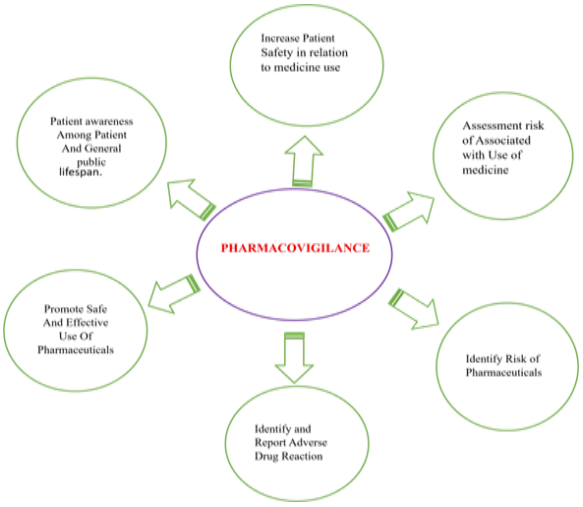
Pharmacovigilance: Digital Era

Pratiksha S. Chende[1], Suhas R. Khandagale[2], Supriya K. Bhagat[3], Dr. Nilesh O. Chachda[4]
[1,2,3,4]*Shri Chhatrapati Shahu Maharaj Shikshan Sanstha Institute of Pharmacy, Maregaon 445303*

***Abstract*—Pharmacovigilance is an important and crucial part of clinical research. Pharmacovigilance is the branch of pharmaceutical research that deals with the detection, assessment, understanding, and avoidance of drug adverse effects, particularly those that are short- and long-term. It is the investigation of the safety of commercially available medications in real world clinical usage scenarios in sizable populations. Pharmacovigilance is an important and vital part of clinical research. Throughout a product's lifecycle, post-marketing pharmacovigilance and clinical trial safety are crucial.**

***Index Terms*—Adverse drug reaction, Clinical trials phases, MedDRA dictionary, Patient safety, SUSAR, SUGAM.**



I. INTRODUCTION

Pharmacovigilance (PV) is a scientific method for evaluating the effectiveness and safety of pharmaceuticals and other medical supplies.[1] Instructions for establishing and maintaining quality-assured pharmacovigilance systems are provided in this Module for the agencies, competent authorities in Member States, and marketing permission holders. Every GVP module describes how the systems of these organizations cooperate to perform pharmacovigilance operations.[2]

Pharmacovigilance employs a range Using techniques to track, identify, and evaluate adverse drug reactions (ADRs) to guarantee the effectiveness and security of medications. Clinical trials, comparative observational research, targeted spontaneous reporting, and passive and active surveillance are some main categories into which these methods can be divided. [3]

I.I. Why Pv Is Important

When a drug is released onto the market and utilized by more people, additional side effects could manifest. Pharmacovigilance is necessary to identify these risks and take remedial measures, such as updating warnings, restricting use, or even stopping the drug.[4]

I.II. Core Activities in Pharmacovigilance

- ADR
- Signal Detection
- Risk Management
- Benefit Risk Management Communication [5]

I.III. Types Of Pv Reports

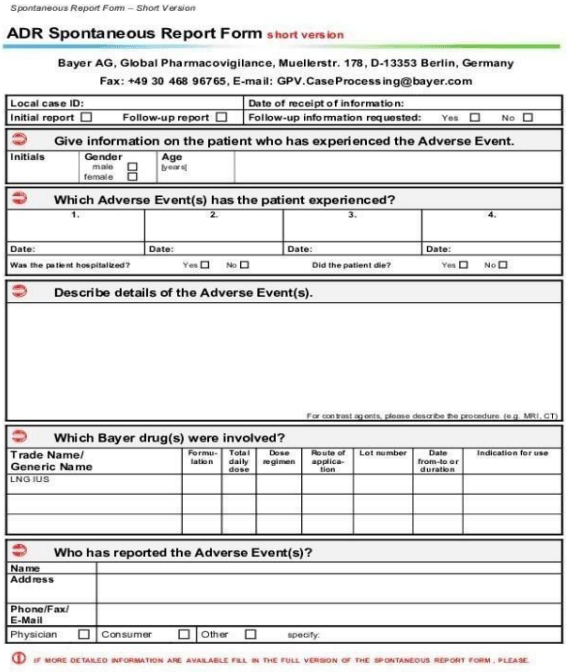
Pharmacovigilance reporting is the crucial process of collecting, evaluating, and transmitting data to regulatory bodies on pharmacological safety concerns, including adverse drug reactions (ADRs), to safeguard the general public's health. [6]

1. Spontaneous Report
2. Periodic Case Safety Reports
3. Individual Case Reports
4. Development Safety Update Reports [7]

I.III I: Spotaneous Report

As a passive method to pharmacovigilance (PV), spontaneous reporting depends solely on people's desire to notify a local or national pharmacovigilance centre about suspected adverse drug reactions (ADRs).[8] Doctors should file such a spontaneous report for adverse drug reactions (ADRs) as part of

their professional code of conduct. Suspicion of an ADR is thought to be sufficient to satisfy this requirement. Still, a sizable portion of physicians do not fulfill this obligation satisfactorily.[9]



Spontaneous Report Form – Short Version

ADR Spontaneous Report Form short version

Bayer AG, Global Pharmacovigilance, Muellerstr. 178, D-13353 Berlin, Germany
Fax: +49 30 468 96765, E-mail: GPV.CaseProcessing@bayer.com

Local case ID:	Date of receipt of information:
Initial report ☐ Follow-up report ☐	Follow-up information requested: Yes ☐ No ☐

Give information on the patient who has experienced the Adverse Event.

Initials	Gender male ☐ female ☐	Age [years]

Which Adverse Event(s) has the patient experienced?

1.	2.	3.	4.
Date:	Date:	Date:	Date:

Was the patient hospitalized? Yes ☐ No ☐ Did the patient die? Yes ☐ No ☐

Describe details of the Adverse Event(s).

For contrast agents, please describe the procedure (e.g. MRI, CT)

Which Bayer drug(s) were involved?

Trade Name/ Generic Name	Formulation	Total daily dose	Dose regimen	Route of application	Lot number	Date from-to or duration	Indication for use
LNG IUS							

Who has reported the Adverse Event(s)?

Name	
Address	
Phone/Fax/ E-Mail	

Physician ☐ Consumer ☐ Other ☐ specify:

IF MORE DETAILED INFORMATION ARE AVAILABLE FILL IN THE FULL VERSION OF THE SPONTANEOUS REPORT FORM , PLEASE.

