pharmacologic data obtained in animal studies; development of a safety profile. [6] PV is commonly considered to have begun as a separate, identifiable activity in the United States with passage of the Drug Efficacy Amendments (also known as the Kefauver-Harris Amendments) of 1962, that were legislated in response to the thalidomide catastrophe that had occurred in Europe. [7] However, there is an earlier history that played an important role in shaping the statute. As early as 1952, the US Food and Drug Administration (FDA) had actively sought information concerning a growing safety issue with the use of chloramphenicol. FDA surveyed its 16 district offices of hospitals, clinics, and medical schools in cities with populations >100,000 to collect reports of aplastic anemia and blood dyscrasias associated with use of chloramphenicol. [8] The term "pharmacovigilance," first proposed in the 1970s, has gradually gained traction to become one of the two common terms of art for the overall discipline,[9] the other, older term being "drug safety." Also in the early 2000s, the basis of regulatory assessment expanded to include "risk," and approaches to creating risk management measures were instituted: in the United States, first as risk minimization action plans, then as risk evaluation and mitigation strategy (REMS), [10] and in the European Union, as risk management plans. This measure is the third core PV function: benefit-risk management. Thus, 3 core functions of PV exist: case management, signal management, and benefit-risk management. [11] To understand how these activities are related to one another, however, it is helpful to look at them from a systems perspective (Figure 2).

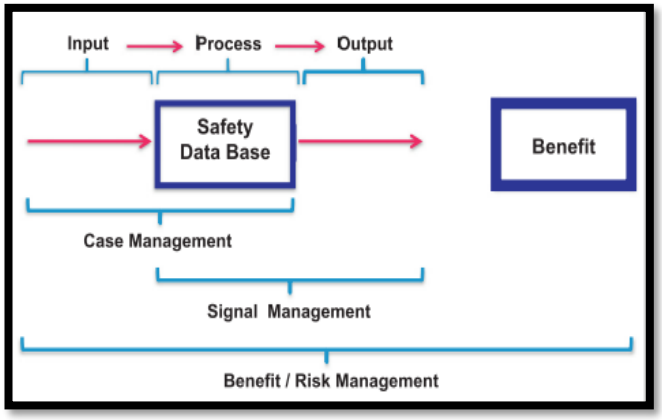


Figure 2: Pharmacovigilance: a systems perspective

1.1 Objectives of Pharmacovigilance

Improvement of patient care and safety about the use of medicines with medical and paramedical interventions remains an important parameter. The main objectives of pharmacovigilance involve exhibiting the efficacy of drugs by monitoring their adverse effect profile for many years from the lab to the pharmacy; tracking any drastic effects of drugs improving public health and safety in relation to the use of medicines; encouraging the safe, rational and cost-effective use of drugs; promoting understanding, education and clinical training in pharmacovigilance; and effective communication to the generic public.[12] In addition, providing information to consumers, practitioners and regulators on the effective use of drugs along with designing programs and procedures for collecting and analyzing reports from patients and clinicians conclude to the objectives of pharmacovigilance studies.[12,13]

1.2 Scope of PV

PV is a booming concept which deals with chemical, botanical, and biological medicines including medical devices. [14,15] The information about suspect products is collected from healthcare providers and patients to detect and prevent abnormalities associated with it. Therefore, PV deals with adverse effects of drug, poly-pharmacy, paradoxical reactions, and severe adverse events. It also covers vaccination failure, irrational use, and lack of efficacy, drug interactions, poisoning, overdose, abuse, medication errors and misuse of drug. [16]

2. Criteria for ADR and its Reporting to Regulatory Authority

2.1 What to report?

Following events can be reported to the nearest reporting center or authority. [17] Life-threatening event or death, Hospitalization of the patient, Congenital anomaly, medically significant event (If the event is considered serious by physician), Lack of efficacy connected with the use of a medical device or drug product. All suspected drug interactions. All known or unknown, serious, non-serious, frequent or rare reaction caused due to use of vaccine or drug must be reported.

2.2 When to report?

All spontaneous case should be reported within 10 days. All suspected ADR should be reported as soon as possible because over reporting is always better than under reporting. Death event must be reported as soon as possible, while all other serious ADR/event needs to report within 7 days only. All non-serious cases must be reported within (Tables 1-2) 30 days. Reporting delay may create serious problem.

