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Review Article

CRITICAL REVIEW ON PHARMACOVIGILANCE AND ADVERSE DRUG REACTION

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ABSTRACT

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, monitoring, and prevention of ADR in humans. Pharmacovigilance has been known to play an important role in the rational use of drugs, by providing information about the adverse effects possessed by the drugs in the general population. India is the world's second-largest populated country with over 1 billion potential drug consumers. India has participated in the Uppsala Monitoring Centre program; it is a contribution to that database is relatively small. Signal assessment is mainly performed to analyze the cause and effect by using the World Health Organization (WHO) scale & Naranjo scale of probability. Signal detection and its assessment are a very vital and complex process. This article gives a systematic review of the PV in India from its origin to the current scenario and also discusses the various strategies, needs, objectives, and proposals to build, maintain and implement a robust PV system and to improve the process of ADR reporting in the country.

KEYWORDS: Pharmacovigilance; Adverse Drug Reactions; spontaneous reporting system; Uppsala monitoring center; causality assessment system;

INTRODUCTION [1-5]

Pharmacovigilance was officially introduced in December 1961 with the publication of a letter in The Lancet by Dr.William McBride, the Australian obstetrician who first suspected a causal link between serious fatal deformities (phocomelia), thalidomide used during pregnancy: Thalidomide was used as an anti-emetic and sedative agent in pregnant women. The term PV was proposed in the mid-70s by a French group of pharmacologists and toxicologists to define the activities promoting 'The assessment of the risks of side effects potentially associated with drug treatment'. In 1968, the WHO promoted the 'Programme for International Drug Monitoring' a pilot project aimed to centralize world data on Adverse Drug Reactions (ADRs). In particular, the main aim of the "WHO Programme" was to identify the earliest possible PV signals. PV serves various roles such as identification, quantification, and documentation of drug-related problems which are responsible for drug-related injuries. It is widely accepted that a drug has to go through various clinical trial phases to establish its safety and efficacy before it is marketed commercially. However, the clinical trials offer various limitations, like; such strict criteria of inclusion and exclusion make it be used in a very selective group of patients; special population groups like children, pregnant women, and old age population are not studied during the trials; and other factors causing drug reactions such as genetic factors, environmental factors, and drug-drug interactions may not have been studied during the clinical trials. PV is mainly the post-marketing surveillance (phase-4 study) of drug development; the main objective of PV is to quantify previously recognized ADRs, identify unrecognized ADRs, evaluate the effectiveness of medicines in real-world situations, and decrease mortality and morbidity associated with ADRs. The UMC located in Uppsala, Sweden coordinates the International Drug Monitoring program (IDM). India is the world's second most populated country with over one billion potential drug consumers. Although India is participating in the UMC program, its contribution to this database is relatively small. This problem is essentially due to the absence of a robust ADRs monitoring system and the lack of awareness of reporting concepts among Indian healthcare professionals. It is very important to focus the medical community's attention on the importance of ADRs to ensure maximum benefits for public health and safety. When the FDA approves a new drug or marketing, its complete adverse events profile may not be known because of the limitation of pre-approval clinical trials. Typically, clinical trials for new drugs are not of short duration and are conducted in populations that number up to 5000, therefore, the most common dose-related ADRs are usually detected in the pre-marketing phase while ADRs are rare and those detected in long term use are not Fig.No.1

Historical background of PV [6,7,12]

The safety of drugs was not an early concern in the history of drugs. The thalidomide tragedy of the 1960s opened the eyes of drug regulators as well as other concerned healthcare professionals to establish a way to ensure drug safety. The milestone in drug safety was the publication of chloroform-related death in The Lancet

journal for the first time in 1893. The safety of drugs became a global concern and different initiatives were taken by different initiatives to safeguard public health safety. The UK Medicines act was enforced in 1968, however, safety monitoring via 'the yellow card system was introduced in 1964. The US FDA act was passed in 1906 for the first time, but it was amended to control misbranding of ingredients and false advertising claims after 107 deaths by the use of diethylene glycol as a solvent for sulphanilamide elixir. There were radical changes in the drug safety issues after the worldwide thalidomide tragedy which was first reported by an Australian obstetrician, Dr. William McBride in December 1961. He reported thalidomide associated serious fatal deformities (phocomelia) used in pregnancy. This drug had not been adequately screened for teratogenicity, but similar malformations were subsequently shown in the rabbit and at high doses in the rat. In West Germany, 4000 individuals were affected. The drug safety issues were globalized, strengthened, and systematized after the establishment of the WHO Programme for IDM in 1968.