Fig: Spontaneous Case Report Format

I.III.II: Periodic Case Safety Reports:

To assess a drug's safety profile after licensing, pharmaceutical companies send Periodic Case Safety Reports (PSURs), formerly known as Periodic Safety Update Reports (PSURs), to regulatory bodies at predetermined intervals. These reports examine and analyse all safety data available globally, including adverse drug responses, to find new safety issues and assess if the medication's overall benefit-risk balance is still favourable. Regulatory agencies such as the European Medicines Agency (EMA) CDSCO in India examine these reports to make informed decisions concerning alerts or product changes. [10]

I.III.III: Individual Case Saftey Reports:

In pharmacovigilance, individual case reports, also known as Individual Case Safety Reports, or ICRs, are detailed documents that describe one or more possible negative medication reactions in a single patient at a particular moment.[11] In order to protect public health, monitor and evaluate product safety, and assist regulating organizations like the FDA and EMA in making educated decisions on drug safety, these reports document patient data, the questionable product, the adverse event, and the outcome. [12]

INDIVIDUAL CASE SAFETY REPORT (ICSR) FORM

Allergy Therapeutics PLC

Please send the filled form to the PV department:
E-Mail:
Telephone:

Submit form

Reporter information:

First name | Last name | Title | Occupation/Specialty

Street | Zip code | City | Country

Hospital/Organization Name | Telephone No. | E-Mail address

Patient information:

Initials (first name, last name) | Date of birth | Age at time of event | years | Gender: ○ Female ○ Male | Pregnancy: ○ Yes ○ No

Marketed product (please complete one report for each SIT administration that led to AE):

Marketed product name | Allergen/bacterial composition

Indication for use | Action taken with product: ○ Product withdrawn ○ Dose reduced ○ Dose increased ○ Dose not changed ○ Unknown

Date of administration | Reference number

Event occurred at a dose of: _____ mL/pumps/drops from ○ Vial 0 ○ Vial 1 ○ Vial 2 ○ Vial 3 ○ Vial A ○ Vial B ○ Not applicable

Concomitant medication (please list all medication that the patient receives concomitantly) ☐ Not applicable

Name of concomitant drug	Indication	Dose	Route of administration	Start date	End date
1.					
2.					
3.					

Description and assessment of event(s):

Event(s) in native language	Event(s) in English	Serious (a)	Event start date	Latency period (with unit)	Event duration (with unit)	Event end date	Intensity(b)	Outcome(c)	Causal relationship(d)
1.									
2.									
3.									
4.									
5.									

PVR-02, vX | Appendix I, vY

Fig: Individual Case Saftey Report Format

I.III.IV: Reports on Development Safety Update:

To provide a uniform standard for the regular reporting by the ICH regions on drugs that are still being developed, including marketed drugs undergoing further research, this recommendation suggests creating an update report on development safety (DSUR). The US and the EU. The EU Annual Safety Report and the US IND Annual Report, which currently meets national standards, which satisfies regional standards, are expected to be replaced by the DSUR when it is filed annually, according to regulators. This guideline recommends the structure and content of a DSUR as well as the factors to be considered while creating and submitting it. [13]

I.IV: Process Of Pv

Figure 1. The Pharmacovigilance Scope

- AE Study Reports
- Aggregates Reporting
- Signal Detection
- Risk Management [14]

I.V: Scope Of Pharmacovigilanc

II. CLINICAL TRIALS PHASES

II.I. Introduction

Clinical trials are investigations that identify, diagnose, and treat a range of medical conditions using human subjects. The objective is to create novel medications or novel combinations of well-known medications to treat illnesses in safer and more efficient ways. [15] A clinical trial that investigates a medication or treatment usually consists of four stages: Phases I, II, III, and IV. Every step serves a specific function in evaluating the safety and effectiveness of the treatment. This article examines the ways in which clinical research phases safeguard research subjects and guarantees the successful creation of novel medications and treatments.[16]

II.II. Clinical Trial Phases:

- Phase I: Evaluation of safety
- Phase II: Side effects & efficacy
- Phase III: Effectiveness confirming security and effectiveness
- Phase IV: After-market surveillance [17]

Phase I: Evaluation of safety

The purpose of a Phase I clinical trial is to evaluate the safety, dosage, and adverse effects of a possible novel medication. Additionally, some Phase I trials are first-in- human (FIH). Investigations, which means that no human test of the drug has ever been conducted.[18]

Participant:

- 20-80 Healthy Volunteer [19]
- Objective
- Is it safe to administer the treatment to people?
- Possible adverse effects of treatment
- What happens to the medicine in the body and how much of it is safe to provide in drug studies. [20]

Assess Safety:

By evaluating the drug's possible adverse effects, toxicity, determine the safety profile is the main objective and human tolerance. [21]

Phase II: Efficacy & Side Effect

An investigational treatment can proceed to the second stage of clinical testing after its success in Phase I is established. Phase II's objective is to further examine the experimental treatment's efficacy and safety. [22]

Participant:

Compared the phase 1 these studies normally involve a larger sample of volunteers [often 100–300 patients] who all suffer from the condition that the study therapy is meant to cure.[23]

Objective:

- Is it safe to administer the treatment to people?
- At what dosages can patients safely receive the medication?
- What are effects of treatment, and how can they be controlled?
- The treatment's efficacy.
- The new treatment's safety and efficacy in comparison to current therapies. [24]

Phase III: Effectiveness confirming security and effectiveness:

Finding determine whether the treatment under study is more successful than what is already offered medicines is the goal of a Phase III trial. [25]

Participant:

Phase III trials typically involve 500–3,000 individuals and are conducted compared to Phase 1 and Phase 2, using a larger population sample trial. To administer various dosages and combinations of therapy, these patients are frequently split into random groups. This enables investigators to investigate. [26]

Objective:

- The effectiveness of the treatment in comparison conventional therapies.
- The efficacy of the treatment at various dosages.
- The kind, frequency, and intensity of adverse events linked to novel vs current therapies.
- How the patient's quality of life is impacted by the treatment plan in relation to conventional therapies. [27]

Phase IV: After-Market Survelience

Post-marketing or therapeutic use studies, or phase IV clinical trials, on medications that have previously undergone testing and approval. Investigating uncommon but severe adverse effects that the new medication or treatment induces is the purpose of this research.[28]

Following a treatment's approval for general population usage, these effects may become more common. To detect and treat any severe side effects in participants, it is imperative that researchers conduct continuous medication studies.