Table 1: Stakeholders and their functional responsibility

Stakeholder at	Functions
AMC's	ADR collection and reporting to PvPI-NCC
	Follow up check and query resolution
	ADR data feeding into Vigi-flow database
	Training and circulation of feedback to physician
PvPI-NCC	Development of SOPs, guidance document and training manuals
	Causality assessment
	CDSCO reporting
	Analysis of cases
Zonal or Sub-zonal CDSCO Offices	Financial and managerial help to AMC
CDSCO, New Delhi	Make decision and action on recommendation of PvPI NCC along with stakeholder awareness about decision.

Table 2: Example of major induced toxicities, reporting in post-marketing surveillance

Marketing surveillance year	Drug	ADR/AE	Remark
1950	Chroramphenicol	Aplastic anemia	Still continued
1961	Thalidomide	Phocomelia	National disaster
1970	Clioquinol	Sub-acute myelo-optic neuropathy	Detected after 30 years of use
1970	Diethylstilbestrol	Cervix Adenocarcinoma	In utero exposure
1975	Practolol	Oculo-mucocutaneous syndrome	5 years of marketing
1976	Zomepirac	Anaphylaxis	Withdrawn
1978	Phenformin	Lactic acidosis	Withdrawn
1980	Ticrynafen	Deaths from liver Disease	After 5 years
1982	Ticrynafen	Hepatitis	Withdrawn
1990	Etretinate	Birth defect	High risk of birth-defect, narrow safety margin
1999	Astimizole	Arrhythmias	Other drugs interaction
2004	Rofecoxib	Myocardial infarction	Withdrawn
2010	Rosiglitazone	Heart attacks	Withdrawn in Europe
2011	Drotrecoginalfa	Prowess-shock study	Withdrawn by Lily
2012	Rimonabant	Depress mood, suicidal tendencies and convulsions	Withdrawn
2012	Sibutramine	Cardiac side effects	Banned

2.3 Who can report?

Professionals working in a healthcare team are the preferred source of information in PV, for example medical specialists, Pharmacists, Dentists, Midwives Along with HCPs patient, patient's relatives, witness or any common person after medical confirmation can report. [18–21]

2.4 How to report?

Duly filled [22] ADR reporting form needs to send to the nearest AMC or directly to the NCC. Dial toll free helpline number-1800 180 3024 to report ADRs. Mailing the filled ADR reporting form directly to pvpi@ipcindia. net or pvpi.ipcindia@gmail.com. Logging on to the http://www.ipc.gov.in, http://www.ipc.gov.in/ PvPI/pv_home.html for list of authorized AMCs of India.

2.5 Where to report?

Various Peripheral, Regional and Zonal centres have been proposed and established in India. [18]

i. **Peripheral PV center:** It is a primary ADR information gathering center. It includes small medical centres, private hospitals, dispensaries, nursing home and pharmacies. ADRs are recognized and synchronized by RPCs or ZPCs. Every state, Union territory and few leading medical colleges in India have this peripheral center.

ii. **Regional PV center:** It's regarded as secondary PV Centre. It is located in medical college having relatively larger facilities. They are identified and coordinated by zonal centres. There are five such regional centres in India.

iii. **Zonal PV centres:** It's regarded as Tertiary PV Centre. Generally located in metro city's medical college having attachment of sufficient facility. It is identified by CDSCO and act as first ADR data collection center. Zonal center for North and East zone is AIIMS.

