JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Perspectives on pharmacovigilance, recent developments, challenges, and different software.

Madhav Jajnure[1], Siddhi Painjane[1] Snehal More[1], Ashwini Badhe[2] , Shubham Deshmukh[1] Prashant Mali[1] and Dr Pravin Badhe[1,2]

1. Sinhgad College of Pharmacy Vadgaon (B.K) Pune
2. Swalife Biotech Ltd, Cork Ireland

Corresponding Author- Dr Pravin Badhe- drbadhepravin@gmail.com

Abstract-

The concept of Pharmacovigilance is defined as the science and activities related to the detection, assessment, understanding, and prevention of adverse effects and any other drug-related problems, which is crucial to ensuring that patients get safe medicines. Pharmacovigilance starts with clinical testing and continues through the drug's lifecycle.

Over the past few years, pharmacovigilance has gained increasing importance for better clinical practice and public health science. Pharmacovigilance involves active surveillance, passive surveillance, stimulated reporting, targeted clinical investigation, comparative observational studies, and descriptive studies.

The new developments in pharmacovigilance are essential in order to keep up with demands and maintain patient health. ADRs are mainly managed using the software. The most commonly used software is Oracle Argus Safety, ArisG, Oracle adverse event reporting, PvNET, and repClinical.

Keywords- Pharmacovigilance, Active surveillance, adverse effects, reporting.

INTRODUCTION

"Pharmacovigilance" is Pharmakon (Greek word for drug) and vigilance (Latin word for "to keep a watch") [1].

According to the World Health Organization, "Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible

drug-related problem, particularly long term and short term adverse effects of medicines" [2]. Pharmacovigilance (PV), also known as drug safety, [3] plays an important role in decision-making in pharmacotherapeutics [4]. Pharmacovigilance is an integral and major part of clinical research.[5]

Table 1: The sequential pharmacovigilance developments with special reference to India: [2][6][7]

Sr no	Year	Development
1	**1747**	Very first known clinical trials by James Lind, proving the usefulness of lemon juice in preventing scurvy
2	**1937**	Death of more than 100 children due to toxicity of sulfanilamide.
3	**1950**	Apalstic anemia reported due to chloramphenicol toxicity.
4	**1961**	Worldwide tragedy due to thalidomide toxicity.
5	**1963**	16th World Health congregation recognize significant to rapid action on Adverse Drug Reactions (ADRs).
6	**1968**	WHO research project for international drug monitoring on pilot scale.
7	**1996**	Global standards level clinical trials initiated in India.
8	**1997**	India attached with WHO Adverse Drug Reaction Monitoring Program.
9	**1998**	Initiation of pharmacovigilance in India.
10	**2002**	67th National Pharmacovigilance Center established in India.
11	**2004 -05**.	India launched National Pharmacovigilance Program.
12	**2005**	Accomplishment of structured clinical trials in India.
13	**2009 -10**	Pharmacovigilance Program (PvPI) started.

Aims of pharmacovigilance:

1. To Increase public protection from the new drugs
2. To contribute to assessment of benefit efficiency and risk of medicines.
3. Endorse healthy communication to the community.
4. To promote rational and safe use of medicines.
5. Efficacy of drug and their monitoring about adverse effects of drugs.
6. Pharmacovigilance keeps way of any drastic effects of medicines. Improve public health and safeties in relation to the use of promote understanding, education and clinical training in pharmacovigilance.[8]

Objectives of Pharmacovigilance:

- Improve patient care and safety in relation to the use of medicines and all medical and Para medical interventions.
- Research the efficacy of drug and by monitoring the adverse effects of drugs right from the lab to the pharmacy and then on for many years.
- Pharmacovigilance keeps track of any drastic effects of drugs.
- Improve public health and safety in relation to the use
- Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use.
- Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public[1][9]

Need of Pharmacovigilance

Resons are as follows:

I. Humanitarian concern - Insufficient evidence of safety from clinical trials Animal experiments Phase 1-3 studies prior to marketing authorization.
II. Medicines are supposed to save lives Dying from a disease is sometimes unavoidable; dying from a medicine is unacceptable.
III. ADR-related cost to the country exceeds the cost of the medications themselves.
IV. Promoting rational use of medicines and adherence.
V. Ensuring public confidence.
VI. Ethics, to know of something that is harmful to another person who does not know, and not telling, is unethical [2][10].