The focus of pharmacovigilance in clinical trials is to assess whether the benefits outweigh the risks. When favourable, drug manufacturers then seek approval to market the new drug, ensuring a thorough evaluation process before its introduction. [29] Clinical trials are rigorously watched by researchers and drug makers, who are supported by independent evaluations. Pharmacovigilance, often known as ph. or ph, provides an additional degree of protection for safe products. Providing the best possible treatment to patients around the world is a shared obligation of drug inventors, producers, and researchers. [30]

Participant: More than 3000 volunteer

II.III. Major Components of Pv in Clinical Trials:

Pharmacovigilance is crucial for ensuring the safety of new medicines, learning from past withdrawals due to severe side effects. [31] To make sure that the safety of new medications and learn from previous withdrawals caused by severe side effects, pharmacovigilance is essential. It entails monitoring unfavorable occurrences, recognizing safety issues, and proactively reducing risks. [32] This protects patients by guaranteeing that they have access to safe and efficient medications. There are three primary parts of pharmacovigilance. A pharmacovigilance system's main elements include:

1. data collection,
2. which can be voluntary or nonvoluntary
3. data analysis and reporting. [33]

Objectives:

1. The prevalence and seriousness of uncommon adverse effects in the general population
2. The treatment's safety for patients experiencing odd side effects
3. The treatment's long-term risks and advantages
4. The therapy's benefits and drawbacks at different dosages
5. The treatment's efficacy in a larger population sample size
6. The treatment's benefits and drawbacks when coupled with other therapies [34]

III.PHARMACOVIGILANCE FUNCTION ACROSS MULTIPLE DEPARTMENTS:

III.I. Regulatory Affairs: -

After a drug is approved, it provides real-world data needed for continuing medication safety monitoring, risk management, and regulatory compliance.

- Post Marketing Surveillance
- Risk identification and assessment
- regulatory compliance and reporting
- risk management
- benefit risk management
- public health protection [35]

III.II. Clinical Research: -

Patient safety is ensured by Adverse drug responses (ADRs) should be systematically monitored, detected, evaluated, and prevented. That would have gone undetected in early trials.

- Patient safety
- Adverse event detection
- Risk assessment and mitigation
- Data collection and analysis
- Informing decisions
- Updating information [36]

III.III. Quality Control: -

Drugs are evaluated for post-market safety to ensure their continued efficacy and safety as well as to identify any potential hazards or issues that may have gone unnoticed during clinical trials.

- Post Market Surveillance
- Evidence Based Design Making
- Continuous Improvement
- Collaboration with quality assurance [37]

III.IV. Quality Assurance

Medication safety monitoring after marketing to detect, assess, and prevent adverse drug reactions, ensure products meet safety standards, and safeguard the public.

- On going safety monitoring
- Risk identification and management
- Maintaining public trust [38]

III.V. Production

From clinical trials conducted before a medicine is put on the market to post-market use, it regularly assesses the drug's safety.

- Continuous safety monitoring
- Identification of unknown risks
- Risk benefit assessment
- Quality assurance
- Lifecycle management [39]

IV.DIFFERENCE BETWEEN ADR & AE

ADR	AE
Causality confirmed link to the drug	May or may not be related to drug
DOSE RELATED? Occurs at normal doses	DOSE RELATED? Can occurs at any time
Ex: Rash from penicillin, Sedation by antihistamine	Ex: fever during treatment,Accident by sedation caused due to an antihistamine
Causal link is required	No causal relationship is needed
It is a drug reaction	It is an event

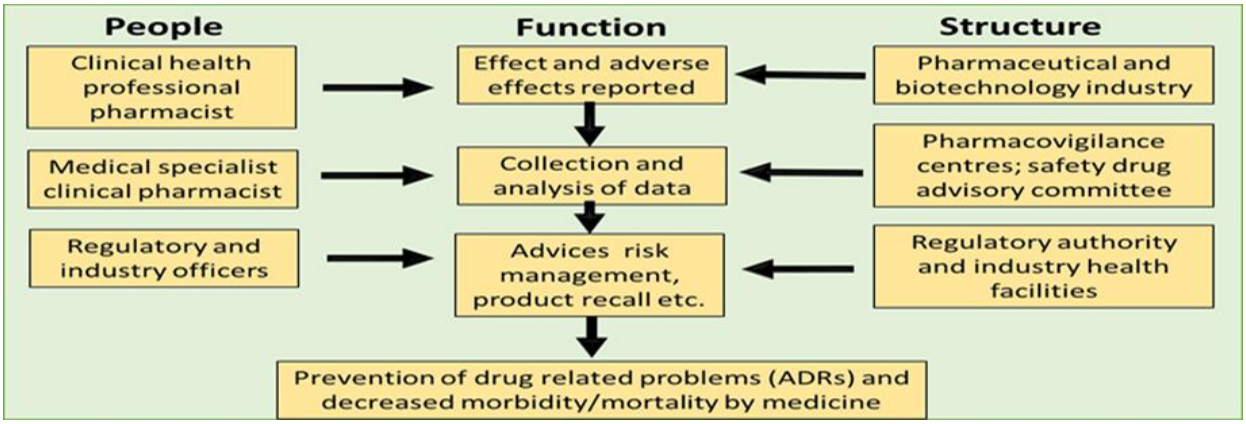


Fig: Role Of Professionals And Their Functions

V: REGULATORY AUTHORITIES INVOLVED IN PHARMACOVIGILANCE

Public health protection is the aim of the three main regulatory agencies: the Central Drug Standard Control Organization (CDSCO) of India, the European Medicines Agency (EMA), and the US Food and Drug Administration (US FDA). [40]

V.I: The USFDA

The US FDA was established in 1906 to regulate the safety of food, drugs, biologics, medical equipment, and cosmetics. Clinical trials, IND applications, new drug, and biologics license applications, etc. are all supervised by the USFDA. The FDA Adverse Event Reporting System (FAERS) is maintained by the FDA through post- marketing surveillance. and upholds

strict guidelines and priority review processes. The FDA Adverse Event the FDA's Adverse Event Reporting System (FAERS) is a database that contains adverse event reports, product quality problems, and medication errors. It provides a post-marketing safety surveillance program for all drugs and biologics following marketing clearance. Terms from the Medical Dictionary for Regulatory Activities (MedDRA) are used by FAERS. and complies with worldwide safety reporting guidelines. [41]

V.II. EMA (European Medicines Agency):

It was established in 1995. It works together with every individual. condition of the European Union. It follows the mutual recognition, decentralized, and centralized processes. Additionally, it supports conditional marketing permission for medications that save lives. To standardize laws among EU countries, it is up to specific bodies like [42]

V.III: CDSCO (The Central Drugs Standard Control Organization):