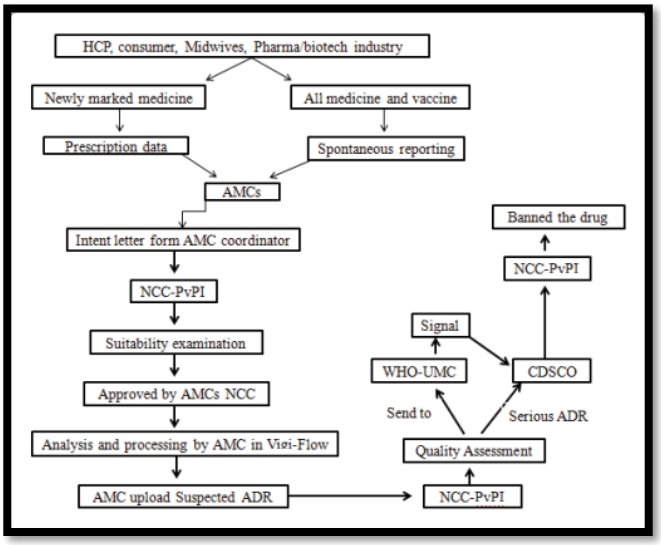


Figure 3: Workflow for PV activity

3. Pharmacovigilance Programme of India (PvPI)

The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in association with Indian Pharmacopeia commission, Ghaziabad is initiating a nation-wide Pharmacovigilance Programme for protecting the health of the patients by promising drug safety. The Programme shall be coordinated by the Indian Pharmacopeia commission, Ghaziabad as a National Coordinating Centre (NCC). The center will operate under the supervision of a Steering Committee. The Pharmacovigilance Programme of India (PvPI) was started by the Government of India on 14th July 2010 with the All-India Institute of Medical Sciences (AIIMS), New Delhi as the National Coordination Centre for monitoring Adverse Drug Reactions (ADRs) in

the country for safe-guarding Public Health. In the year 2010. [23] ADR monitoring centers including AIIMS, New Delhi was set up under this Programme. To safeguard implementation of this programme in a more effective way, the National Coordination Centre was shifted from the All-India Institute of Medical Sciences (AIIMS), New Delhi to the Indian Pharmacopoeia Commission, Ghaziabad, Uttar Pradesh on 15th April 2011.[24]

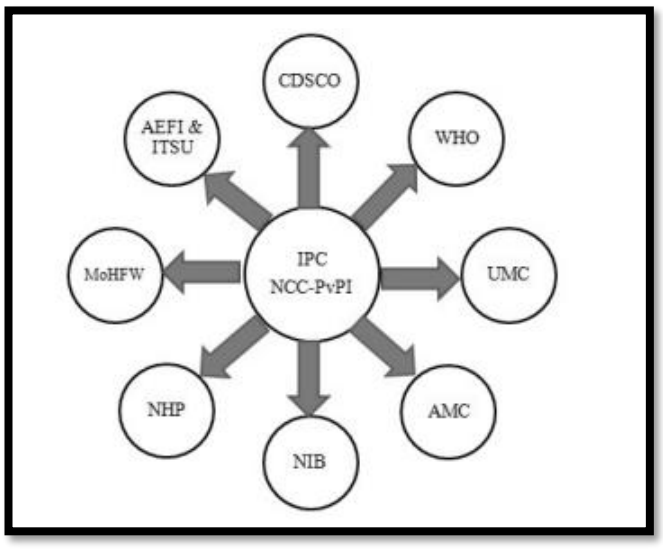


Figure 4: Various authorities with NCC-PvPI

3.1 Chronological Development of PV

- **1747:** James Ling reported clinical trial showing effectiveness of lemon juice in prevention of scurvy.
- **1937:** Sulphanilamide disaster, where sulphonamide was dissolved in diethyleneglycol leading to death of more than 100 people because of renal failure.
- **1938:** The preclinical toxicity and pre-marketing clinical studies made mandatory by FDA.
- **1950s:** Aplastic anaemia caused due to use of chloramphenicol.
- **1960:** The FDA started hospital-based drug monitoring program.
- **1961:** Thalidomide disaster.
- **1963:** 16th world health assembly recognized importance to rapid action on ADR.
- **1968:** Establishment of International Drug Monitoring Program by WHO.
- **1970s:** Clioquinol was found to be linked with Sub-acute-myelooptic neuropathy.
- **1980s and 1990s:** Many drugs with serious adverse effects were recorded.
- **1996:** India started global standard clinical trial.
- **1997:** India joined ADR Monitoring Program.
- **1998:** PV activity initiated in India.
- **2002:** 67th National Pharmacovigilance Centre established in India.
- **2005:** India started conducting structured clinical trials.
- **2009-2010:** PV plan of India was initiated and implemented.

3.2 Three main tasks in the field of pharmacovigilance.

i. **Drug–event pair extraction:** For this task, we usually use either structured data from EHRs [25,26] or the natural language processing (NLP)-based machine learning/ deep learning (ML/DL) method to extract drug–event co-occurrence pairs from the unstructured texts. [27–29] Note that those pairs only indicate a potential associative "relationship" between the drug and the event and cannot be considered a "confirmed" ADE yet. The symptoms experienced might be caused by a variety of medical conditions other than the ADE. Thus, we still need further proof using other statistical analyses or data sources.

