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Review Article

NEW ERA OF PHARMACY TOWARDS PHARMACOVIGILANCE TO REPORT ADVERSE DRUG REACTION OF MEDICINES

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ABSTRACT

In India, all medicines are having a trade-off between the benefits and the potential for harm. Pharmacovigilance is a formal adverse drug reaction (ADR) monitoring system and case study reporting program, under the supervision of the drug controller of India. In 1998. India was joined the World Health Organization (WHO) program for International Drug Monitoring which was not successful. In 2005, India launched the Nation Programme of Pharmacovigilance which was renamed in 2010 as the Pharmacovigilance Programme pf India(PVPI). Pharmacovigilance plays important role in detection, assessment, understanding and prevention of ADRs. In Pharmacovigilance, Adverse events reported for potentially benefit to the community due to their proximity to both population and public health practitioners, in terms of language and knowledge, enables easy contact with reporters by for example by telephone, Email, text massages by mobile phones. PV helps to the patients to manage optimally, avoid illness is a collective responsibility of industry, drug regulators, clinicians and other healthcare professionals to enhance their contribution to public health. Traditionally, PV involved in mining spontaneous reports submitted to national surveillance systems but recently focus is shifting toward the use of data generated from platforms outside the conventional framework

such as electronic medical records, biomedical literature, and patient-reported data in health forms. This review summarized objectives and methodologies used in Pharmacovigilance.

KEY WORDS: Pharmacovigilance, Adverse drug reactions, Clinical trials, PVPI, Case study report, etc.

INTRODUCTION

Pharmacovigilance was introduced in December 1961 with the publication of a letter (case report) in the Lancet by W. McBride, the Australian doctor who first suspected a causal link between serious fetal deformities (phocomelia) and thalidomide, a drug used during pregnancy: Thalidomide was used as an antiemetic and sedative agent in pregnant women's[1]. In 1968, the World Health Organization was promoted the "Programme for International Drug Monitoring" which is a pilot project with aimed to centralize world data on adverse drug reactions. The Pharmacovigilance was proposed in the mid-70s by a French group of pharmacologists and toxicologists which define the activities promoting "The assessment of the risks of side effects potentially associated with drug treatment"[2].

According to WHO, Pharmacovigilance is the science of collecting, monitoring, researching, assessing, preventing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, blood products, herbals, vaccines, medical device, traditional and complementary medicines with a view to identifying new information about hazards associated with products and preventing harm to patients[3]. The challenge of maximizing drug safety and maintaining public confidence has become increasingly complex in india. Pharmaceutical and biotechnology companies must monitor, proactively estimate and manage drug risk throughout a product's lifecycle, from development to post-market[4].

PV is concerned with ADRs or drug responses that are noxious and unintended which occur at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function[5]. In PV, Continuous monitoring of drug effects, side effects, contraindications and outright harmful effects which could result in a high degree of morbidity, and in some cases, mortality are essential to maximize benefits and minimize risks. There is no degree of care and caution at the pre-clinical and clinical testing stages can guarantee absolute safety, when a drug is marketed and prescribed to large populations across the country and outside. Clinical trials involved several thousands of patients, less common side effects and ADRs are not known at the time a drug enters the market. Post marketing PV tools are such as data mining and investigation of case reports to identify the relationships between drugs and ADRs. The drug regulatory agencies have responsibility of a well-developed PV system to monitor ADRs during the drug development phase and post marketing surveillance[6]. A complex relationship between partners in the practice of drug safety monitoring and pharmaceutical associations, poisons information centers, health professionals, patients, consumers and media. If future challenges are to be met in order to develop and flourish then sustained collaboration and commitment are vital [7-8].

In India, new drug was launched for the first time, no major compulsion to have a strong PV system to detect ADRs of marketed products. The drug was used for several years before its introduction in India while used by the companies and the regulatory agencies to assess the safety parameters and take corrective actions, such as the withdrawal or banning of the drug. The evolution of a new patent in the Indian pharmaceutical and biotechnology industries as a Trade Related Intellectual Property Rights and Services (TRIPS) makes it incumbent upon India to no longer copy patented products and market them without license from the innovator company [9-12]. The leading Indian companies, realizing the compulsions of the new regime and already have initiated investments of substantial resources for the discovery and development of new drugs needed for both Indian and International markets. This means that during the coming year, research and development by the Indian pharmaceutical and biotech companies will lead to new drugs based on pre-clinical and clinical data generated mostly in India. In such cases, the Indian regulatory agencies cannot count on the experience of other markets to assess the incidence and prevalence of importance of a properly designed PV system [13-15]. Then Indian companies have capacity to develop and market new drugs out of their own research efforts, it is important that adequate PV standards are introduced to monitor ADRs of products first launched in India [16].