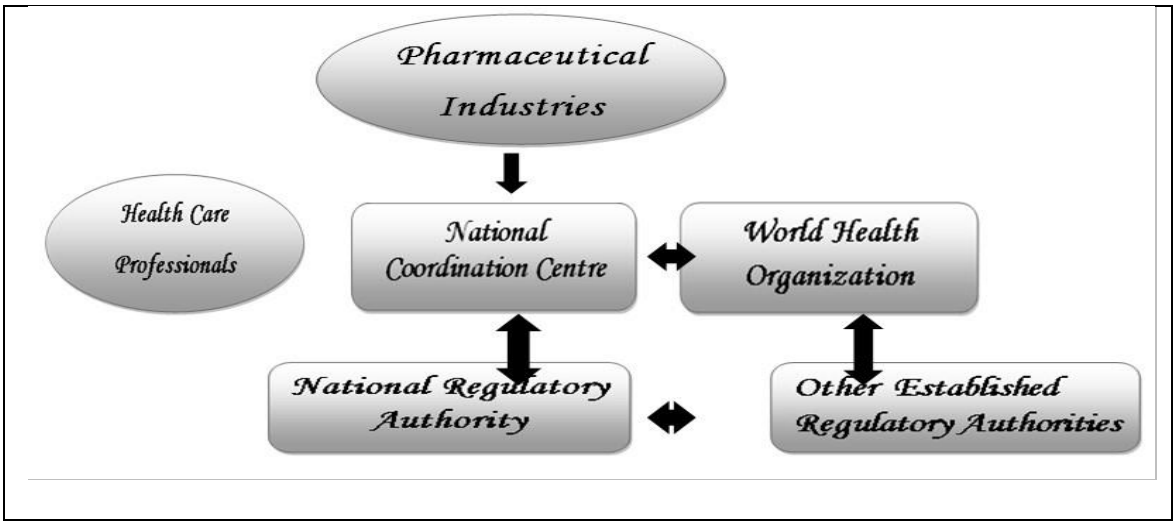

Fig.No.01 Diagrammatic presentation

Types of adverse drug reactions.[10]

In the pre-approval of clinical experience with a new medicinal product. particularly as the therapeutic dose may not be established: all noxious and unintended responses to a medicinal product related to a dose should be considered ADRs. Table No.1

Type	Type of effect	Characteristics	Example
A	Augmented	Dose-dependent predicted from the known pharmacology of the drug	Hypoglycemia-insulin
B	Bizarre	Unpredictable dose-independent rare, fatal	Anaphylaxis penicillin
C	Chronic	Prolong treatment	Analgesic neuropathy
D	Delayed	After years of treatment	Antipsychotic-tardive dyskinesia
E	End of fuse	Withdrawal effect	GC withdrawal-adrenocortical

Table no.1 Types of adverse drug reactions

Purpose of Pharmacovigilance

Pharmacovigilance is the science and activities related to the detection, assessment, and prevention of adverse effects. It includes complimentary medications, biological products, and traditional medicines. Many other issues relevant to the science

1. Substandard medicines
2. Medication errors
3. Lack of efficacy report
4. Use of medicines for the indication that is not approved and for which there is an inadequate scientific basis.
5. Case reports of acute and chronic poisoning.
6. Assessment of drug-related mortality.
7. Abuse and misuse of medicines.
8. Adverse interaction of medicines with chemicals, medicines, and food.

Need of pharmacovigilance [8,9]

Pharmacovigilance is widely accepted that the clinical development of medicines is a complex process and required a huge amount of time for its completion. Hence need for pharmacovigilance arises which include

1. Insufficient evidence of safety
2. Limitation of animal experiments
3. Limitation of clinical trials before marketing
4. Dying from a disease may be inevitable, dying from medicine is unacceptable

5. Before drugs become available to the patients, they are subjected to rigorous clinical studies. However, some ADRs are often detected only after marketing
6. ADR is expensive

Objective of pharmacovigilance [11]

1. Improve patient care and safety regarding the use of medicines and paramedical intervention
2. Improve public health and safety
3. Contribute to the assessment of the benefit, effectiveness, and risk of medicines encourage their safe and rational use and
4. Promoting education and clinical training in pharmacovigilance and effective communication to the community

Pharmacovigilance has been developed and will continue to develop in response to the needs and according to the particular strengths of members of the WHO program. It is a source of vigor and originality that has contributed too much to international practice and standards.