The CDSCO is governed by the Ministry of Health and Family Welfare, and it is India's national regulatory body. In India, it supervises the control of biologics, medical devices, and pharmaceuticals. The CDSCO, India's primary regulatory body, is managed by the Ministry of Family and Health.[43] Investigational New Drug (IND) applications, clinical trial approval It is responsible for subject expert committee (SEC) evaluation, new medicine approval, and other matters. In times of necessity, the organization expedites the approval of necessary
pharmaceuticals, collaborates with state regulatory bodies, and adheres with the Rules of 1945 and the 1940 Drugs and Cosmetics Act.[44]

V.IV. PMDA (Medical Devices and Pharmaceuticals Agency of Japan):

To address the unique difficulties of approving and overseeing regenerative medical products which are made from living cells and tissues the PMDA has put in place procedures and improved reviewer competence. [45]

To authorize medical items for sale in Japan, the PMDA carries out scientific evaluations to make sure they adhere to safety, efficacy, and quality criteria. [46] After medical products are put on the market, the agency keeps an eye out for any safety concerns.[47]

V.V. The MHRA

The United Kingdom's Medicines and Healthcare Products Regulatory Agency. [48] The United Kingdom government agency to oversees the control of drugs, medical supplies, and blood components used in transfusions to protect public health. As the Department of Health and Social Care executive agency, which permits marketing of products, ensures their safety and effectiveness, and supports innovation in healthcare through research and development. [49] It participates in scientific research and development to advance medical knowledge and patient responses to treatments.[50]

MedDRA [Medical Dictionary for Regulatory Activities]:

- MedDRA the foreign Council for Alignment (ICH) created a standardized medical language that guarantees uniform, comparable, and understandable reporting of adverse event data across international jurisdictions, including academic and pharmaceutical corporations.[51]
- The five levels of the hierarchical MedDRA framework each give varying degrees of detail.
- The highest level is the System Organ Class (SOC)., groups adverse events into disease categories or body systems.[52]
- The term with the lowest level (LLT), which offers most precise information, is the minimum level. Preferred High-Level Group Terms (HLGT), High-Level Terms (HLT), and Terms (PT)
- are intermediate levels that enable more precise classification and grouping.[53]
- Every two years, MedDRA is updated to reflect new advancements in medicine and to advance medication safety. Adverse drug reactions (ADRs) can be reported worldwide using standard medical terminology according to MedDRA, and its standardized vocabulary makes it easier to record ADRs consistently across a range of platforms, including post-marketing surveillance and clinical trials. Using consistent terminology, it facilitates efficient communication between pharmaceutical companies, regulatory agencies, and healthcare professionals. Standardized coding aids in signal detection. MedDRA is used by regulatory bodies

including the FDA, EMA, and CDSCO for pharmacovigilance.[54]

- To streamline the drug approval process, pharmaceutical companies record adverse drug reactions (ADRs) during clinical trials that adhere to MedDRA. For uses other than clinical trials, periodic safety update reports (PSURs), ICSR, and ADRs safety summaries, and MedDRA are useful. Accurate coding, which is necessary for signal integrity, requires a thorough comprehension of MedDRA nomenclature.[55] detection shown in Following table

Table 1: Regulatory agencies of different countries and their means of reporting [34 – 40]

Sl No	Name of the Form	Country	Regulatory authority
1	Suspected Adverse Drug Reaction Reporting Form	India	PvPI, CDSCO
2	MedWatch Form FDA 3500	USA	US FDA
3	Yellow Card Scheme	United Kingdom (UK)	MHRA (Medicines and Healthcare Products Regulatory Agency
4	Canada Vigilance ADR Form	Canada	Health Canada
5	Adverse Drug Reaction Reporting Form (Blue Card)	Australia	Therapeutic Goods Administration
6	EUDRA (European Union Drug Regulatory Authoritis) Vigilance ICSR Form	European Union (EU)	European Medicines Agency (EMA)
7	ADR Reporting Form (Japanese PMDA)	Japan	Pharmaceuticals and Medical Devices Agency (PMDA)

Table: Regulatory bodies across nations and how they report

VI: REPORT ON PERIODIC SAFETY UPDATES (PSUR)

After a pharmaceutical product is approved, its risk-benefit ratio is assessed using a pharmacovigilance document known as a Periodic Safety Update PSUR Report [56] A PSUR's primary goal is to offer a thorough and critical evaluation of the authorized pharmaceutical product's safety and efficacy data, considering any new or developing safety data in light of the body of knowledge regarding risks and benefits.[57] In order to for pharmaceutical products to continue to be safe and effective, this report is crucial. Marketing authorization holders (MAHs) are required to submit PSURs for their approved products to regulatory bodies like the European Medicines Agency (EMA) and the United Kingdom Medicines & Healthcare Products Regulatory Agency (UK MHRA). [58]

VII: (DSUR)DEVELOPMENT SAFETY UPDATE REPORT

This guideline's recommended Development Safety Update Report (DSUR) is intended to serve as the benchmark for the ICH regions' regular reporting on pharmaceuticals that are still in development, including marketed medications that are undergoing further investigation. The DSUR, which is submitted annually, is seen by US and EU regulators as a potential replacement for the EU Annual Safety Report and the current US IND Annual Report. because it would satisfy national and regional standards, respectively. One This guideline outlines the elements that should be considered while preparing and submitting a DSUR, as well as the suggested format and content.A DSUR should be brief and include details that reassure authorities that sponsors are keeping a careful eye on and assessing the experimental medicine's changing safety profile. The DSUR text should cover all safety issues found during the reporting period, but it should not be used to explain how new safety issues are found or to inform people of important new safety information. Data and findings from interventional clinical trials are the focus of the DSUR. (henceforth referred to as “clinical trials") of biologicals and medications that are being studied, regardless of whether they have received marketing permission. A drug's clinical development often continues after it is approved for sale, therefore the DSUR should also include pertinent data from post- marketing trials. Information about comparators should only be included where it is pertinent to trial participants' safety; if not, the DSUR should focus mostly on investigational medication.

VII.I. Dsur Connect with Psur:

Currently, a few ICH nations and areas permit the submission of a Periodic Safety Update Report (PSUR) to meet national and regional requirements for routine reporting on the security of authorized medications. Despite the DSUR's emphasis on experimental medications, some repetition is to be expected and there may be content overlap between the DSUR and PSUR. Information from marketing experience, for instance, which is recorded in the PSUR, may be pertinent to clinical development and, as such, be reported in the DSUR. While safety results from clinical trials involving marketed medications would be reported in the PSUR and included in the DSUR, they would also be relevant to post marketing safety. Because they cover distinct topics and have different periodicals and recipients, the DSUR and PSUR should both be thorough and independent.