SCOPE OF PHARMACOVIGILANCE

There is need to meet the challenges of the increasing range and potency of pharmaceutical and biological medicines including vaccines, which carry an inevitable and unpredictable potential for harm to humans[17-19]. The risk of harm occurs when adverse effects and toxicity appear, particularly when previously unknown in association with the medicine, so that it is essential to analyze and communicate effectively to patients has the knowledge to interpret the information.

- To improve patient care and safety in relation to the use of medicines, medical and paramedical devices
- To contribute the assessment of benefits, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective use
- To promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public

Fig. 1 – Scope of Pharmacovigilance

CLINICAL TRIALS IN INDIA

In India, global pharmaceutical companies preferred destination for clinical trials. Indian clinical research space and opportunities are having four phases of clinical trials [20-22] :

1. Clinical trial phase I
2. Clinical trial phase II
3. Clinical trial phase III
4. Clinical trial phase IV

Clinical trials having most advantages are as follows:

- Having high degree of compliance to international guidelines such as ICH /ICH-GCP
- The regulations lay down by the US Food and Drug Administration
- For availability of well qualified English speaking research professionals
- To ongoing support and cooperation from the government
- To compare lower cost
- To increase prevalence of illnesses common to developed and developing countries
- To good infrastructure availability
- Since January 2002, changes in Patent Laws

Strengths for Analysis of Indian Clinical Sector [23-24]

- Pharmaceutical and biotechnical industry base with availability of skilled persons
- Large population of over 1.2 billion, about 16% of the world's population
- In the world, third largest players with 500 different pharmaceutical ingredients
- In the world, currently accounts for 8% of global pharmaceutical production
- Data mining related to safety profile of drugs possibilities due to large population

AGENCIES INVOLVED FOR CLINICAL RESEARCH REGULATION IN INDIA

In India, there are various regulatory agencies and their prominent roles in Clinical trial are [25] show in below table No. 1.

Table 1 – Regulatory agencies and their roles

Regulatory Agencies	Role of Agencies
Drug controller General of India (DGGI)	Implementation of the National Pharmacovigilance
Central Drug Standard Control Organization (CDSCO)	To operate under the supervision of the National Pharmacovigilance Advisory Committee to recommend.
Department of Biotechnology (DBI)	To provides product evaluation and validation through support for large scale clinical trials of

	agriculture products and clinical trials for health care products
Ministry of Environment & Forests (MOEF)	To approve guidelines for making data entries of the information provided by the environmental experts
Indian Council of Medical Research (ICMR)	Brought out the Policy Statement on Ethical Considerations involved in Research on Human Subjects in 1980 and revised as Ethical guidelines for Biomedical Research on Human Subjects in 2000
Central Bureau of Narcotics (CBN)	To monitor all clinical trials requires additional narcotics compliances relating to storage, import-export quotas and investigational drugs movement
Ministry of Health and Family Welfare (MHFW)	An autonomous body for setting of standards for drugs, pharmaceuticals and healthcare
National Pharmacovigilance Advisory committee (NPAC)	To collates, analyzes and archives adverse drug reaction data for creating healthy environment for the regulatory authorities to analyze the drug to be marketed in india

DATA MINING FOR PHARAMCOVIGILANCE

Pharmacovigilance is a drug safety surveillance. It is a science of enhancing patient care and patient safety regarding with the use of medicines by collecting, monitoring, assessing, preventing and evaluating information from healthcare providers [26]. That's why PV can be divided into two stages such as premarketing surveillance includes information regarding ADRs is collected from pre-clinical screening and phases I to III clinical trials and post-marketing surveillance includes data accumulated in the post approval stage and throughout a drug's market life [27-29].

Pharmacovigilance is relied on biological experiments or manual review of case reports due to the vast quantities and complexity of data to be analyzed, computational methods that can accurately detect ADRs. Large-scale compound databases in pharmacovigilance, is containing structure, bioassay, and genomic information, as well as comprehensive clinical data sets such as electronic medical record databases [30-32].

1. Premarketing surveillance

The pre-marketing stage in PV has been devoted to predict or assess potential ADRs early in the drug development. The application of preclinical study is in vitro Safety Pharmacology Profiling by testing compounds with biochemical and cellular assays [33]. If a compound binds to a certain target, then its effect

may translate into possible occurrence of an adverse drug reaction. The experimental detection of adverse drug reaction have challenging in terms of cost and efficiency. The numerous research activities devoted to developing computational approaches for ADRs using preclinical characteristics of the compounds or screening data. Many existing research can be categorized into protein target-based and chemical structure-based approaches [34-37].