Vigi-flow (India) [15]

Vigi-flow is a web-based database that contains a summary of case reports of suspected adverse drug reactions, submitted to adverse drug reaction monitoring centers across India. It can also be used by pharmaceutical companies or clinical research organizations for monitoring their individual case safety report. Vigi-flow is based on the ICH E2B standard and is a trademark of the UMC and maintained by the UMC in Uppsala, Sweden. VIGIBASE is the name of the WHO ICSR database

measure stratified in different ways and is useful for filter capabilities. It has been used for more than 30 years, it is located in Uppsala since 1978 and is designed for spontaneous reports, maintained by the UMC. Yellow Card Scheme [13,14]

Yellow card schemes were applied to spontaneous reporting systems. It was established in 1964 as a result of the thalidomide tragedy. Spontaneous reports are one of the major international pharmacovigilance resources. The yellow cards are classified into seven priorities by a member of the scientific staff according to the drugs and the nature of the ADRs. The YCS is run jointly by the Medicines Control Agency (MCA) which is the regulatory agency and the Committee on Safety of Medicines (CSM) which is the expert's committee. Since 1991, the YCS has been enhanced by a new computer system, the

ADROIT (Adverse Drug Reaction Online Information Tracking) system. ADROIT is different from other databases. Multiple users can view any yellow card on the screen at the same time. The reports are prioritized so that serious adverse drug reactions receive early attention. Fig.No.02

The WHO-UMC causality assessment system [16,17]

The WHO-UMC system has been developed in consultation with the National Centres participating in the Programme for IDM and is meant as a practical tool for the assessment of case reports. With few

Causality term	Assessment criteria
Certain	1. Event laboratory test abnormality, with plausible time relationship to drug intake 2. Cannot be explained by disease or other drugs 3. Response to withdrawal plausible 4. Event definitive pharmacological or phenomenologically 5. Rechallenge satisfactory, if necessary
Probable/Likely	1. Event or laboratory test abnormality, with reasonable time relationship to drug 2. Unlikely to be attributed to disease or other drugs 3. Response to withdrawal clinically reasonable 4. Rechallenge not required
Possible	1. Event or laboratory test abnormally, with reasonable time relationship to drug intake 2. Could also be explained by disease 3. Information on drug withdrawal may be lacking or unclear
Unlikely	1. Event or laboratory test abnormality, with time to drug intake that makes a relationship improbable 2. Disease or other drugs provided plausible explanations
Conditional/unclassified	1. Event or laboratory test abnormality 2. More data for proper assessment needed 3. Additional data under examination

Unclassified/unclassifiable	1. Report suggesting an adverse reaction 2. Cannot be judged because the information is insufficient 3. Data cannot be supplemented or verified

Table No. 2

exceptions, case reports describe suspected ADRs. The likelihood of a causal relationship between drug exposure and adverse events must be validated. It is a combined assessment taking into account the clinical pharmacological aspects of the case history and the quality of the documentation of the observation. Pharmacovigilance is particularly concerned with the detection of unknown and unexpected adverse drug reactions. It is recognized that the semantics of the definitions are critical and that individual judgments may therefore differ. other algorithms are either very complex or too specific for general use. This method gives guidance to the general arguments which should be used to select one category over another. The various causality categories are listed in Table. No.2. The assessment criteria of the various categories are shown in a point-wise way, as has been developed for practical training during the UMC Training courses.