Importance of Pharmacovigilance

When a pharmaceutical drug is introduced in the market there are still a lot of things that are unknown about the safety of the new drug. These medicines are used by various patients for different diseases who might be using several other drugs and must be following different traditions and diets which may adversely affect the impact of medicine in them. Also the same medicine might differ in the manner of their production and ingredients [11,12].

Additionally adverse drug reactions might also occur when drugs are taken along with traditional and herbal medicines which should be monitored through pharmacovigilance. In some cases, adverse drug reactions of certain medicine might occur only in one country or region. To prevent all undue physical, mental and financial suffering of patients, pharmacovigilance proves to be an important monitoring system for the safety of medicines in a country with the support of doctors, pharmacists, nurses and other health professionals of

the country [3,11].

The importance of pharmacovigilance is as follows.

• Safety monitoring of medicinal products
• Clinical trials
• Pharmacoepidemiological studies
• Case reports
• Developing case series
• Analysis of case series
• Use of data mining to identify product -event combination
• Spontaneous reporting. [3,11,12,13]

Challenges Related to Pharmacovigilance

Challenges facing in relation with Pharmacovigilance nowadays are

- Non - priority in healthcare delivery.
- Personal bias related drug in healthcare delivery system
- Poor staffing, poor funding and mostly political pressures creating barrier in implementation of Pharmacovigilance programme
- Limited number of health professionals as compare to the many prescriber.
- Non-covering of drug safety in medical training.
- Low motivation of health professionals due to their busy schedule.
- Lack of continuing medical education as well as difficulty in availability of drug information.
- Availability of many types of drugs in households as well as dispensing the drugs by untrained persons.
- Some other drug use problems include wide spread use of in- jections, high levels of antibiotic use, Inadequate treatment guidelines, poor prescribing and dispensing practices,counterfeit drugs and using of traditional medicine
- Confounding illness in diseases like tuberculosis, HIV/AIDS,malnutrition requires multiple drug therapy and adverse event occurs due to drug interactions, leading to severe health hazard [14] [10][15][16].

Clinical trials

When a compound deserving trial in man is identified by animal studies, the regulatory authorities are approached who on satisfaction issue an ‘investigational new drug’ (IND) licence. The drug is formulated into a suitable dosage form and clinical trials are conducted in a logical phased manner. To minimize any risk, initially few subjects receive the drug under close supervision. Later, larger numbers are treated with

only relevant monitoring. Standards for the design, ethics, conduct, monitoring, auditing, recording and analyzing data and reporting of clinical trials have been laid down in the form of 'Good Clinical Practice' (GCP) guidelines by an International Conference on Harmonization (ICH). National agencies in most countries, including ICMR in India, have also framed ethical guidelines for clinical trials. Adherence to these provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected as enunciated in the Helsinki Declaration of the World Medical Association. The requirements and regulations for the conduct of clinical trials on a new drug in India have been laid down in the schedule Y of the Drugs and Cosmetics Rules [1,17,18].

The clinical studies are conventionally divided into 4 phases.

Phase I: Human pharmacology and safety

The first human administration of the drug is carried out by qualified clinical pharmacologists/trained physicians in a setting where all vital functions are monitored and emergency/ resuscitative facilities are available. Subjects (mostly healthy volunteers, sometimes patients)are exposed to the drug one by one (total 20–80 subjects), starting with the lowest estimated dose and increasing stepwise to achieve the effective dose. The emphasis is on safety,tolerability, and to detect any potentially dangerous effects on vital functions, such as precipitous fall/rise in bloof pressure or heart rate,arrhythmias,bronchospasm, seizures, kidney/liver damage, etc.Unpleasant side effects are noted and an attempt is made to observe the pharmacodynamic effects in man. The human pharmacokinetic parameters of the drug are measured for the first time. No blinding is done: the study is open label.

Phase II: Therapeutic exploration and dose ranging

This is conducted by physicians who are trained as clinical investigators, and involve 100–500 patients selected according to specific inclusion and exclusion criteria. The primary aim is establishment of therapeutic efficacy, dose range and ceiling effect in a controlled setting. Tolerability and pharmacokinetics are studied as extension of phaseI. The study is mostly controlled and randomized,and may be blinded or open label. It is generally carried out at 2–4 centres. The candidate drug may get dropped this stage if the desired level of clinical efficacy is not obtained.