2. Post-marketing surveillance

A drug undergoes screening before its approval by the Food and Drug Administration (FDA), adverse drug reactions may still be missed because the clinical trials are often small, short, and biased by excluding patients with diseases [38]. It is important to continue the post marketing surveillance. Pharmacovigilance plays an essential role in the post-market analysis of newly developed drug. Competition between pharmaceutical companies with rigorous regulatory evaluation procedures empowers a complex research and development process before launching a new drug in market [39-42].

3. Spontaneous reports

A spontaneous report is nothing an unsolicited communication by health care professionals or consumers to a company, regulatory authority, or other organization that describes one or more adverse drug reaction in a patient [43]. Spontaneous reports plays role in the identification of safety signals. Spontaneous reporting of adverse drug reactions and adverse events is an important for gathering the safety information for early detection. Case reports collected by this system and represent the source of information providing the lowest level of evidence and highest level of uncertainty regarding causality [45]. It has advantage that is available immediately after a new product is marketed, continues indefinitely and covers all patients receiving the drug. It is the most likely method of detecting new, rare adverse drug reactions and frequently generates safety signals which need to be further examined [45]. The limitations are the difficulty in recognizing previously unknown reactions, particularly events that are not usually thought of as being ADRs, and under-reporting [46].

4. Yellow card Scheme

Yellow card schemes were used to spontaneous reporting systems. It was established in 1964 and onwards that the system has become the major international pharmacovigilance resources[47]. The yellow cards are classified into seven priorities by a member of the scientific staff which shown in Following Figure-