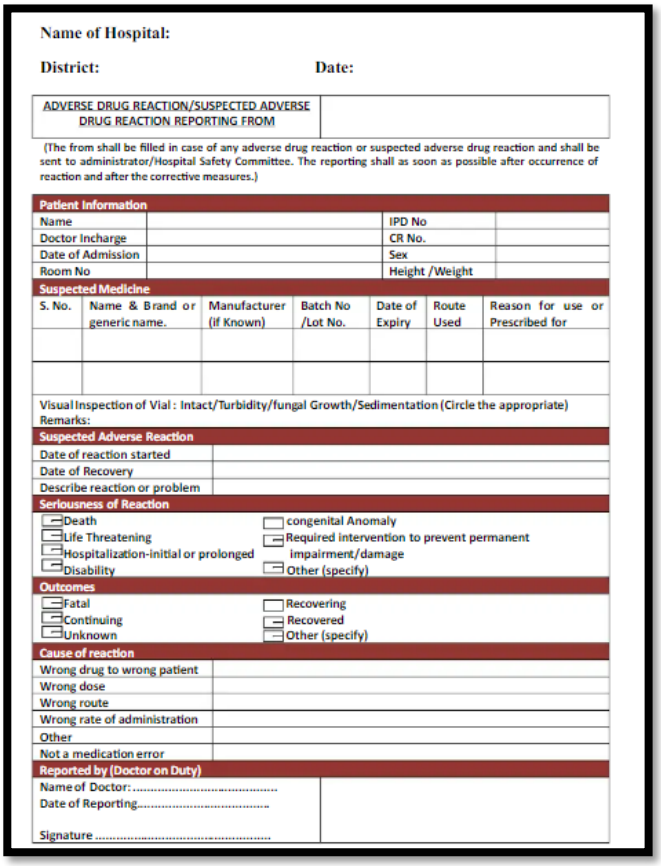
ii. **Adverse drug event detection:** For traditional pharmacovigilance, the most important task is to detect ADEs for these post-marketing drugs in time. The ADE detection task aims to identify and confirm ADEs from "real world" medication usage information as early as possible. We consider ADE detection as a task providing a higher-level associative relationship compared with disproportionality or NLP-based drug–event co-occurrence pair extraction. However, ADE detection is only associative without further

confirmation if using SRS owing to the limitation of the data source (no control group can be matched, and no causality evaluation can be performed). Adverse drug event detection using an RWD database, however, can be evaluated for causality if a proper study design was adopted.

iii. **Adverse drug event prediction:** Adverse drug event prediction, or ADE discovery, could be conducted only if the event data have accumulated to a certain amount. Thus, there was a time difference from drug launch to ADE prediction. Adverse drug event prediction focuses on discovering potential ADEs before being observed. The predictive power (forecast future events from data generated previously) of many ML/DL models made ADE prediction possible. Using literature and knowledge bases, researchers can predict ADEs at the premarketing stage. After launching and as more data accumulate, researchers can use RWD and social media data for post-marketing pharmacovigilance. While ADE prediction may not only depend on causal relationships, establishing causal relationships can facilitate feature selection and greatly improve model performance and generalizability. [30–34]

3.3 Adverse Drug Reactions Reporting Forms

For the convenience of Indian citizens, NCC-PvPI has launched ADR reporting forms that are posted on the website of IPC. [35] If the forms are received directly at the NCC, they are first sent to the nearby AMC where the PV associate gets in touch with the person who has reported the AEs. The PV associate then takes sufficient information from the patient and then after filling the necessary information sends the report back to NCC as ICSRs. These forms are also available in the National Formulary of India, on the website of CDSCO and as hard copies at nearby AMCs where local PV associates help the consumer to fill the reporting form and further send it to NCC for review purpose. These forms are available in two different variants. First use of smart phones and mobile applications, health-care services can be made to reach quickly to public. The application "ADR-PvPI" is available on Android platform with plans to expand to iOS soon and can be downloaded on any smart phone supporting Android v5.0 or above[36]. Since the inception of this mobile application in September, 2017, awareness of reporting ADRs is increasing among HCPs.[36]



Name of Hospital:

District: **Date:**

ADVERSE DRUG REACTION/SUSPECTED ADVERSE DRUG REACTION REPORTING FROM

(The from shall be filled in case of any adverse drug reaction or suspected adverse drug reaction and shall be sent to administrator/Hospital Safety Committee. The reporting shall as soon as possible after occurrence of reaction and after the corrective measures.)