VIII: CASE REPORT

Since McBride's report on thalidomide's hazards, case series have frequently been used as a technique to monitor the effectiveness and security of medications.[59] The majority of the medication market withdrawals throughout history have been based on case series, which are also a fundamental component of drug safety surveillance.[60] However, individual instances and data from case reports or case series no l The initial step in learning new scientific information is frequently the reporting of particular incidents.[61] longer constitute a significant source of data for the evaluation of treatment effectiveness ss due to the advent of procedures that provide greater evidence levels, including randomized clinical trials.[62] Orphan medications may be an exception, as the extremely limit ed patient population does not usually permit the application of quantitative research techniques.[63]

VIII.I: Case Report Format

The study design, The standardized information matrix that contained Each case series' features were determined by the kind of adverse effect (International Classification of Diseases, 10th edition [ICD-10] codes)., the country, the type of data source, the source population, the primary suspected drug, the number of patients in the case series, the duration of follow-up for observational cohort studies, and the patient recruitment period.[64]

IX: SUSAR

Serious adverse events that have a plausible probability of being brought on by the experimental medication are known as Suspected Unexpected Serious Adverse Reactions (SUARs).[65] "Unexpected" describes an adverse reaction whose type or intensity does not correspond with the pertinent product information, such as an A product description for an authorized product or an investigator's brochure for an unapproved exploratory product. [66]. A SUSAR that is deemed life-threatening and/or results in death within seven calendar days must be reported. Within fifteen calendar days, a SUSAR that is not deadly or potentially fatal must be submitted to the regulatory authorities.[67]

IX.I. Significance of Susar

- Patient Safety: To guarantee clinical trial participants' safety, SUSARs must be reported and tracked. They assist in locating any dangers connected to novel medications that might not have been apparent in their initial stages of creation.
- Compliance with Regulations: To support continuous safety evaluations, regulatory bodies demand that SUSARs be reported on time. If these reactions are not reported, future clinical trials may be compromised and regulatory penalties may result.
- Data Integrity: Proper documentation and reporting of SUSARs helps to guarantee the accuracy of data from clinical trials, which helps sponsors and regulatory agencies decide whether to continue or alter studies.[68]

X. SUGAM

The CDSCO (Central Drugs Standard Control Organization) of India established online regulatory compliance interface known as SUGAM.[69] Under the Drugs and the purpose of the Cosmetics Act is to expedite the approval procedures for medications, clinical studies, and cosmetics.[70] SUGAM facilitates a clear, effective, and user-friendly process

for regulatory applications and approvals, making it an essential digital platform for researchers, pharmaceutical companies, and other stakeholders. The Sanskrit term SUGAM means "easy to approach."[71]

X.1: Importance Of Sugam

- Improved Transparency & Accountability: Ensures equitable practices by substituting a digital, trackable process for manual documentation.
- Enhanced Efficiency: Makes it easier to submit, review, and decide on medications, cosmetics, and medical devices.
- Better Accessibility: Offers applicants a single-window, easy-to-use interface to monitor their progress and access rights.
- Simplified Regulatory Compliance: Makes it simpler for importers, manufacturers, and other stakeholders to follow the rules.
- Facilitates Industry Growth: Encourages quicker clearance procedures, cutting down on delays and assisting in the expansion of the pharmaceutical industry in India.[72]

XI: WORK OF YELLOW CARD IN PHARMACOVIGILANCE

- For potential adverse medication reactions, the YCS acts as a proactive detective system by collecting information and suggestions from top pharmacists, medical professionals, and the public. Since its inception, Yellow Card reporting has been essential in detecting several critical safety concerns, such as:
- Drug side effects and adverse reactions.
- Injuries or risks of injuries resulting from medical devices are known as adverse events.
- Pharmaceutical defects and problems with quality suspected fake medications or medical equipment the safety of a medication or equipment may be impacted by unclear usage instructions or issues with markings and labelling.[73]

XI.I: Importance of Yellow Card In Pv

- Improving Drug Safety: The Yellow Card Scheme's main contribution is its capacity to improve drug safety. Through a centralized method for reporting adverse drug reactions, the program assists in identifying any safety issues that might not have been apparent during clinical trials.
- Informing Regulatory Actions: The MHRA examines reports that are submitted to the Yellow Card Scheme. The government may take regulatory action, such as revising the medicine's safety information, limiting its use, or, in the worst situations, removing the drug from the market, if a pattern of adverse responses is found.
- Encouraging Patient Involvement: By providing a direct avenue for patients to report their experiences with drugs, the Yellow Card Scheme empowers them.[74]

XII. CAREER IN PHARMACOVIGILANCE

They work and show their responsibility as an:

1. Pharmacovigilance Officer:Focuses on signal detection and risk management.[75]
2. PV Scientist: Conducts safety assessments and ensures compliance with global regulatory standards.
3. Manager/Senior Roles: Supervises pharmacovigilance operations and works with regulatory agencies.
4. Medical Writer Risk Management Specialist: Develops strategies to mitigate risks associated with drug use.[76]
5. Specializes in writing documents related to pharmacovigilance.[77]

XII.I. Opportunities in Pharmacovigilance

- Officer of pharmacovigilance
- entry-level jobs that concentrate on processing cases and reporting bad events.
- Scientist of pharmacovigilance
- Mid-level positions requiring signal identification, risk management, and regulatory reporting are held by pharmacovigilance scientists.
- Reviewer of medicine
- examining and evaluating adverse event reports' medical components.
- Team lead of pharmacovigilance
- overseeing teams, ensuring compliance with regulations, and managing pharmacovigilance operations.[78]

In the future, pharmacovigilance will be one of the most crucial areas of safety monitoring and medication development.[79]

XIII: SOME OF THE TOP PHARMACEUTICAL COMPANIES THAT EMPLOYE PHARMACOVIGILANCE ARE AS FOLLOWS

- Lupin
- Cipla
- Piramal
- Sun pharmaceuticals
- Pfizer
- Dr Reddys Laboratories
- Mylan Pharmaceuticals
- Johnson & Johnson
- Merck and co. [81]

XIV. AI IN PHARMACOVIGILANCE

The quantity of reports of suspected adverse events (AEs) in the PV database is currently rising dramatically. Important parties, including as regulatory agencies, pharmaceutical firms, medical professionals, and PV specialists, and managers of National

Pharmacovigilance Programs, face difficulties in processing the wide range and quantity of data sources, putting it to good use, and sorting "needles from haystack." ICSR case processing often requires crucial components, including patient and reporter information, adverse reaction data, suspected and concurrent drug information, and outcome.[82]

XIV.I Importance of Ai in Pv

XIV.I.I: Regulatory:

AI has been initiated and utilized in different areas of PV, but it lacks the maturity for widespread implementation. The COVID-19 pandemic illustrated the necessity of an agile, swift approach as new drugs were expedited through the FDA's newly established regulatory routes. Prior to the pandemic, the FDA published a 5-year plan aimed at incorporating AI into the existing PV framework.