WHO-Uppsala Monitoring Centre and India [18-21]

is accountable for the gathering of knowledge concerning adverse drug reactions from around the world particularly from countries that are members of the WHO together with India. Member countries send their reports to the UMC wherever they are processed, evaluated, and entered The WHO program for IDM provides a forum for WHO member states that has India to collaborate within the monitoring of drug safety. At intervals, the program, individual case reports of suspected adverse drug reactions are collected and kept in exceeding common information containing over 3.7 million case reports. Since1978, the UMC in Sweden has dispensed the program. The UMC into the WHO International information. When there are several reports of adverse reactions to a particular drug, this process may lead to the detection of a signal- an alert about a possible hazard communicated to member countries. This happens solely once elaborated analysis and expert review. These ADR reports are assessed regionally and will cause the action at intervals in the country. Through membership in the WHO International Drug Monitoring Program, a rustic will recognize if similar reports are being created elsewhere. India is a country with a large patient pool and healthcare professionals, yet ADR reporting is in its infancy

Pharmacovigilance Programme of India (PvPI) [22,23]

A National PV center is located in the Department of Pharmacology, All India Institute of Medical Sciences New Delhi, and two WHO Special centers are located in Mumbai and Aligarh. The Central Drug Standard Control Organization, Directorate General of Health Services under the aegis of Ministry and Family Welfare, Government of India in association with Indian Pharmacopeia Commission, Ghaziabad (U.P). PV program shall be coordinated by the Indian Pharmacopeia commission Ghaziabad (U.P). The PV program of India was

started on 14th July 2010 with the All Indian Institute of Medical Science, New Delhi as the National Coordinating Center for monitoring adverse drug reactions in the country for safeguarding Public Health. In the year 2010, 22ADR monitoring centers including AIIMS, New Delhi set up under this program. To ensure the implementation of this program in a more effective way, the coordination center was shifted from the AIIMS, New Delhi to the IPC, Ghaziabad, Uttar Pradesh on 15th April 2011.

Mission

Safeguard the health of the Indian population by ensuring that the benefits of use of medicine out weight the risks associated with its use.

Objectives

1.To create a nation-system for patient safety reporting 2. To identify and analyze the new signal from the reported cases 3. To analyze the benefit-risk ratio of marketed medications 4. To generate evidence-based information on the safety of medicines 5. To support regulatory agencies in the decision-making process 6. To communicate the safety information on the use of medicines to various stakeholders to minimize the risk 7. To provide training and consultancy support to other national PV centers located globally

International Collaboration

The following organization plays key collaborative role in the global oversight of pharmacovigilance.

- The World Health Organization
- The International Council For Harmonisation (ICH)

The Council for International Organizations of Medical Science (CIOMS)

CONCLUSION

Pharmacovigilance play an important role in meeting the challenges offered by the increased range and potency of medicines. After the appearance of adverse effects and drug toxicities, it is essential that these are reported, analysed and communicated to the general public having knowledge to interpret the information. PV in India continues to grow, evolve, and improve. India is the largest producer of pharmaceuticals and now emerging as an important clinical trial hub in the world. The DCGI has shown its commitment to ensure safe use of drugs by establishing the National PV Program. PV may not rely upon one single method, but needs a strategy of complementary activities. The quality of the reports can be increased through proper training and retraining of the personnel engaged in the PV activity. A suitably working PV system is important if medicines are to be used prudently. It will be advantageous for healthcare professionals, regulatory authorities, pharmaceutical companies and consumers to monitor medicines for risk. Thus, a world class PV system can definitely be empowered in India.

Version-1.2

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION

(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India
Sector-23, Raj Nagar, Ghaziabad-201002

FOR AMC/NCC USE ONLY

AMC Report No. :

Report Type ☐ Initial ☐ Follow up

Worldwide Unique No. :

A. PATIENT INFORMATION

1. Patient Initials _____

2. Age at time of Event or Date of Birth _____

3. M ☐ F ☐ Other ☐

4. Weight_____Kgs

12. Relevant tests/ laboratory data with dates

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)

14. Seriousness of the reaction: No ☐ if Yes ☐ (please tick anyone)

☐ Death (dd/mm/yyyy) ☐ Congenital-anomaly
☐ Life threatening ☐ Required intervention to Prevent permanent
☐ Hospitalization/Prolonged impairment/damage
☐ Disability ☐ Other (specify)

15. Outcomes

☐ Recovered ☐ Recovering ☐ Not recovered
☐ Fatal ☐ Recovered with sequelae ☐ Unknown

C. SUSPECTED MEDICATION(S)

S.No	8. Name (Brand/Generic)	Manufacturer (if known)	Batch No. / Lot No.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates		Indication	Causality Assessment
								Date started	Date stopped		
i											
ii											
iii											
iv											