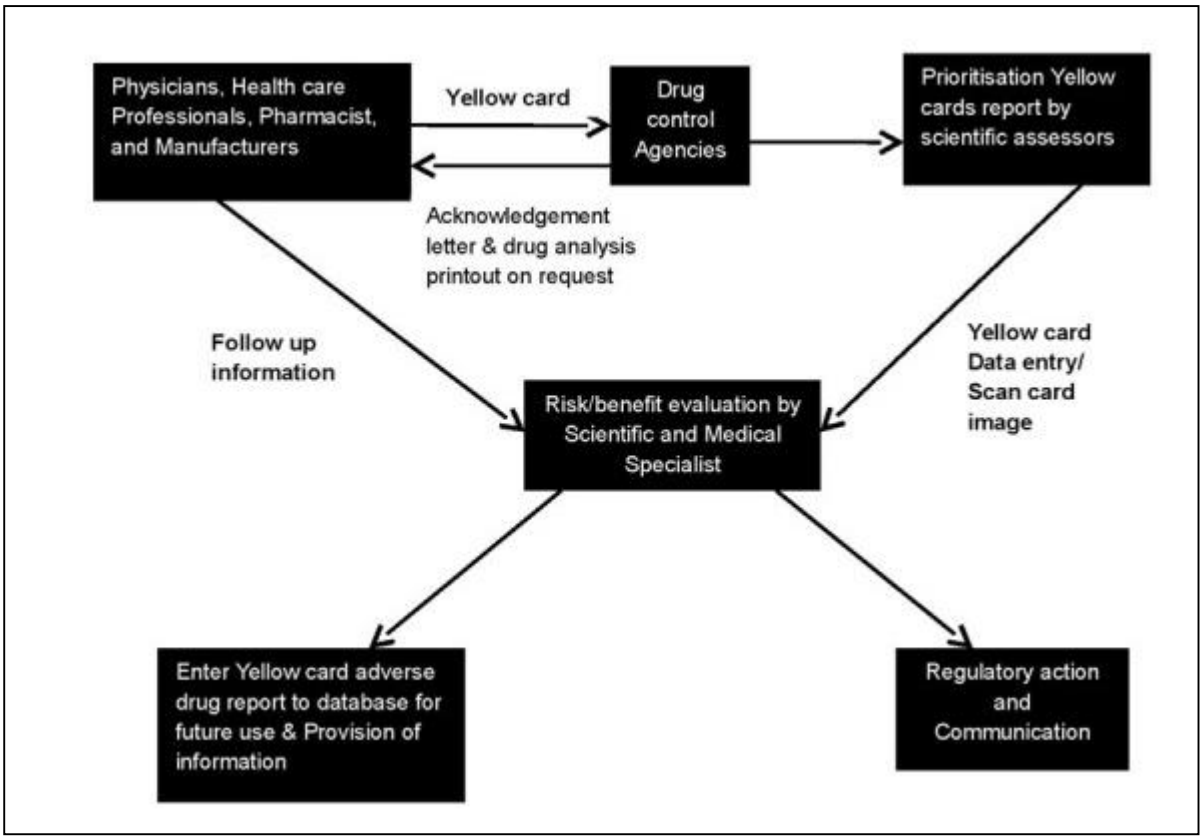
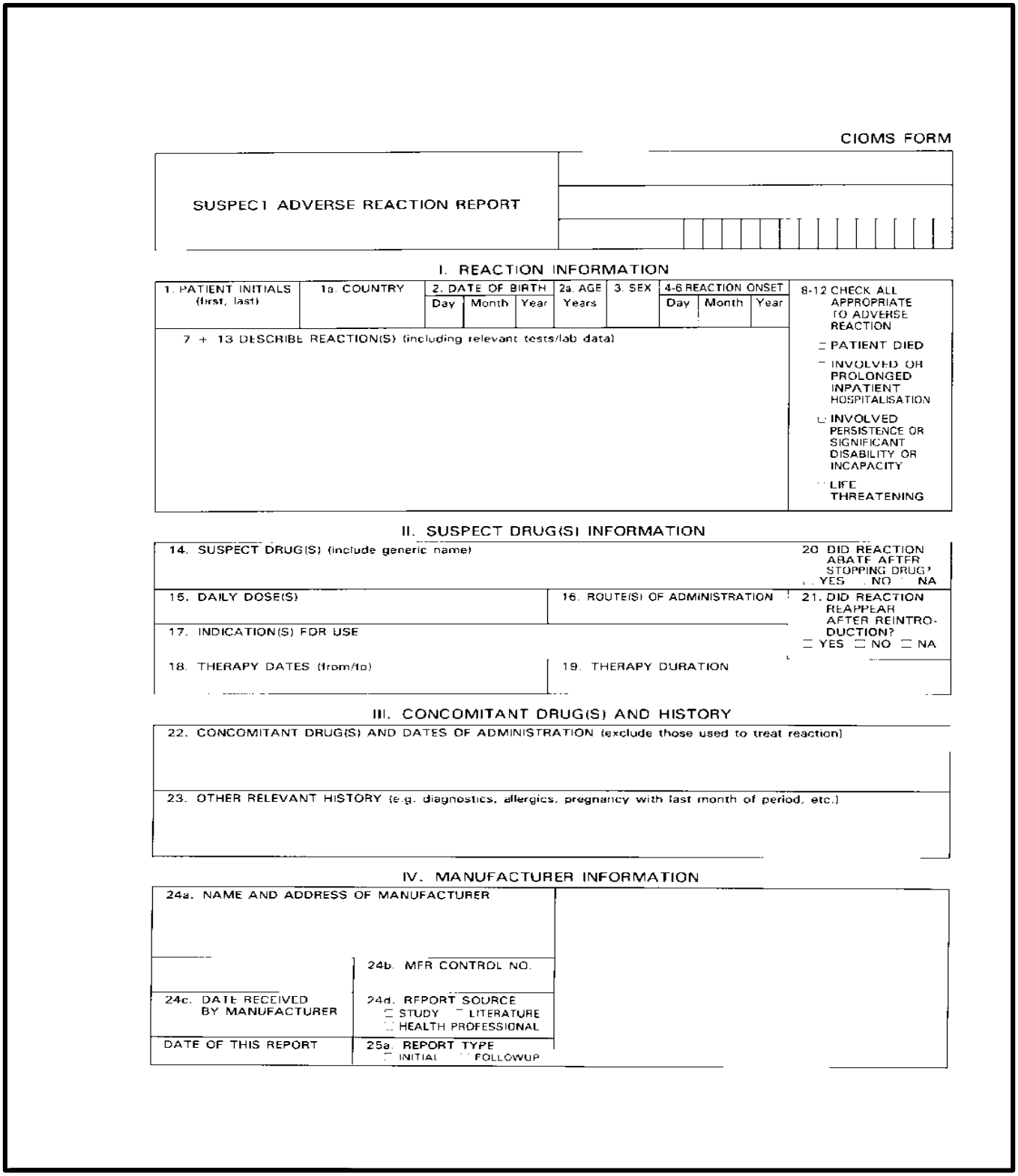


Fig. 2 – Adverse drug reactions online information tracking and yellow card system Sources of data

The Yellow Card Scheme is worked jointly by the Medicines Control Agency and the Committee on Safety of Medicines. The yellow card scheme has enhanced by Adverse Drug Reaction Online Information Tracking system based on computer. It stores the details of the report as well as the image of the yellow card in the optical system. The reports are prioritized that's why serious adverse drug reactions have early attention[48].