Phase III: Therapeutic confirmation/comparison

Generally these are randomized double blind comparative trials conducted on a larger patient population (500–3000) by several physicians (usually specialists in treating the target disease) at many centres. The aim is to establish the value of the drug in relation to existing therapy. Safety and tolerability are assessed on a wider scale,while pharmacokinetic studies may be conducted on some of the participants to enlarge the population base of pharmacokinetic data. Indications are finalized and guidelines for therapeutic use are formulated. A 'new drug application' (NDA) is submitted to the licencing authority, who if convinced give marketing permission.

Phase IV: Postmarketing surveillance/studies

After the drug has been marketed for general use, practicing physicians are identified through whom data are collected on a structured proforma about the efficacy, acceptability and adverse effects of the drug (similar to prescription event monitoring). Patients treated in the normal course form the study population: numbers therefore are much larger uncommon/idiosyncratic adverse effects, or those that occur only after long-term use and unsuspected drug interactions are detected at this stage. Patterns of drug utilization and additional indications may emerge from the surveillance data. Further therapeutic trials involving special groups like children, elderly, pregnant/lactating women, patients with renal/hepatic disease, etc.(which are generally excluded during clinical trials) may be undertaken at this stage. Modified release dosage forms, additional routes of administration, fixed dose drug combinations, etc. may be explored. As such, most drugs continue their development even after marketing [17,18]

Causality assessment

When a patient undergoing drug therapy experiences an adverse event, it may be due to the drug, or the disease or some other causes. Most of the time, a clear-cut 'yes/no' cause and effect relationship between a drug and the adverse event cannot be pronounced[19].

Causality is assessed on the basis of:

- Temporal relationship: How the time-sequence of the event is related to drug administration.
- Previous knowledge: Whether the drug is known to produce the event in earlier recipients with a certain degree of consistency.
- Dechallenge: Whether the event subsided on stopping the drug.
- Rechallenge: Whether the event reappeared when the drug was administered again after a gap during which the event had subsided. Many times rechallenge is unethical/dangerous, and is not done.

Assessed on the basis of the above criteria, causality has been graded as:

1. Definite: Causality is proven.
2. Probable: Though not proven, drug is the likely cause of the event.
3. Possible: Drug as well as other causes could be responsible for the event.
4. Doubtful: Drug unlikely to be the cause, but cannot be ruled out.[20]

Adverse drug reactions (ADRs)

An adverse drug reactions (ADRs) can be defined as an unintended and noxious responses to a health product which causes at the doses usually used or tested for the diagnosis, prevention or treatment of a disease or the alteration of an organic function.[21][2].

Though, it is difficult to recognize the causative agent related with the adverse drug reactions (ADRs) encountered because the medicinal preparations generally contain more than ingredients. All drugs are capable of producing adverse drug reactions (ADRs) and whenever a drug is given a risk is taken. The magnitude of risk has to be considered along with magnitude of expected therapeutic benefit in deciding whether to use or not to use a particular drug in a given patient.

The adverse drug reactions (ADRs) may develop promptly or only after prolonged medication or even after stoppage of drug. Adverse drug reactions (ADRs) are not rare; an incidence of 10- 25% has been documented in different clinical settings and are more common with the multiple drug therapy[22].

Adverse drug reactions (ADRs) have been classified in to two ways; [23]

Type-A Predictable Reactions

These are based on pharmacological properties of drug like augmented but quantitatively normal response to the drug which include side effects, toxic effects and consequences of drug withdrawal. They are more common dose related and mostly preventable and reversible. Eg.anaphylactic reaction[22]

Type-B Unpredictable Reactions

These are based on peculiarities of patient and not on drug's known actions; include allergy and idiosyncrasy. They are less common, often non dose related, generally more serious, not pharmacologically predictable and can include hypersensitivity reactions (e.g. anaphylaxis with beta- lactam antibiotics). require withdrawal of drug.