Patient Information

Name		IPD No	
Doctor Incharge		CR No.	
Date of Admission		Sex	
Room No		Height /Weight	

Suspected Medicine

S. No.	Name & Brand or generic name.	Manufacturer (if Known)	Batch No /Lot No.	Date of Expiry	Route Used	Reason for use or Prescribed for

Visual Inspection of Vial : Intact/Turbidity/fungal Growth/Sedimentation (Circle the appropriate)
Remarks:

Suspected Adverse Reaction

Date of reaction started	
Date of Recovery	
Describe reaction or problem	

Seriousness of Reaction

☐ Death ☐ congenital Anomaly
☐ Life Threatening ☐ Required intervention to prevent permanent impairment/damage
☐ Hospitalization-initial or prolonged ☐ Other (specify)
☐ Disability

Outcomes

☐ Fatal ☐ Recovering
☐ Continuing ☐ Recovered
☐ Unknown ☐ Other (specify)

Cause of reaction

Wrong drug to wrong patient	
Wrong dose	
Wrong route	
Wrong rate of administration	
Other	
Not a medication error	

Reported by (Doctor on Duty)

Name of Doctor: .....
Date of Reporting.....

Signature .....

Figure 5: ADR reporting form

3.4 Applications in Pharmacovigilance

As drug safety and pharmacovigilance organizations develop more sophisticated data analytics capabilities, they are starting to move from basic descriptive analysis towards predictive analysis and the development of predictive models. Predictive analytics uses existing information to make predictions of future outcomes or future trends in all areas of Medicine and Health Care. [37] The importance of being one step ahead of (adverse) events is most clearly seen in the framework of signal detection, and of the

identification and characterization of individuals with a specific risk for developing an adverse event after the exposure to a medicine, both in clinical development [38,39] and in post-marketing settings. [40]

i. Identification of risks from spontaneous reports

Predictive modeling can be used for the identification of previously unrecognized risks of medicines in pharmacovigilance reports. A nice example of this use is VigiRank, a data-driven predictive model for emerging safety signals, which has been shown to outperform disproportionality analysis alone in real world pharmacovigilance signal detection. [41] VigiRank is to be applied in VigiBase, in which predictive models have been proven useful to detect safety signals that were eventually validated, in pediatric populations. [42]

ii. Evaluation of unexpected increase in reporting frequency

Similarly, the European Medicines Agency developed an algorithm to detect unexpected increases in frequencies of reports, in particular quality defects, medication errors, and cases of abuse or misuse. The algorithm applied to the EudraVigilance database showed encouraging results. [43]

iii. Risk prediction of adverse experiences after exposure to a drug

Predictive models have been also used to predict the relationship between exposure to an investigational medicinal product and the risk of adverse events. For example, Niebecker [44] characterized the relationship between exposure to afatinib and diarrhea and rash/acne adverse event trajectories, with the final goal of developing a modeling framework to allow prospective comparison of dosing strategies and study designs with respect to safety. In another other example, predictive models have been used for the prediction of adverse reactions after administration of rituximab in patients with hematologic malignancies. [45]

iv. Predictive models in clinical development and post market signal detection

The combination of different predictive modeling techniques like random forest, L1 regularized logistic regression, support vector machine, and neural models were successfully applied to detect signals arising from laboratory-event-related adverse drug reactions. The authors combined features from each of the modeling techniques into a machine learning model. The application of this model to an electronic health record environment was considered satisfactory for signal detection purposes.[46] Supervised machine learning signal detection methods have been tested for the identification of adverse drug reactions. In the world of medication dispensing data, sequence symmetry analysis (SSA) has been used to detect signals of adverse drug reactions. This precise study shows how a gradient boost classifier complements well SSA.[47]

v. Specific subpopulations like hospitalized patients

Predictive analysis and model development shows interesting uses in the evaluation of risks as in this case, where the authors used mathematical models to determine the probability of adverse drug experiences in the surgical setting at the time of hospital admission, identifying the patients that are at a higher risk of an adverse drug experience during the hospital stay[46]. In another study focused on drug safety in hospitals, the authors perform a systematic review of predictive risk models for adverse drug events during hospitalization.[48]

vi. Prediction of hepatotoxicity and interactions

To predict drug-induced hepatotoxicity based on gene expression and toxicology data, by means of a multi-dose computational model.[49] Use of predictive models for the

prediction of adverse drug reactions induced by drug-drug interactions.[50]

vii. **Predictive models for comparative safety** Leonard CE et al. utilized a Cox proportional hazard model to identify comparative safety differences among 3 sulfonylureas and the risk of sudden cardiac arrest and ventricular arrhythmia.[51]

