PHARMACOVIGILANCE: A WORLDWIDE MASTER KEY FOR DRUG SAFETY MONITORING.

1.GOVINDU DIVYA JYOTHI

B-Pharmacy

Krishna Teja Phamacy College, Tiupati.

Email;djgovindu@gmail.com

Mobile Number; 9550872700

2.Mrs.U.NIRUPAMA, M.Pharm

Assistant Professor, Department Of Pharmaceutical Analysis And Quality Assurance, Krishna Teja Pharmacy College,Chadalawada Nagar , Renigunta Road , Tirupati, Chittoor dist, Andhara Pradesh , 517506.

Email; nirupamaurakana@gmail.com

Mobile number; 9550056738.

3.TAMATAM REDDEMMA

Krishna Teja Pharmacy College, Tirupati.

4.VANAM ROOPA

Krishna Teja Pharmacy College, Tirupati.

5.GADIYARAM THEJASREE

Krishna Teja Phamacy College, Tirupati.

6.CH. JYOTHIRMAYEE

Krishna Teja Pharmacy College, Tirpati.

ABSRACT

Pharmacovigilance is the science of detection, assessment, understanding and prevention of adverse drug effects or any other possible drug related problems. Man must have experienced the adverse drug reactions when he first started using plants as medication and evidences of awareness to adverse drug effects can be observed in literature. Pharmacovigilance supports the safe and correct use of medicines. However, there is significant under- reporting of side effects has become a major problem in developing countries. Science and activities related to the discovery, evaluation, understanding other drug- related problems plays an important role in ensuring that patients receive safe medication level increase Pharmacovigilance. Pharmacovigilance knowledge can be the basis for these interventions to improve reporting rates and reduce adverse events. Pharmacovigilance involves more than spontaneous reporting, and is more than just evaluating marketed medications. It has grown from a minor component of drug control to a major activity and expanded its scope to encompass the assistance for patient safety during clinical trials by ensuring adequate informed consent and institutional review boards (ethical committees); development of a safety profile for proper use of a new molecular entity and appropriate communication of that information to a range of relevant stakeholders; selection of the first safe dose for use in humans based on pharmacologic data obtained in animal studies; development of a safety profile. This study implicates the growth of Pharmacovigilance in assessing the safety of drugs.

Keywords:

Adverse drug reactions, History, Legislation, Thalidomide Signal detection, Intensive monitoring, Pharmacovigilance, Spontaneous reporting, Transparency.

INTRODUCTION

Pharmacovigilance:

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. Recently, its concerns have been widened to include …

• Herbals

• Traditional and complementary medicines

• Blood products

• Biological

• Medical devices

• Vaccines.

Pharmacovigilance Programme of India (PVPI)

Launched by the MOHFW, Govt. of India in the year 2010 at AIIMS New Delhi as

♣ National Coordinating Centre (NCC).

The Programme transferred to IPC as NCC in April, 2011 by a Notification issued by the

♣ MOHFW, Govt. of India.

IPC-PVPI became the NCC for Materiovigilance Programme of India (MVPI) from July, 2015

IPC, NCC-PVPI became a WHO Collaborating Centre for Pharmacovigilance in Public Health Programme & Regulatory services from July, 201

Pharmacovigilance in Acts & Rules

• Pharmacy Council of India: Pharmacovigilance as one of the subjects in Pharmacy Under Graduate curriculum

• Drugs & Cosmetic Act & Its rules 1945: establishment of Pharmacovigilance cell in the pharmaceutical industry is mandatory.

• Drugs & Cosmetic Act & Its rules 1945: establishment of Pharmacovigilance cell in the pharmaceutical industry is mandatory.

HISTORY OF INVOLVEMENT IN DRUG SAFETY MONITORING BY WHO

This chapter introduces the events and ideas that have underpinned the foundation and early development of Pharmacovigilance over the last thirty years under the aegis of the World Health Organization. In 2002, more than 65 countries have their own Pharmacovigilance canters. Membership of the WHO Programme for International Drug Monitoring is co-ordinate by the WHO Collaborating Centre for International Drug Monitoring, known as the Uppsala Monitoring Centre (UMC)

The evolution of Pharmacovigilance in recent years and its growing importance as a science critical to effective clinical practice and public health science are described. The national Pharmacovigilance centers have become a significant influence on the drug regulatory authorities, at a time when drug safety concerns have become increasingly important in public health and clinical practice. Pharmacovigilance is now firmly based on sound scientific principles and is integral to effective clinical practice. The discipline needs to develop further to meet public expectations and the demands of modern public health

The etymological roots for the word "Pharmacovigilance" are: *Pharmakon* (Greek) = medicinal substance, and *Vigilia* (Latin) = to keep watch.