- Type C (continuing) reactions describe those that persist for a relatively long time (eg osteonecrosis of the jaw with bisphosphonates).
- Type D (delayed) reactions, which become apparent some time after the use of a medicine (eg leucopenia)

Adverse Drug Reactions (ADRs) Reporting/ Adverse Event (AE) Reporting

Adverse Drug Reactions (ADRs) Reporting/ Adverse Event (AE) Reporting is the most commonly associated with Pharmacovigilance (PV) and consumes a considerable amount of resources of government agencies or drug regulatory authorities or drug safety departments in pharmaceutical organizations [24].

Adverse Event (AE) reporting includes the receipt, triage, data maintaining, evaluation, distribution, reporting of AE data [22]. The foundation of AE reports may include solicited reports from patient support programs, reports from clinical or post-marketing studies, spontaneous reports from healthcare professionals or patients or other intermediaries, reports from literature sources, reporting is a regulatory requirement in most countries, reports from the media including social media and websites and reports reported to drug regulatory authorities themselves [24,25]

For pharmaceutical companies AE reporting also provides data that play an important in assessing the risk-benefit profile of a given drug. The following are several elements of Adverse Event (AE) Reporting: [25]

[26]

1. An identifiable patient.
2. An identifiable reporter.
3. A suspect drug.
4. An adverse event.

Advice about reporting:

Report adverse experiences with medications:

1. Report serious adverse reaction : Reaction is serious when patient outcome is – Death ,life threatening ,hospitalization ,required intervention to prevent permanent impairment or damage
2. Who can report: Any health care professional (doctors including dentists, nurses, and pharmacists) Where to report: please return the completed form to the nearest Adverse Drug Reaction Monitoring Center or to National Coordinating center.
3. What happens to the submitted information: information provided in this form is handled in strict confidence. The causality assessment is carried out at ADR monitoring centers by using WHO –UMC scale .the analyses form forwarded to national centers through ADR database.
4. The report are periodically review by national coordinating centers. The information generated on the basis of this report helps in continuous assessment of the benefit risk ratio of medicines.[14]

Drugs Adverse Drug Reaction

1. Thalidomide -Phocomelia, Multiple Defects.
2. Methotrexate- Multiple defects, Fetal death.
3. Androgen -Virilization of limb, esophageal, cardiac defects.
4. Progestin -Virilization of female fetus
5. Stilbesterols -Vaginal carcinoma in teenage female offspring
6. Tetracycline -Discolored or deformed teeth, retarded bone growth
7. Warfarin -nose, eye and hand defects, growth retardation
8. Phenytoin -Various malformations
9. Lithium -Fetal goiter, cardiac and other abnormalities
10. Aspirin/Indomethacin -Premature closer of ducts arteriosus
11. Quinidine -Ringing in ear Alcohol Low IQ baby, growth retardation
12. Carbamazepine -Neural tube defects
13. Rifampicin -Orange color urine
14. Chloramphenicol- Grey baby syndrome.
15. Anticancer drugs -Cleft palate, multiple defects.
16. Valproate sodium -Spina bifida, limb abnormalities.
17. Isotretenoin- Heart and CNS defects

Benefits of ADR monitoring

An ADR monitoring and reporting program can furnish following benefits:

1. It caters information about quality and safety of pharmaceutical products.
2. It initiates risk-management plans.
3. It prevents the predictable adverse effects and helps in measuring ADR adherence.
4. It instructs health care team i.e., patients, pharmacists and nurses about adverse drug effects and creates awareness regarding ADRs. The main objective of ADR monitoring is to disclose the quality and frequency of ADRs and to identify the risk factors that can cause the adverse reactions.[27]

Prevention of adverse effects to drugs

Adverse drug effects can be minimized but not altogether eliminated by observing the following practices:[28]

1. Avoid all inappropriate use of drugs in the context of patient's clinical condition.
2. Use appropriate dose, route and frequency of drug administration based on patient's specific variables.
3. Elicit and take into consideration previous history of drug reactions.
4. Elicit history of allergic diseases and exercise caution (drug allergy is more common in patients with allergic diseases).
5. Rule out possibility of drug interactions when more than one drug is prescribed.
6. Adopt correct drug administration technique (e.g. intravenous injection of vancomycin must be slow).
7. Carry out appropriate laboratory monitoring (e.g. prothrombin time with warfarin, serum drug levels with lithium)[29].