5. Detection and reporting

A healthcare professional and marketing authorization holder reports suspected adverse drug recation and adverse event related to medicinal products, to pharmacovigilance centre. These adverse drug reaction reports are made on writing report forms, by telephone, electronically, or by other way[49]. These reports are collected and validated by centre. Then, they are usually entered into a database. Serious reactions related with drug should be handled with the highest priority. The database is used to identify potential signals, analyze data in order to clarify risk factors, and apparent changes in reporting profiles etc[50]. A typical ADR reporting form is as shown in Figure 3.



CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)	20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S) / 16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE	
18. THERAPY DATES (from/to) / 19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	
	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

From spontaneous reports, the systematic methods for the detection of safety signals have been used. This includes the calculation of the proportional reporting ratio, use of Bayesian and techniques for signal detection. Data mining techniques have also been used to examine drug-drug interactions [51]. Techniques of data mining should be used in conjunction with analyses of single case reports. This technique facilitate the evaluation of spontaneous reports to detect potential signals for further evaluation as shown in figure

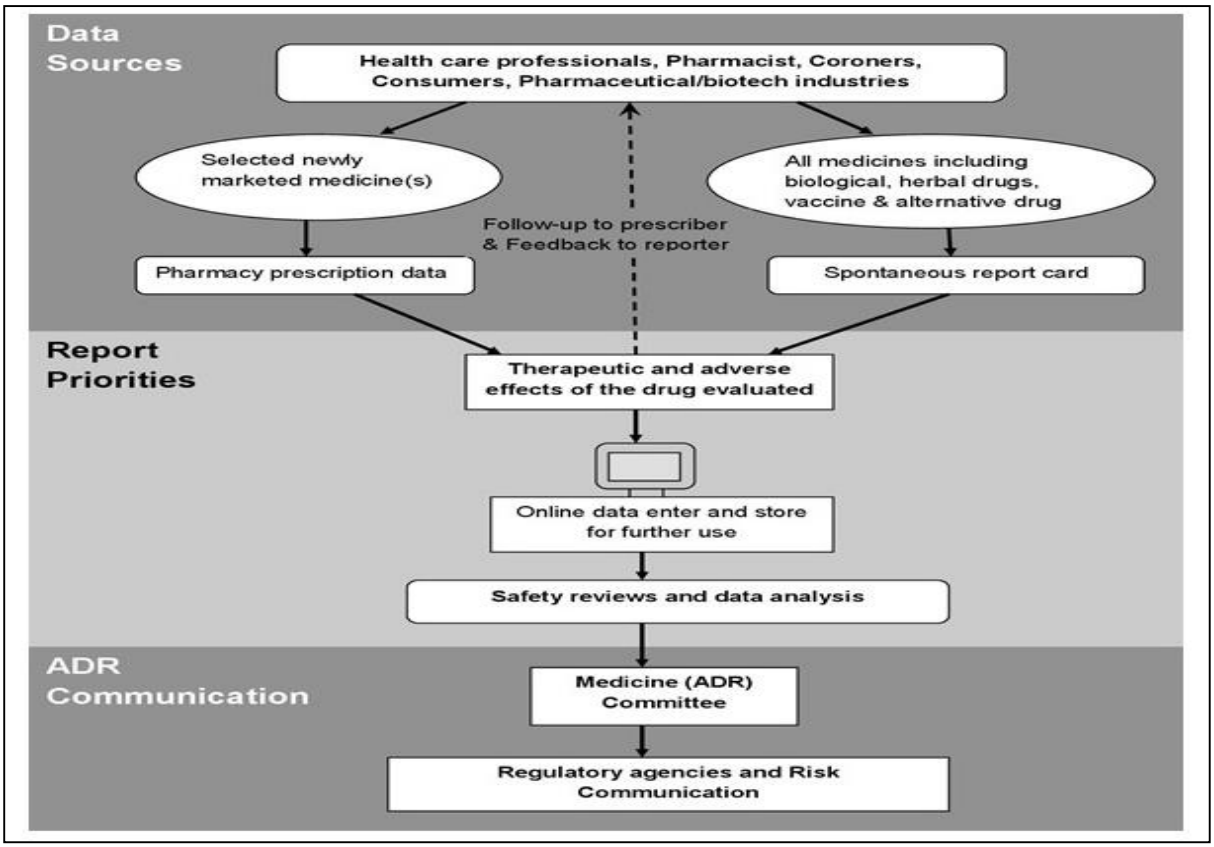


Fig. 4 - Pharmacovigilance systematic methods for the Evaluation of Spontaneous Reports collected from different data sources