XIV.I.II: Clinically:

A drug needs about 10 to 12 years to gain approval and enter the market, which includes a clinical trial period of 5 to 6 years. Some processes involved in clinical trials, like patient recruitment and site selection, are lengthy and can result in trial failure for various reasons.[83]

XIV.II: Impact Statements of Ai in Pv

- Through advanced data processing, artificial intelligence (AI) is improving pharmacovigilance by automating the identification of adverse drug reactions (ADRs), enhancing signal identification, and facilitating real-time risk assessments.[84]
- Unlike traditional approaches, AI models can reveal concealed patterns in pharmacovigilance datasets, which facilitates earlier signal detection and accelerates safety interventions.[85]
- Even with their potential, AI tools encounter difficulties concerning data quality, regulatory acceptance, and algorithm transparency. This underscores the necessity for thorough validation and outputs that can be easily understood.[86]
- To bridge the gap between the potential of AI and routine pharmacovigilance practice, it is essential to establish standardized frameworks, ensure regulatory alignment, and foster trust in automated decision support systems.[87]

17. Figure: Challenges in Pharmacovigilance

XV. CONCLUSION

The many facets of pharmacovigilance were examined in this review,

including the significance of risk management, the function of medical professionals, the changing technology environment, and the effects of pharmacogenomics. With an emphasis

on strengthening international cooperation, we also looked at the present issues, like underreporting, and the methods to enhance ADR reporting systems.[89]

Globally, pharmacovigilance is a component of healthcare systems. The WHO provides technical support for ADR reporting and supervises pharmacovigilance initiatives. Even though many countries have established pharmacovigilance systems, the actual rate of adverse drug reactions (ADRs) is much higher than what is reported. Both the quality of reports and the underreporting of ADRs are significant issues. Pharmacovigilance's primary goals are patient safety, safe medication usage and, the preservation of public health. The public and medical professionals should be encouraged to report more by national authorities and international organizations. AD to accomplish this aim.[90]

REFERENCES

[1] Benninger, P., 2018. Pharmacovigilance: an overview. Clinical therapeutics, 40(12),pp.1991- 2004.

[2] World Health Organization, 2021. Global patient safety action plan 2021-2030: towards eliminating avoidable harm in health care. World Health Organization.

[3] Brown, E.G., Wood, L. and Wood, S., 1999. The medical dictionary for regulatory activities (MedDRA). Drug safety, 20(2), pp.109-117.

[4] World Health Organization, 2002. The importance of pharmacovigilance. In The importance of pharmacovigilance.

[5] Benninger, P., 2020. Signal management in pharmacovigilance: a review of activities and case studies. Clinical therapeutics, 42(6), pp.1110-1129

[6] Anestina, N., Obiageli, C., Anthony, O., Alade, A., Mustapha, A. and Oluwaferanmi, A., 2025. Ensuring Drug Safety: Comprehensive Pharmacovigilance Strategies for Public Health.

[7] Jalali, R.K., 2018. Individual Case Safety Reports. In Pharmaceutical Medicine and Translational Clinical Research (pp. 413-418). Academic Press.

[8] Srba, J., 2014. Pharmacovigilance: Spontaneous reporting systems.

[9] https://www.advarra.com/blog/phases-of-clinical-research-a-detailed-overview/

[10] https://www.ajprd.com/index.php/journal/article/download/1569/1604

[11] Kumar, R., Kumar, P., Kalaiselvan, V., Kaur, I. and Singh, G.N., 2016. Best practices for improving the quality of individual case safety reports in pharmacovigilance. Therapeutic innovation & regulatory science, 50(4), pp.464-471.

[12] eec.eaeunion.org/upload/medialibrary/eb1/EECC-Decision-_-87-Rules-of-Good-Pharmacovigilance-Practice-of-the-Eurasian-Economic-Union.pdf

[13] SAE and SUSAR management services - Arriello

[14] Herz, M., Friesen, G., Jahn, U., Koentges, M., Lindig, S. and Moser, D., 2023. Identify, analyze, and mitigate—Quantification of technical risks in PV power systems. Progress in Photovoltaics: Research and Applications, 31(12), pp.1285-1298.

[15] assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1093177/MHRA_Annual_Report_and_Accounts_2021-22.pdf

[16] Hardys, A., 2021. Phase IV clinical trials (Doctoral dissertation, University of Zagreb. School of Medicine. Department of Internal Medicine).

[17] Vikan, M., Haugen, A.S., Bjørnnes, A.K., Valeberg, B.T., Deilkås, E.C.T. and Danielsen, S.O., 2023. The association between patient safety culture and adverse events–a scoping review. BMC health services research, 23(1), p.300.

[18] Orme, M., Harry, J., Routledge, P. and Hobson, S., 1989. Healthy volunteer studies in Great Britain: the results of a survey into 12 months activity in this field. British journal of clinical pharmacology, 27(2), pp.125-133.

[19] Vandenbroucke, J.P. and Psaty, B.M., 2008. Benefits and risks of drug treatments: how to combine the best evidence on benefits with the best data about adverse effects. Jama, 300(20), pp.2417-2419.

[20] Dorato, M.A. and Engelhardt, J.A., 2005. The no-observed-adverse-effect-level in drug safety evaluations: use, issues, and definition (s). Regulatory toxicology and pharmacology, 42(3), pp.265-274.

[21] Stahlmann, R. and Lode, H., 2000. Safety overview: toxicity, adverse effects, and drug interactions. The quinolones, pp.397-453.

[22] Jain, R.K., Lee, J.J., Hong, D., Markman, M., Gong, J., Naing, A., Wheler, J. and Kurzrock, R., 2010. Phase I oncology studies: evidence that in the era of targeted therapies patients on lower doses do not fare worse. Clinical Cancer Research, 16(4), pp.1289-1297.

[23] Emanuel, E.J., Bedarida, G., Macci, K., Gabler, N.B., Rid, A. and Wendler, D., 2015. Quantifying the risks of non-oncology phase I research in healthy volunteers: meta-analysis of phase I studies. bmj, 350.

[24] Strober, B.E., Crowley, J.J., Yamauchi, P.S., Olds, M. and Williams, D.A., 2011. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. British Journal of Dermatology, 165(3), pp.661-668.

[25] Stahlmann, R. and Lode, H., 2000. Safety overview: toxicity, adverse effects, and drug interactions. The quinolones, pp.397-453.

[26] Holford, N.H., Kimko, H.C., Monteleone, J.P. and Peck, C.C., 2000. Simulation of clinical trials. Annual review of pharmacology and toxicology, 40(1), pp.209-234.