Softwares used in field of Pharmacovigilance

1)Vigibase
2)Vigiflow
3)Vigimed
4)Arisg
5)PvNET
6)RepClinical
7)Oracle AERS

1) VigiBase

VigiBase is the world's largest database, which is maintained by UMC in collaboration with WHO which comprises of all the ICSRs since 1968[30]. Approximately, for more than 20 years, the process of signal detection was limited to the manual statistical disproportion of combination of signals by 30–35 pharmacovigilance scientists. However, in 1998, database for detecting signals has become automated which since then works upon quarterly Bayesian confidence propagation neural network (BCPNN) scan. The upgraded database maintains the integrity of data as previously data got lost or distorted due to the manual exchange of data. However, reports are recently entered into the database in a sorted manner and can be labeled according to the quality of data such as completeness, seriousness, precision or accuracy. Such characteristics can be utilized for the signal generation. Moreover, filtering processes are imperial in process of signal management especially in larger databases but at the UMC, human skills are combined with the automated part of the signal generation in order to optimize the public health safety. For instance, in first quarter, 75 000 of drug and adverse drug reaction combinations were reported in the database and out of which 20 000 cases were shortlisted which represents the most occurred cases than expected, and this depicted that BCPNN had significant outcome and can be used optimistically. However, manual reviewing of 20 000 cases is still a difficult task which indicates the need of better automated strategy[31].

2) VigiFlow

VigiFlow is an ICSRs management system for countries that require an electronic pharmacovigilance database for the collection, processing and sharing of ICSRs for efective data analysis. It was initially developed for Switzerland's regulatory agency Swissmedic. Today it is ofered to national centres in low- and middle-income countries as a low-cost way of managing their pharmacovigilance data. Previously, a free version of VigiFlow with limited functionality was also available to support countries reporting ICSRs to VigiBase[32]. VigiFlow is compatible with the international ICH E2B standard—and uses the international Medical Dictionary for Regulatory Activities (MedDRA) terminology—for efcient data exchange between pharmaceutical companies and regulatory agencies using xml fles. It supports the setup of a decentralised system for data collection, allows integration with an electronic form for the general public and healthcare professionals to report adverse events with medicines or vaccines (eReporting), and ofers direct sending of ICSRs to VigiBase. Currently, VigiFlow is used by more than 90 countries worldwide. The system is continuously updated, and the latest version of VigiFlow launched in January 2018 is compliant with the updated standard ICH E2B(R3), which includes improvements in manual data entry and data structure of ADR and AEFI (adverse events following immunisation) reports, as well as better workfow support for pharmacovigilance centres. The new version of VigiFlow is the same for all countries, with a free, limited version no longer available [32].

3) Vigi med:

Vigimed is a worldwide e-mail discussion group maintained by the UMC. It has been in place since -1997, uses e-mail and related technology, and aims to improve and accelerate the sharing between its users of information regarding drug-related problems to aid problem solving and decision making[33] . Vigimed allows rapid exchange of information and opinions on drug safety matters between NPCs around the world as well as the UMC. Membership is restricted to persons connected to NPCs or drug regulatory agencies in participating countries, including 'associate member countries'. Some of the UMC and WHO-headquarters staff is also on the list of Vigimed members. At the time of the study, there were 71 countries collaborating in the Vigimed. System In each country, one or more persons have access to Vigimed [34]. It is the only e-mail discussion group connecting all NPCs participating in the international pharmacovigilance programme. The e-mail messages mostly concern announcements or questions and the subsequent answers . The message flow is not moderated; in other words, there is no manual filter between the submission of a message and the distribution to list members. Thanks to complete storage of all messages in the Vigimed system, it can also be used as a unique source of information regarding factual daily practice of governmental pharmacovigilance and the procedures and discussions in problem solving and decision making [33,34].

4) ARISg

ARISg is also one of the most widely utilised pharmaceutical company pharmacovigilanc tools.

More than 300 companies around the world utilise ARISg to keep track of their crucial medication safety data. ARISg has all of the features needed to manage adverse event reporting and adverse reaction regulations set forth by various regulatory agencies across the world. It supports all pharmacovigilance processes, including CIOMS 1, MedWatch 3500A, and many others, from case input through the automatic compilation of submission-ready adverse event (AE) reports.

ARISg is a key component of an integrated pharmacovigilance and risk management system, allowing corporations to keep track of their goods and detect potential safety issues ahead of time. With its flexible workflow and advanced analytics, ARISg helps speed up the management of Adverse Drug Reactions [35].