When using such techniques, it should be given to the threshold established for detecting signals, which have implications for the sensitivity and specificity of the method [52]. The factors that influence spontaneous adverse event reporting are not removed by data mining. Data mining reports should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system [53]. Large differences in reporting rate from different drug and potential biases inherent in spontaneous reporting. All signals of ADRs should be evaluated recognizing the possibility of false positives. If the signal not observed then the absence of a signal does not mean that a problem does not exist [54].

FUTURE PROSPECTIVES

As to increase future, Pharmacovigilance systems able to detect new ADRs, and taking regulatory actions are needed to protect public health. Thus little emphasis has been put into generating information that can assist a healthcare professional or a patient in the decision-making process. In this information about the safety of drug active surveillance is necessary. When develop new methods for active post-marketing surveillance, need to focus on the important to collect complete and accurate data on every serious reported event. Spontaneous reporting is a useful tool in generating signals, but the relatively low number of reports received for a specific association makes it less useful in identifying patient characteristics and risk factors. PV tools must be able to describe which patients are at risk of developing an ADR. This approach would be consistent with the growing patient involvement in drug safety as a source of information. The PV plays a role in identifying individual

risk factors for the occurrence of certain ADRs. In the future, PV must have to concentrate on the patients as a source of information in addition to the more traditional groups, such as the health professionals.

Today, DCGI should act to improve PV to integrate Good Pharmacovigilance Practice (GPP) into procedures to help ensure regulatory compliance and enhance clinical trial safety and post marketing surveillance. It will beneficial to the healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. Post-marketing PV is currently a challenging and laborious process, not only pharmacutical industry-wide, but also for regulatory agencies.

The primary aim of the PV is to receive the information, documentation of the work and knowledge online while giving priority to the new and important safety issues. Non-serious events have less priority than serious events in this but important in comparing the changes in health. Now, GlaxoSmithKline has created a powerful new approach to PV, integrating traditional, case-based PV methods with disproportionality and data visualization tools. These tools exist with a system framework that facilitates in-stream review, tracking of safety issues and knowledge management. This is very innovative tool which help to advance PV by improving efficiency and providing new analytical capabilities. Need transparency and communication would strengthen consumer reporting, which are positive steps towards involving consumers more in PV.

CONCLUSION

PV is applicable to detection, assessment, prevention and communication of adverse drug reactions of medicinespotentially benefit to the community due to their proximity to both population and public health practitioners, in terms of language and knowledge, enables easy contact with reporters by for example by telephone, Email, text massages by mobile phones. In India, Pharmacovigilance has important in public health issue as regulators, drug manufactures, consumers and health professionals are faced many challenges. Among all countries, India is the largest producer of pharmaceuticals & now having emerging trends in clinical trial hub. Now PV involved in Data Mining Technology in spontaneous reports submit to the national surveillance systems. This reporting is important to identify factors that increase the risk of unwanted outcomes from drug therapy and prior to commencing drug treatment and in tailoring drug treatment for individual patients.

The PV has an important public health issue as regulators, drug manufacturers, consumers, and healthcare professionals are faced with a number of challenges. It continues to grow, evolve, and improve. Pharmacovigilance helps to identify factors that increase the risk of unwanted outcomes from drug therapy and prior to commencing drug treatment and in tailoring drug treatment for individual patients. It is involved in Data Mining Technology in spontaneous reports submit to the national surveillance systems. In India, PVPI is coordinated at IPC through NCC under the control of Indian Government to generate an independent data on safety of medicines, which will be at par with global drug safety monitoring standards. National and regional PV systems are well-adapted bodies, assigned to the intricate collection and analysis of ADR data that leads to timely alerts and interventions to protect population health.