[27] Little, R.J., D'agostino, R., Cohen, M.L., Dickersin, K., Emerson, S.S., Farrar, J.T., Frangakis, C., Hogan, J.W., Molenberghs, G., Murphy, S.A. and Neaton, J.D., 2012. The prevention and treatment of missing data in clinical trials. New England Journal of Medicine, 367(14), pp.1355-1360.

[28] Dickersin, K. and Rennie, D., 2003. Registering clinical trials. Jama, 290(4), pp.516-523.

[29] Pocock, S.J., 2013. Clinical trials: a practical approach. John Wiley & Sons.

[30] Härmark, L. and van Grootheest, A., 2008. Pharmacovigilance: methods, recent developments, and future perspectives. European journal of clinical pharmacology, 64(8), pp.743-752.

[31] Pore, A.V., Bais, S.K. and Kamble, M.M., 2024. Pharmacovigilance in clinical research. International Journal of Pharmacy and Herbal Technology, 2(1), pp.759-775

[32] Santoro, A., Genov, G., Spooner, A., Raine, J. and Arlett, P., 2017. Promoting and protecting public health: how the European Union pharmacovigilance system works. Drug safety, 40(10), pp.855-869.

[33] Day, S., 2007. Dictionary for clinical trials. John Wiley & Sons.

[34] Gorja, A., Reddy, C.D., Sucharitha, K. and Tanmai, S., 2024. INSIGHTS OF REGULATORY AFFAIRS IN THE PHARMACEUTICAL INDUSTRY–A. World, 3(2).

[35] Alqarny, A.A.M., Alqrni, S.M.B., Alqarni, S.A.A., Alshehri, S.A.A., Alshehri, A.S.M., Al Shehri, H.A.A., Al Barqi, S.A.A., Alshehri, M.S., Alshehri, A.T.M. and Al-Shehry, F.A.G., 2024. Adverse Drug Reactions Detection and Management Strategies Overview. Journal of International Crisis and Risk Communication Research, 7(S8), p.2356.

[36] Alghamdi, M.H., Alotaibi, G.M., Almutairi, A.R. and Alharbi, F.F., 2025. Post-Marketing Drug Safety Sources: An Evaluation of the FDA's Drug Safety Communications in the Past 10 Years. Saudi Journal of Clinical Pharmacy, 4(1), pp.3-7.

[37] Burke, S.P., Stratton, K. and Baciu, A. eds., 2007. The future of drug safety: promoting and protecting the health of the public. National Academies Press.

[38] Chen, B.K. and Yang, Y.T., 2013. Post-marketing surveillance of prescription drug safety: past, present, and future. Journal of Legal Medicine, 34(2), pp.193-213.

[39] Makrani, M.F., Goyal, A., and Sayeed, S.Y., 2025. A Comparative Overview of Global Regulatory Authorities: Ensuring Quality, Safety, and Efficacy in Medicines. Int. Res. J. Pharm. Med. Sci, 8(2), p.150.

[40] Vieira, I., Sousa, J.J. and Vitorino, C., 2021. Paediatric medicines–regulatory drivers, restraints, opportunities, and challenges. Journal of Pharmaceutical Sciences, 110(4), pp.1545-1556.

[41] European Medicines Agency (EMA). Pharmacovigilance [Internet]. Amsterdam: EMA; [cited 2025 Mar 29]. Available from:

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance

[42] Collignon, O., Koenig, F., Koch, A., Hemmings, R.J., Pétavy, F., Saint-Raymond, A., Papaluca-Amati, M. and Posch, M., 2018. Adaptive designs in clinical trials: from scientific advice to marketing authorisation to the European Medicine Agency. Trials, 19(1), p.642.

[43] Bhalke, P.D. and Dhewale, S., 2024. DRUG REGULATORY AGENCIES IN INDIA AND USA.

[44] Sharma, A.K., Shrivastava, T.P., Singh, M.A., Ahuja, J., and Goyal, R.K., 2024. Regulations in India. In Global Regulations of Medicinal, Pharmaceutical, and Food Products (pp. 133-152). CRC Press.

[45] Kondo, H., Sugita, T., Ida, N., Fukushima, H. and Yasuda, N., 2017. A comparison of PMDA and EMA consultations for regulatory and scientific matters in drugs and regenerative medicine products. Therapeutic Innovation & Regulatory Science, 51(3), pp.355-359.

[46] Tamura, A. and Matsukawa, K., 2022. Japan: Medical device regulatory system. In Medical Regulatory Affairs (pp. 491-534). Jenny Stanford Publishing.

[47] Friedman, M.A., Woodcock, J., Lumpkin, M.M., Shuren, J.E., Hass, A.E. and Thompson, L.J., 1999. The safety of newly approved medicines: do recent market removals mean there is a problem?. Jama, 281(18), pp.1728-1734.

[48] Richards, N. and Hudson, I., 2016. UK medicines regulation: responding to current challenges. British Journal of Clinical Pharmacology, 82(6), pp.1471-1476.

[49] Collier, J., 2005. New arrangements for the Medicines and Healthcare products Regulatory Agency. BMJ, 330(7497), p.917.

[50] Geissler, J., Ryll, B., di Priolo, S.L. and Uhlenhopp, M., 2017. Improving patient involvement in medicines research and development: a practical roadmap. Therapeutic Innovation & Regulatory Science, 51(5), pp.612-619.

[51] Ojha, A. and Bhargava, S., 2022. International council for harmonisation (ICH) guidelines. In Regulatory affairs in the pharmaceutical industry (pp. 47-74). Academic Press.

[52] Bousquet, C., Lagier, G., Louët, A.L.L., Le Beller, C., Venot, A. and Jaulent, M.C., 2005. Appraisal of the MedDRA conceptual structure for describing and grouping adverse drug reactions. Drug Safety, 28(1), pp.19-34.

[53] Jansen, L.J., 2010. Analysis of land change with parameterised multi-level class sets: exploring the semantic dimension. Wageningen University and Research.

[54] Mozzicato, P., 2009. MedDRA: an overview of the medical dictionary for regulatory activities. Pharmaceutical Medicine, 23(2), pp.65-75.

[55] Brown, E.G., Wood, L. and Wood, S., 1999. The medical dictionary for regulatory activities (MedDRA). Drug safety, 20(2), pp.109-117.

[56] Sharma, R., Kant, K. and Kumar, A., 2020. Overview of Periodic Safety Update Reports: Where Have We Reached? Applied Clinical Research, Clinical Trials and Regulatory Affairs, 7(1), pp.4-11.

[57] Klepper, M.J., 2004. The periodic safety update report as a pharmacovigilance tool. Drug Safety, 27(8), pp.569-578.