3.5 Challenges faced in pharmacovigilance

These challenges are listed below:

Reporting of ADR- Reporting is the base for detection of ADR, especially in case of new and undiscovered adverse drug events. Despite all excellence of reporting low reporting is one of the barriers to the development of PV. [52] Data mining should be practiced after keeping the fact of low reporting system of different medicine, also signals thus be assessed while acknowledging the chances of faulty positives. [53] Low-income countries have a low rate of reporting when compared to developed countries. [54]

4. Automation

Automation is a term for technology applications where human input is minimized. This includes business process automation (BPA), IT automation, personal applications such as home automation and more. [55]

Figure 6: Automation

4.1 Types of automation

There are various types of automation that we can use to make ease of our life.

i. **Basic automation:** Basic automation takes simple, rudimentary tasks and automates them. This level of automation is about digitizing work by using tools to streamline and centralize routine tasks, such as using a shared messaging system instead of having information in disconnected silos. Business process management (BPM) and robotic process automation (RPA) are types of basic automation.

ii. **Process automation:** Process automation manages business processes for uniformity and transparency. It is typically handled by dedicated software and business apps. Using process automation can increase productivity and efficiency within your business. It can also deliver new insights into business challenges and suggest solutions. Process mining and workflow automation are types of process automation.

iii. **Integration automation:** Integration automation is where machines can mimic human tasks and repeat the actions once humans define the machine rules. One example is the "digital worker." In recent years, people have defined digital workers as software robots that are trained to work with humans to perform specific tasks. They have a specific set of skills, and they can be "hired" to work on teams.

iv. **Artificial intelligence (AI) automation:** The most complex level of automation is artificial intelligence (AI) automation. The addition of AI means that machines can "learn" and make decisions based on past situations they have encountered and analyzed. For example, in customer service, virtual assistants powered can reduce costs while empowering both customers and human agents, creating an optimal customer service experience. [55]

4.2 Benefits of Automation

a. **Improved Software Quality:** No manual errors. All the tasks have been given the same

priority while execution. This improves accuracy. Besides, automation is written in such a way that it ensures the highest quality standards.

b. Reduced Cost: No employee will waste his/her time waiting for something to get completed. An engineer can work on other tasks while keeping multiple executions running in the background. This improves productivity and in the end the cost.

c. Increase in Return on Investment: Automation may require the initial investment. However, in the end, the significant increase in efficiency and productivity generates a high return on investment. Automation saves you money and time, which translates into a Return on investment.

d. Faster Development and Release: Automation makes things faster. It saves a lot of time in execution. This results in faster development as well as testing and at the end faster delivery to

e. Boosts morale of the Employee: Employee is saved from doing repetitive work. Automation gives an employee a chance to focus on other important work while executing the same task by automation in the background. Moreover, we all know a positive mindset is everything we need. [56]

4.3 Automation in Pharmacovigilance

Automation in pharmacovigilance entails using cognitive technologies such as machine learning (ML) and advanced analytics to transform legacy data compilation processes and information gathering for regulatory approval. The use of new-age technology in PV is modeled around improving practices of a drug's risk-benefit profile assessment, methods sought to select optimal treatments, and increase overall patient safety through product quality. [57]

i. Awareness- Lack of awareness about PV program among the population, pharmacist and other health care professional is the factor that play role in obstructing PV program in developing countries. It is also the main problem in reporting ADR which is the main step for detection of ADR. [58,59]

ii. Financing budget- Low economic countries mostly have a very finite budget for the healthcare system and financing in PV is not the priority of these countries. Low funding is a heartfelt obstruction that developing countries face. [60]