5) PvNET

PvNET is a comprehensive pharmacovigilance solution and one of the top tools used in pharmacovigilance with Adverse Event reporting, Adverse Drug Reaction (ADR) data management, and ICSR (Individual Case Safety Report) regulatory reporting that goes beyond simply compliance. PvNET assists users in making key decisions by incorporating safety information from the early stages of development to post-marketing. PvNET has passed GMP, 21 CFR, and ICH E2B drug safety audits across the board.

The following are only a few of PvNET's many features:

1)Workflow that separates Data Entry, Quality Control (Review), and Scientific Assessment/Medical Review.

2)Validate case files for E2B compliance with extensive data validation and cross-field validation checks.

3) Dictionary administration and global dictionary support (MedDRA version management)

4)Audit records for operations including safety data management

5) Management Dashboard: Provides users with information to call attention to anomalies and outliers, allowing them to take action quickly [36].

6) RepClinical

RepClinical is a secure web-based solution that aids in the timely and cost-effective management of important pharmacovigilance tasks. You may gather adverse event data, prepare regulatory reports, and exchange ICSRs with a variety of regulatory agencies and business partners using repClinical. All of this is done in a straightforward, user-friendly, and effective manner. RepClinical's clutter-free displays and handy features make it simple to create exact E2B reports.

Rep's data The data in the Individual Case Safety Reports is closely modelled by clinical (ICSRs). Data from cases can be saved and followed. Safety reports can be used to preserve and track administrative and identifying information from case reports. Finally, in Messages, data from messages can be saved and tracked [37].

7) Oracle AERS

Biopharmaceutical businesses, vaccine companies, medical device companies, and Contract Research Organizations (CROs) are all faced with the issue of achieving time-critical regulatory criteria while working with limited resources. They must recognise and manage safety events before they become problems, as well as adhere to ever-changing rules. They demand comprehensive visibility into their data to handle crucial business activities.

To tackle the challenges of managing your international safety information, Oracle AERS provides a single global solution with sophisticated automation and productivity tools. Oracle AERS facilitates the collection, management, reporting, and analysis of major adverse event and product compliance cases for all medical items, including pharmaceuticals, medical devices, vaccines, biologics, and gene treatments, from both clinical and non-clinical sources [38].

Conclusion

Rational use of drugs includes right drug, right dose, and right time with the right patient could improve the quality of the public. Both healthcare professionals and non-healthcare professionals should aware about Pharmacovigilance programme.

This would be achieved by best pharmaceutical care. Communication related to drug safety information to patients and healthcare professionals is essential for achieving the objectives of pharmacovigilance in terms of promoting the safe and effective use of medicine, prevention harm from adverse reaction and contributing

to the protection of public health.

Communication in PvPI improves patient care, understanding, promotes transparency and accountability. All the communication with WHO-UMC are managed by National Coordinating Centre (NCC). The NCC is responsible to publish/ communicate any findings from NCC database to journals/ media/online- web whereas the other stakeholders are required to get prior approval from NCC to publish/communicate any data or matter related to PvPI.

References-

[1] S. A. Naik, "Review on Pharmacovigilance," *Asian J. Pharm. Res.*, vol. 10, no. 2, p. 123, 2020, doi: 10.5958/2231-5691.2020.00024.6.

[2] R. Soni and B. Kesari, "A review on pharmacovigilance," *Int. J. Pharm. Sci. Rev. Res.*, vol. 26, no. 2, pp. 237–241, 2014.

[3] J. K. M. Rajgopal, K. Shilpi, and S. Ak, "Pharmacovigilance : a review article," *Innovare J. Med. Sci.*, vol. 4, no. 4, pp. 6–7, 2016.

[4] R. K. Patil and A. D. H. C. Patil, "A Review on Pharmacovigilance : methods , recent developments , future perspectives and software .," vol. 8, no. 12, pp. 303–311, 2021.

[5] A. Gadhawe, S. Dandnaik, H. V Kamble, and S. Waghmare, "REVIEW ON PHARMACOVIGILANCE : DRUG SAFETY & MONITERING," vol. 8, no. 9, pp. 424–433, 2021.