S.No as per C	9. Action Taken (please tick)						10. Reaction reappeared after reintroduction (please tick)			
	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown	Yes	No	Effect unknown	Dose (if reintroduced)
i										
ii										
iii										
iv										

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

S.No	Name (Brand/Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates		Indication
					Date started	Date stopped	
i							
ii							
iii							

Additional Information:

D. REPORTER DETAILS

16. Name and Professional Address:_____

_____

Pin:_____E-mail_____

Tel. No. (with STD code)_____

Occupation:_____ Signature:_____

17. Date of this report (dd/mm/yyyy):

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

REFERENCES:

1. Pharmacovigilance. World Health Organization. 2017;
2. WHO The Importance of Pharmacovigilance: Safety Monitoring of medicinal products. 2002;
3. Pharmacovigilance. Mann RD, Andrews EB, eds. John Wiley & Sons Ltd, Chichester, 2002;
4. WHO Policy Perspectives on Medicines. Geneva: WHO; 2004. Geneva: World Health Organization. Looking at the Pharmacovigilance: ensuring the safe use of medicines
5. Singh KNM and Kanase HR. Pharmacovigilance Programme of India: The Beginning, Current Status, and Recent Progress. Adv Pharmacoepidemiol Drug Saf. 2017;6(4):1-4. Doi: 10.4172/2167- 1052.1000219;
6. McBride WG. Thalidomide and congenital abnormalities. Lancet. 1961;278(7216):1358.
7. Olsson S. The role of the WHO Programme for International Drug Monitoring in coordinating worldwide drug safety efforts. Drug Saf. 1998;19(1):1-10.
8. Edwards IR. The accelerating need for pharmacovigilance. J R Colle Physicians Lond. 2000;34(1):48-51
9. Olsson S. Pharmacovigilance training with a focus on India. Ind J Pharmacol 2008;40: S28-S30.
10. Williams D and Feely J. Underreporting of adverse drug reactions: attitudes of Irish doctors. Ir J Med Sci. 1999;168(4):257-261. 10. McBride WG. Thalidomide and congenital abnormalities. Lancet. 1961;278(7216):1358
11. Edwards IR. The accelerating need for pharmacovigilance. J R Colle Physicians Lond. 2000;34(1):48-51
12. Shuka SS, Gidwani Bina, Pandey R, Rao SP, Singh V and Vyas Amber, "Importance of Pharmacovigilance in Indian Pharmaceutical Industry", Asian Journal of Research in Pharmaceutical Science, 2, 2012, 04-08
13. . Gupta SK. Drug Discovery and Clinical Research. Jaypee Brothers Medical Publishers (P) Ltd. First Edition 2011. [Google Scholar]
14. 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. 10.2196/jmir.2614 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
15. Kalaiselvan Vivekanandan, Jai Prakash, Gyanendra Nath Singh. Pharmacovigilance Programme of India. Archives of Pharmacy Practice. 2012; 3(3) pp 229-232.
16. World Health Organization (WHO). Uppsala Monitoring Centre: The use of the WHO-UMC system for standardized case causality assessment. 2005;
17. The use of the WHO-UMC system for standardized case causality assessment. [Last accessed on 2012 Dec 10]. Available from: http//www.whoumc.org/Graphics/24734.pdf.
18. Panja B, Bhowmick S, Chowrasia V R. Bhattacharya S, Chatterjee R N, Sen A, et al. A cross-sectional study of adverse drug reactions reporting among doctors of a private medical college in Bihar. India Indian J Pharmacol. 2015; 47(1): 126-127.
19. Magazine R, Shahul H A, Chogtu B. Kamath A. Comparison of oral montelukast with oral zileuton in acute asthma: A randomized, double-blind, placebo-controlled study. Lung India. 2016; 33(3): 281-286.
20. 17. Chyka PA and McCommon SW. Reporting of ADRs by poison control centers in the US. Drug Saf. 2000;23(1):87-93.
21. Dal Pan GJ. Ongoing challenges in pharmacovigilance. Drug Saf. 2014;37(1):1-8. Doi: 10.1007/s40264-013-0123-x
22. Folb PI and Olliaro P. Pharmaceutical policies and regulatory control. WHO Drug Information. 2000;14(2):82-84.
23. Evans SJ. Pharmacovigilance: a science or fielding emergencies? Stat Med. 2000;19(23):3199-3209