REFERENCES

1. McBride WG. 1961. Thalidomide and congenital abnormalities. Lancet. 278, 1358 10.
2. Bégaud B, Chaslerie A, Haramburu F. 1994. Organization and results of drug vigilance in France. Rev Epidemiol Sante Publique. 42, 416-23.
3. WHO. The Importance of Pharmacovigilance, Safety Monitoring of medicinal products. World Health Organization 2002.
4. Report E. Effective communications in Pharmacovigilance. International Conference on Developing Effective Communications in Pharmacovigilance, Erice, Sicily 1997; 24-27.
5. Shuka SS, Gidwani B, Pandey R, Rao SP, Singh V, et al. 2012. Importance of Pharmacovigilance in Indian Pharmaceutical Industry. Asian J. Res. Pharm. Sci. 2, 4-8.
6. Hornbuckle K, Wu H-H, Fung MC. 1999. Evaluation of spontaneous adverse event reports by primary reporter - a 15-year review (1983 to 1997). Drug Inf J. 33, 1117-24.
7. WHO 2000. Consumer reporting of ADRs. WHO Drug Information. 14, 211-15.
8. Egberts GPG, Smulderes M, De Konig FHP, et al. 1996. Can adverse drug reactions be detected earlier?: a comparison of reports by patients and professionals. BMJ. 313, 530-31.
9. Norwood PK, Sampson AR. 1988. A statistical methodology for postmarketing surveillance of adverse drug reaction reports. Stat Med. 7, 1023-30.
10. WHO. Immunization safety surveillance: Guidelines for managers of immunization programmes on reporting and investigating adverse events following immunization. Immunization Focus: WHO Regional Office for the Western Pacific. Manila 1999.
11. WHO. Global programme for vaccines and immunization: Expanded Programme on Immunization. Surveillance of adverse events following immunization: Field guide formanagers of immunization programmes. Geneva 1997.
12. Simonsen L, Kane A, Lloyd J, Zaffran M, Kane M. 1999. Unsafe injections in the developing world and transmission of bloodborne pathogens: a review. Bull World Health Organ. 77, 789-800.
13. Strom BL. Overview of automated databases in pharmacoepidemiology (ed). Pharmacoepidemiology Chichester. UK, John Wiley & Sons. 2005; 219–22.
14. Butlen S, Ducuing F. 2010. European medicines agency support mechanisms fostering orphan drug development. Drug News Perspect. 23, 71-81.
15. Giezen TJ. 2009. Evaluation of post-authorization safety studies in the first cohort of EU risk management plans at time of regulatory approval. Drug Saf. 32, 1175-87.
16. Herret E. 2010. Validation and validity of diagnoses in the general practice research database. J Clin Pharmacol. 69, 4-14.
17. Abenhaim L. 1996. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med. 335, 609-16.
18. Kaufman DW. 2001. Signal generation and clarification: Use of case-control data. Pharmacoepidemiol Drug Saf. 10, 197-203.
19. Greene W. The Emergence of India's Pharmaceutical Industry and Implications for the U.S. Generic Drug Market. U.S. International Trade Commission 2007.
20. Iskander J. 2005. Monitoring vaccine safety during an influenza pandemic. Yale J Biol Med. 78, 265-75.
21. Stefano F, Tokars J. 2010. H1N1 vaccine safety monitoring: Beyond background rates. Lancet. 375, 1146-47.
22. Chen RT. 2000. The vaccine safety datalink: Immunization research in health maintenance organizations in the USA. Bull World Health Organ. 78, 186-94.
23. Vander H, Stichele R. 2004. European Surveillance of Antimicrobial Consumption (ESAC): Data collection performance and methodological approach. Br J Clin Pharmacol. 58, 419-28.
24. Martirosyan LA. 2010. Systematic literature review: Prescribing indicators related to type 2 diabetes mellitus and cardiovascular risk management. Pharmacoepidemiol Drug Saf. 19, 319-34.
25. Von NC, Schwappach DL, Koeck CM. 2003. The epidemiology of preventable adverse drug events: A review of literature. Wien Klin Wochenschr. 115(12), 407-15.
26. Aneesh TP, Sonal Sekhar M, Jose A, Chandran L, Zachariaha SM. 2009. Pharmacogenomics: The Right Drug to the Right Person. J Clin Med Res. 1, 191-94.