[6] P. Tyagi, "Pharmacovigilance - A Review," *Res. Rev. J. Pharmacol. Toxicol. Stud.*, vol. 5, no. 1, pp. 12–17, 2017, [Online]. Available: http://www.rroij.com/open-access/pharmacovigilance--a-review-.php?aid=82417.

[7] P. A. Batista *et al.*, "The antinociceptive effect of (-)-linalool in models of chronic inflammatory and neuropathic hypersensitivity in mice," *J. Pain*, vol. 11, no. 11, pp. 1222–1229, 2010, doi: 10.1016/j.jpain.2010.02.022.

[8] Suke SG, Kosta P, Negi H. Role of Pharmacovigilance in India: An overview. Online J Public Health Inform. 2015 Jul 1;7(2):e223. doi: 10.5210/ojphi.v7i2.5595. PMID: 26392851; PMCID: PMC4576445." .

[9] S. I. Majagi, P. A. P. Pharmacovigilance, S. I. Majagi, and P. A. Patil, "Pharmacovigilance," vol. 3, no. January, pp. 33–34, 2011.

[10] S. Khattri, V. Balamuralidhara, K. T. M. Pramod, R. Valluru, and M. P. Venkatesh, "Pharmacovigilance regulations in India: A Step forward," *Clin. Res. Regul. Aff.*, vol. 29, no. 2, pp. 41–45, 2012, doi: 10.3109/10601333.2012.692688.

[11] H. Davies, P. J. Noble, G. Pinchbeck, and D. Killick, "Reporting of adverse drug reactions," *Vet. Rec.*, vol. 185, no. 14, pp. 446–447, 2019, doi: 10.1136/vr.l5891.

[12] I. L. Anusha, M. Aashritha, K. Teja, and R. Sridhar, "A REVIEW ON PHARMACOVIGILANCE AND ITS IMPORTANCE," vol. 6, no. 1, pp. 300–310, 2017, doi: 10.20959/wjpps20171-8280.

[13] S. Monitoring, "of PHARMACOVIGILANCE," 2002.

[14] E. Wright, "Pharmacovigilance review," *EBR - Eur. Biopharm. Rev.*, vol. 8, no. SUMM, pp. 58–59, 2009, doi: 10.21474/ijar01/10289.

[15] R. D. Bawankar, R. Mundhadad, P. S. Wake, and A. S. Kedia, "Pharmacovigilance and Drug Safety in India - An Unmet Need or Challenge ?," vol. 2017, no. 05, pp. 10–12, 2017, doi: 10.29011/JPPT-124.

[16] T. Bush, "Adverse drug reactions in hospitalized patients.," *JAMA*, vol. 280, no. 20, 1998, doi: 10.1097/01.wox.0000412144.27167.4e.

[17] P. F. Thall, "A review of phase 2-3 clinical trial designs," *Lifetime Data Anal.*, vol. 14, no. 1, pp. 37–53, 2008, doi: 10.1007/s10985-007-9049-x.

[18] J. Sims and V. A. Miracle, "Phases of a clinical trial," *Dimens. Crit. Care Nurs.*, vol. 21, no. 4, pp. 152–153, 2002, doi: 10.1097/00003465-200207000-00009.

[19] A. Li, W. Po, and M. J. Kendall, "Causality Assessment of Adverse Effects When Is Re-Challenge Ethically Acceptable ?," vol. 24, no. 11, pp. 793–799, 2001.

[20] P. Pereira, D. Ferreira-santos, A. Silva, and J. Polónia, "Arti fi cial Intelligence In Medicine Causality assessment of adverse drug reaction reports using an expert- de fi ned Bayesian network," *Artif. Intell. Med.*, no. November 2017, pp. 0–1, 2018, doi: 10.1016/j.artmed.2018.07.005.

[21] N. Datta, M. Pal, U. Roy, R. Mitra, and A. Pradhan, "World Journal of Pharmaceutical Research," *Infection*, vol. 13, no. 1, p. 15, 2014.

[22] M. Rupesh Kumar, S. Bodhanapu, T. Tamizh Mani, P. Phaneendra, and O. M. Fasalu Rahiman, "Pharmacovigilance and its importance in drug regulation: An Overview," *Der Pharm. Lett.*, vol. 3, no. 2, pp. 165–179, 2011.