iii. Reporting form- Information about any ADR can be shared in various ways; ADR form is one of the main ways for sharing the information. The ADR form should be well-designed, easy to understand, correct and must contain necessary points about patient information and the suspected ADR. [61] Automation technologies have strong potential to automate routine work and balance resource use across safety risk management and other pharmacovigilance activities. [62] Intelligent automation can contribute to the quality and consistency of case processing and assessment, leading to a timely assessment of safety signals. When such technology solutions are implemented to assist in processing AE cases, regulations require pharmaceutical companies to validate this software. [63] Computerized system validation (CSV) is the process of establishing and documenting that the specified requirements of a computerized system are fulfilled consistently from design until decommissioning of the system and/ or transition to a new system. The approach to validation should focus on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results. [64]

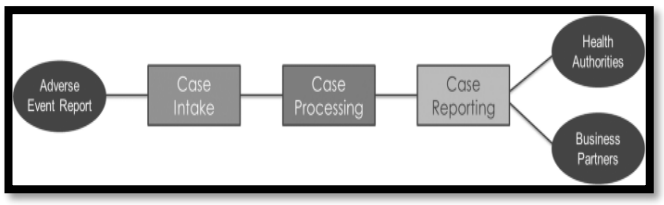


Figure 7: The end-to-end individual case safety report (ICSR) process

4.3.1 Classification of Automation Systems in Pharmacovigilance

i. **Rule-based static systems:** Automation is achieved via static rules designed to obtain the desired outcome. Examples include expedited reporting rule configuration, auto coding, and robotic process automation for case intake.

ii. **AI-based static systems:** System configuration includes components that are AI informed but subsequently "frozen," i.e., systems based on AI or ML that do not adapt in production (after "golive"). These are also called "locked" models. Re-training of the model is not applied automatically and is limited to the occurrence of events/triggers that require modification (e.g., the output needs change, expansion of training data set to improve quality). Examples include an auto-translation system of source documents and a model based on ML for causality assessment of individual case safety reports.

iii. **AI-based dynamic systems:** System configuration includes components that are AI informed and can adjust their behavior based on data after initial implementation in production, using a defined learning process. These are like AI-based static systems but are continually updated once in production, based on a set cadence or trigger, to include new source data. These systems are sometimes referred to as online algorithms. [65,66]

Workflow, Automation, and 21st Century Health Care Delivery: Health care in the 21st century includes a combination of complex tasks1 and processing an ever-expanding amount of data[67–69] Health care delivery involves a series of interconnected clinical, administrative, and population-level workflows, or "the sequence of physical and mental tasks performed by various people within and between work environments,"[70,71] that involve patients, caregivers, clinicians, and staff. "Digitized" paper-based workflows that simply copy how a paper-based workflow is performed have led to an ecosystem that contributes to burnout[71,72] and impedes the full use of technology to optimize patient care through the use of automation.[73,74] Inefficient workflows are a pervasive problem that affect everyone in health care,[75–77] including clinicians facing burnout due to managing care delivery tasks,[78] and patients and caregivers facing complex care management tasks. The increased adoption and use of health information technology (IT)[79,80] and the availability of modern computational technology [81,82] provide new opportunities for more effective and efficient workflows through automation. In particular, automation, or "the creation and application of technology to monitor and control the delivery of products and services," [83] can improve efficiency in health care delivery in the United States across several health care domains as Figure 8 illustrates. Automation integration into daily workflows in health care has not been the same as in other industries.[84,85] Lessons learned from the use of automation in these nonhealthy care industries may offer key insights for health care.[85]As the lead health IT policy agency in the United States, [86] the Office of the National Coordinator for Health Information Technology (ONC) recently led a project to identify priorities that could accelerate healthcare workflow automation through the use of health IT and modern computing.[84] A multistep approach was taken including conducting semi-structured interviews with key automation experts across multiple

industries and analyzing peer-reviewed and gray literature that included sources both within and outside health care.[85]