[58] Klepper, M.J., 2004. The periodic safety update report as a pharmacovigilance tool. Drug Safety, 27(8), pp.569-578.

[59] Stafford, N., 2018. William McBride: alerted the world to the dangers of thalidomide in fetal development.

[60] Wysowski, D.K. and Swartz, L., 2005. Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002: the importance of reporting suspected reactions. Archives of internal medicine, 165(12), pp.1363-1369.

[61] Vandenbroucke, J.P., 2001. In defense of case reports and case series. Annals of internal medicine, 134(4), pp.330-334.

[62] Braunholtz, D.A., Edwards, S.J. and Lilford, R.J., 2001. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect." Journal of clinical epidemiology, 54(3), pp.217-224.

[63] [63.] Braun, M.M., Farag-El-Massah, S., Xu, K., and Coté, T.R., 2010. Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years.

a. Nature
b. Reviews Drug Discovery, 9(7), pp.519-522.

[64] Arnaiz, J.A., Carné, X., Riba, N., Codina, C., Ribas, J. and Trilla, A., 2001. The use of evidence in pharmacovigilance: case reports as the reference source for drug withdrawals. European journal of clinical pharmacology, 57(1), pp.89-91.

[65] Perez, C., Olivier, P., Lortal, B., Duranton, S., Montastruc, J.L., Colin, A.L., Toulza, E., Becker, M., Hamy, L., Crepin, S. and Roussillon, C., 2018. Detection of drug safety signals from clinical trials data: role of SUSARs. Pharmacological Research, 131, pp.218-223.

[66] Van Puijenbroek, E.P., 2006. Case reports and drug safety. Drug safety, 29(8), pp.643- 645.

[67] Larsen, E.M., Grarup, J., Gey, D.C., Jensen, K.B. and Kirk, O., 2010. Notification of suspected and unexpected serious adverse reactions according to the Clinical Trials Directive—A descriptive analysis of the legislation and the requirements in a European context. Clinical Research and Regulatory Affairs, 27(4), pp.108-120.

[68] Loke, Y.K., Price, D., Derry, S., and Aronson, J.K., 2006. Case reports of suspected adverse drug reactions—systematic literature survey of follow-up. bmj, 332(7537), pp.335-339.

[69] Dole, S.D. and Darade, R.B., Indian Pharmaceutical Regulatory Authority.

[70] Kondal, A., Krishna, G.M. and Bansal, D., 2016. Clinical trial regulations in India: progress and challenges arising from recent amendments to schedule Y of the drugs and cosmetics (D&C) act 1940 (D&C rules 1945). Pharmaceutical Medicine, 30(1), pp.1- 13.

[71] Kondal, A., Krishna, G.M. and Bansal, D., 2016. Clinical trial regulations in India: progress and challenges arising from recent amendments to schedule Y of the drugs and cosmetics (D&C) act 1940 (D&C rules 1945). Pharmaceutical Medicine, 30(1), pp.1- 13.

[72] https://www.freyrsolutions.com/what-is-sugam#:~:text=SUGAM%20is%20an%20online%20e, at%20sales@freyrsolutions.com.

[73] https://cosmosimpactfactor.com/page/journals_details/886.html

[74] Avery, A.J., Anderson, C., Bond, C.M., Fortnum, H., Gifford, A., Hannaford, P.C., Hazell, L., Krska, J., Lee, A.J., Mclernon, D.J. and Murphy, E., 2011. Evaluation of patient reporting of adverse drug reactions to the UK'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. Health Technology Assessment, 15(20), pp.1-234.

[75] O'Donovan, B., Rodgers, R.M., Cox, A.R. and Krska, J., 2019. Making medicines safer: Analysis of patient reports to the UK's Yellow Card Scheme. Expert opinion on drug safety, 18(12), pp.1237-1243.

[76] [76.] Tang, Y., Liu, Y., Liao, H., Yuan, Y. and Jiang, Q., 2023. Current career situations of Chinese pharmacovigilance professionals working for pharmaceutical companies: an exploratory survey. BMC Health Services Research, 23(1), p.152.

[77] Tang, Y., Liu, Y., Liao, H., Yuan, Y. and Jiang, Q., 2023. Current career situations of Chinese pharmacovigilance professionals working for pharmaceutical companies: an exploratory survey. BMC Health Services Research, 23(1), p.152.

[78] Barnes, P., 2003. Careers in Drug Safety and Pharmacovigilance. Careers with the Pharmaceutical Industry, pp.213-222.

[79] Härmark, L. and van Grootheest, A., 2008. Pharmacovigilance: methods, recent developments, and future perspectives. European journal of clinical pharmacology, 64(8), pp.743-752.

[80] Frederick, S., 2025. The Pharmaceutical Global Value Chain: Participation and Opportunities for Latin America and the Caribbean.

[81] Desai, M.K., 2024. Artificial intelligence in pharmacovigilance–Opportunities and challenges. Perspectives in Clinical Research, 15(3), pp.116-121.

[82] Aronson, J.K., 2022. Artificial intelligence in pharmacovigilance: an introduction to terms, concepts, applications, and limitations. Drug safety, 45(5), pp.407-418.

[83] Ahire, Y.S., Patil, J.H., Chordiya, H.N., Deore, R.A. and Bairagi, V.A., 2024. Advanced applications of artificial intelligence in

pharmacovigilance: Current trends and future perspectives. J Pharm Res, 23(1), pp.23-33.

[84] Anthony, O.C., AI Driven Pharmacovigilance Systems for Real-Time Detection of Adverse Drug Events in Multi-Centre Health Networks.

[85] Marwala, T., 2024. Transparency Versus Truth. In The Balancing Problem in the Governance of Artificial Intelligence (pp. 69-85). Singapore: Springer Nature Singapore.

[86] Barbieri, M.A., Battini, V., Carnovale, C., Cocco, M., Papoutsi, D.G., Heckmann, N.S., Dong, G., Rossi, A., Peker, S., Van Manen, R.P. and Thapar, S., 2025. Artificial intelligence in pharmacovigilance signal management: a review of tools, implementations, research, and regulatory landscape. Expert Opinion on Drug Safety, pp.1-16.

[87] Kumar, R., Prakash, J., Bhushan, S., Rawat, A.D., Ray, R.S. and Raghuvanshi, R.S., 2024. Training and education in pharmacovigilance: The experience from the Pharmacovigilance Programme of India. Indian journal of pharmacology, 56(5), pp.348-357.

[88] Mann, R.D. and Andrews, E.B. eds., 2007. Pharmacovigilance. John Wiley & Sons.

[89] 628 Indian Journal of Pharmacology - Vol 48, Issue 6, December 2016