[23] M. Kaur, S. Kosey, N. Mehra, and R. Kumar, "Knowledge and Awareness of Adverse Drug Reactions," *Int. J. Pharm. Sci. Res.*, vol. 6, no. 11, pp. 4601–4610, 2015, doi: 10.13040/IJPSR.0975-8232.6(11).4601-10.

[24] V. L. Reddy, S. K. J. Pasha, D. M. Rathinavelu, and D. Y. P. Reddy, "Assessment of Knowledge, Attitude and Perception of Pharmacovigilance and Adverse Drug Reaction (ADR) Reporting among the Pharmacy Students in South India," *IOSR J. Pharm. Biol. Sci.*, vol. 9, no. 2, pp. 34–37, 2014, doi: 10.9790/3008-09233437.

[25] R. M. Elkalmi, M. A. Hassali, M. I. M. Ibrahim, R. T. Widodo, Q. M. A. Efan, and M. A. Hadi, "Pharmacy students' Knowledge and perceptions about pharmacovigilance in Malaysian public

universities," *Am. J. Pharm. Educ.*, vol. 75, no. 5, 2011, doi: 10.5688/ajpe75596.

[26] P. S. Bhutada, Y. R. Mundhada, K. U. Bansod, P. V Dixit, S. N. Umathe, and D. R. Mundhada, "Pharmacology , Biochemistry and Behavior Inhibitory in fl uence of mecamylamine on the development and the expression of ethanol-induced locomotor sensitization in mice," *Pharmacol. Biochem. Behav.*, vol. 96, no. 3, pp. 266–273, 2010, doi: 10.1016/j.pbb.2010.05.015.

[27] N. Moore, "The role of the clinical pharmacologist in the management of adverse drug reactions," *Drug Saf.*, vol. 24, no. 1, pp. 1–7, 2001, doi: 10.2165/00002018-200124010-00001.

[28] G. G. Meadows, D. Ph, H. Zhang, and D. Ph, "Effects of Alcohol on Tumor Growth , Metastasis , Immune Response , and Host Survival," pp. 311–330, 2014.

[29] "Original 021.pdf." .

[30] D. Wadhwa, K. Kumar, S. Batra, and S. Sharma, "Automation in signal management in pharmacovigilance — an insight," vol. 00, no. September, pp. 1–9, 2020, doi: 10.1093/bib/bbaa363.

[31] M. Lindquist, "Use of Triage Strategies in the WHO Signal-Detection Process," vol. 30, no. 7, pp. 635–637, 2007.

[32] M. Vogler, H. Ricci, C. Karla, D. A. Ferreira, and F. Moreira, "Electronic Reporting Systems in Pharmacovigilance : The Implementation of VigiFlow in Brazil," *Pharmaceut. Med.*, vol. 34, no. 5, pp. 327–334, 2020, doi: 10.1007/s40290-020-00349-6.

[33] Olsson S. The role of the WHO programme on International Drug Monitoring in coordinating worldwide drug safety efforts. Drug Saf. 1998 Jul;19(1):1-10. doi: 10.2165/00002018-199819010-00001. PMID: 9673854.

[34] A. M. Api *et al.*, "RIFM fragrance ingredient safety assessment, Linalool, CAS registry number 78-70-6," *Food Chem. Toxicol.*, no. 78, pp. 1–10, 2015, doi: 10.1016/j.fct.2015.01.005.

[35] Gill, S.K., Christopher, A.F., Gupta, V. and Bansal, P., 2016. Emerging role of bioinformatics tools and software in evolution of clinical research. *Perspectives in clinical research*, *7*(3), p.115.

[36] Pant, J. ., & Singh, R. M. . (2021). Drug Safety Monitoring (Pharmacovigilance) in India and Different Tools for Detection and Monitoring of Adverse Effects. *SPAST Abstracts*, *1*(01)

[37] Pallavi , R.K. Patil, Ankita Dutta H.C. Patil, A Review on Pharmacovigilance: methods, recent developments, future perspectives and software. Journal of Emerging Technologies and Innovative Research.

[38] Harpaz, R., DuMouchel, W., LePendu, P., Bauer-Mehren, A., Ryan, P. and Shah, N.H., 2013. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. *Clinical Pharmacology & Therapeutics*, *93*(6), pp.539-546.