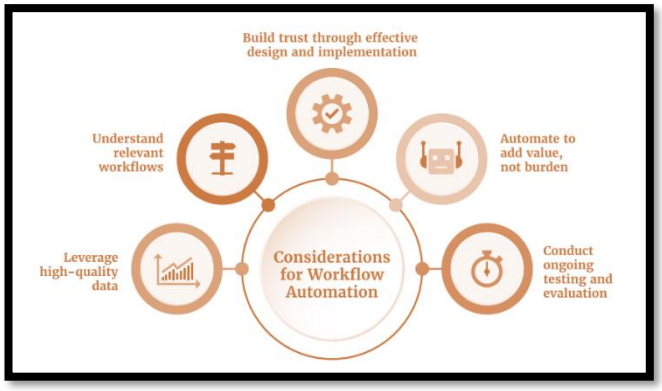


Figure 8: Advancing health care workflow automation

4.3.2 Benefits of Automation in Pharmacovigilance

i. Improved Employee Productivity

While the business case for automation in pharmacovigilance primarily centers around gaining process efficiency, a more significant benefit is the freeing of resources to allocate the same for performing value-added tasks. Monitoring and evaluating adverse drug reactions, real-world evidence analysis, and signal investigation forms the basis of functions executed by resources freed up due to automation in pharmacovigilance. An additional consequence of automating drug safety programs is improved quality assurance, accuracy and consistency in testing cycles, and reduced PV costs.

ii. Case Intake in Pharmacovigilance

Most pharmaceuticals and medical devices organizations spend an overwhelming part of their PV budgets on case processing. Further, to make things complicated, case volumes grow at an incremental rate year on year. Naturally, driving cost out of case processing is often the primary goal for leaders in the pharmaceutical industry. By automation, they can take advantage of scale and generate cost savings per individual case safety report (ICSR). Productivity drivers to this end include native automation and "bolt-on" technologies that reduce the manual effort required to carry out duplicate checks, speed up coding functions, and streamline case writing. Automation also helps in generating proofs of concept across the entire PV value chain. While optimizing functions at the level of ICSR can help pharma companies deal with overall case intake, the aspect of ensuring regulatory requirements and enhancing patient safety is entirely dependent on their ability to automate more and more of their PV activities.

iii. Improvements in Drug's Risk-Benefit Profile

Legacy methods of assessing a drug's risk-benefit profile entail the use of signal detection. Most pharmaceutical companies still use traditional investigative models to track individual reports of adverse events, mine databases, and opportunities for intervention in clinical trials. While some findings may indicate a better safety profile or therapeutic benefit of a drug, others may reveal side effects, making the drug unfavorable. Considering the lack of time to react to adverse events, leaders in the pharma industry are now migrating towards predictive signaling. This calls for short-term investments in dashboards for real-time visualization of clinical trials and a long-term focus on data integration technologies. Automation essentially improves the quality and consistency of data generated during a clinical trial. Safety information can be used far more effectively with reduced gaps in the discovery phase of a drug's risk-benefit profile.

Figure 9: Benefits of Automation in Pharmacovigilance

iv. Faster Hypothesis to Testing Cycles

Automation in PV testing cycles brings forth a significant opportunity to formulate faster hypotheses. A 2018 pilot study conducted by the American Society for Clinical Pharmacology and Therapeutics (ASCPT) takes cognizance of the same. The said study tested the feasibility of using Robotic Process Automation (RPA) and Artificial Intelligence (AI), among other new-age technologies, to automate the processing of adverse event reports. Proposed solutions by three commercial vendors who participated in this pilot study were simultaneously tallied against Pfizer.

v. Cost Savings

As a natural result to improved productivity in pharmacovigilance case intake and optimizing resources allocated in the process flow, pharma companies can save up majorly on costs. To put this into perspective, let us take a look at Birlasoft's very own collaboration with a pharmaceutical major. The client, which has a support staff of 5000 people working round the clock, scanning 400,000 literature abstracts annually to identify potential safety signals, was faced with process inefficiency. Only 50% of the documents were worthy of scanning, and upon analysis, a mere 5-8% reportable adverse events would be cited on an average. Their legacy methodologies required a complete overhaul. With the right automation tools, the pharmaceutical company could reduce its compliance cost and handle a 25% increase in reviewable data volume with its existing set of resources. [57]

5. Conclusion

In this paper, we review the applications of automation in pharmacovigilance. Pharmacovigilance is an important field that is concerned with all types of iatrogenic toxicities and seeks to reduce patient suffering and promote the safe and rational use of drugs by capturing and reporting on issues of drug risks before the risk has been spread too broadly. Automation has been a disruptive healthcare innovation. These findings inform a reconceptualization of compassion as an automation system of intelligent caring comprising several applications.

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