27. Brockmöller J, Tzvetkov MV. 2008. Pharmacogenetics: data, concepts and tools to improve drug discovery and drug treatment. Eur J Clin Pharmacol. 64, 133-57.
28. Kalow W, Meyer U, Tyndale R. Pharmacogenomics 2nd edition, Taylor and Francis 2005;156:341–51.
29. Hodgson J, Marshall A. 1998. Pharmacogenomics: will the regulators approve. Nat Biotechnol. 16, 243-46.
30. Warren LL, Hughes AR, Lai EH, Zaykin DV, et al. 2007. Use of pairwise marker combination and recursive partitioning in a pharmacogenetic genome-wide scan. Pharmacogenomics J. 7, 180-89.
31. Berlin JA, Glasser SC, Ellenberg SS. 2008. Adverse Event Detection in Drug Development: Recommendations and Obligations Beyond Phase 3. Am J Public Health. 98, 1366-71.
32. Kahn MG, Ranade D. 2010. The impact of electronic medical records data sources on an adverse drug event quality measure. J Am Med Inform Assoc. 17, 185-91.
33. Whitebread S, Hamon J, Bojanic D, Urban L. 2005. Keynote review: in vitro safety pharmacology profiling: an essential tool for successful drug development. Drug Discov Today. 10, 1421-33.
34. McClure DL. 2009. Improving Drug Safety: Active Surveillance Systems Should be Paramount. Pharmaceutical Medicine. 23, 127-30.
35. Shibata A, Hauben M. Pharmacovigilance, signal detection and signal intelligence overview. Proceedings of the 14th International Conference on Information Fusion (FUSION-2011). Chicago, IL. 2011; pp. 1-7
36. Lopes P, Nunes T, Campos D, Furlong LI, Bauer-Mehren A, et al. 2013. Gathering and Exploring Scientific Knowledge in Pharmacovigilance. PLoS ONE. 8(12), e83016. 10.1371/journal.pone.0083016
37. Stahl M, Edwards IR, Bowring G, Kiuru A, Lindquist M. 2003. Assessing the Impact of Drug Safety Signals from the WHO Database Presented inSIGNAL': Results from a Questionnaire of National Pharmacovigilance Centres. Drug Saf. 26, 721-27
38. Lazarou J, Pomeranz BH, Corey PN. 1998. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 279, 1200-05.
39. Meyboom RHB, Lindquist M, Egberts ACG, Edwards IR. 2002. Signal Selection and Follow-Up in Pharmacovigilance. Drug Saf. 25, 459-65.
40. De Bruin ML, Van Puijenbroek EP, Egberts AC, Hoes AW, Leufkens HG. 2002. Non-sedating antihistamine drugs and cardiac arrhythmias– biased risk estimates from spontaneous reporting systems? Br J Clin Pharmacol. 53, 370-74.
41. Coloma PM, Schuemie MJ, Trifirò G, Gini R, Herings R, et al. 2011. Combining electronic healthcare databases in Europe to allow for largescale drug safety monitoring: the EU-ADR Project. Pharmacoepidemiol Drug Saf. 20, 1-11.
42. Härmark L, van Grootheest AC. 2008. Pharmacovigilance: methods, recent developments and future perspectives. Eur J Clin Pharmacol. 64, 743-52.
43. Xu L, Anchordoquy T. 2011. Drug delivery trends in clinical trials and translational medicine: Challenges and opportunities in the delivery of nucleic acid-based therapeutics. J Pharm Sci. 100, 38-52.
44. Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, et al. 2012. The US Food and Drug Administration's Sentinel Initiative: Expanding the horizons of medical product safety. Pharmacoepidemiol Drug Saf. 21, 9-11.
45. Waller PC, Evans SJ. 2003. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Saf. 12, 17-29.
46. Kurz X. 2010. The Eudra Vigilance database of spontaneous adverse reactions as a tool for H1N1 vaccine safety monitoring. Pharmacoepidemiol Drug Saf. 19, 330-31.
47. Gupta SK. Drug Discovery and Clinical Research. Jaypee Brothers Medical Pubishers (P) Ltd. First Edition 2011.
48. Yom-Tov E, Gabrilovich E. 2013. Postmarket Drug Surveillance Without Trial Costs: Discovery of Adverse Drug Reactions Through Large-Scale Analysis of Web Search Queries. J Med Internet Res. 15, e124.
49. Bate A, Evans SJ. 2009. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 18, 427-36.
50. Hauben M. 2004. Application of an empiric Bayesian data mining algorithm to reports of pancreatitis associated with atypical antipsychotics. Pharmacotherapy. 24, 1122-29.

51. Harpaz R, DuMouchel W, Shah NH, Madigan D, Ryan P, et al. 2012. Novel Data-Mining Methodologies for Adverse Drug Event Discovery and Analysis. Clin Pharmacol Ther. 91, 1010-21.
52. Edwards LD, Fox AW, Stonier PD. Principles and Practice of Pharmaceutical Medicine. 3rd Edition, Wiley-Blackwell 2011.
53. Kulkarni RD. 1986. Reporting system for rare side effects of non-narcotic analgesics in India: Problems and opportunities. Med Toxicol. 1, 110-13.
54. Moride Y, Haramburu F, Requejo A, Begaud B. 1997. Under-reporting of adverse drug reactions in general practice. Br J Clin Pharmacol. 43(2), 177-81.