In this short article, we describe the milestones (as represented in Fig. 1) That led to the evolution of Pharmacovigilance activities in the last century.

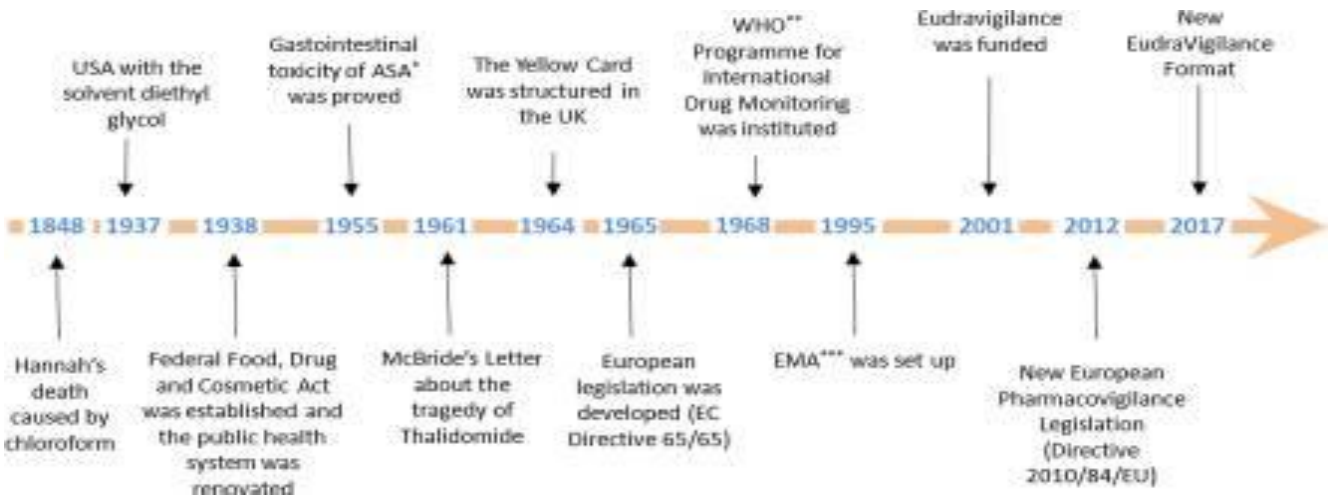

Figure.1. Timeline of the historical evolution of Pharmacovigilance

*ASA: acetylsalicylic acid
*WHO: World Health Orgnaisation
*EMA: European Medicines Agency

The history of Pharmacovigilance started 169 years ago, on Jan 29, 1848, when a young girl (Hannah Greener) from the north of England died after receiving chloroform anesthetic before removal of an infected toenail. Sir James Simpson had discovered that chloroform was a safer and powerful anesthetic, and he had introduced it in clinical practice. The cause of Hannah's death was investigated to understand what happened to Hannah, but it was impossible to identify what killed her. Probably she died of a lethal arrhythmia or pulmonary aspiration [1].
As a result of other deaths and alerts raised by the clinicians and the public about the safety of anesthesia, *The Lancet* Journal established a commission to take on this problem. The commission exhorted English doctors, including the doctor in colonies, to report deaths caused by the anesthesia. The results were published in The Lancet in 1893 [2].

The US Federal Food and Drug Act were formed on June 30, 1906, and it established that drugs must be pure and free of any contamination. Furthermore, in 1911, this organization forbade false therapeutic indications of drugs [2]. In 1937, there were 107 deaths in the USA, because of the use of sulfanilamide elixir, containing diethyl glycol as the solvent. This solvent was considered the cause of deaths, but the manufactory companies were not aware about its toxicity at that time [1, 2, and 3]. Consequently, the Federal Food, Drug and Cosmetic Act were established in 1938; its aim was to renovate the public health system. Indeed, the new system foresaw that the safety of drugs should be demonstrated before their market approval, and introduced the possibility of conducting factory inspections [5]. In 1938, Douthwaite supposed that acetylsalicylic acid (ASA) could cause melena [6]. The study of the gastrointestinal toxicity of ASA showed different outcomes. However, in 1955, it was proved that ASA can cause gastrointestinal diseases and therefore it is currently contraindicated in patients with gastrointestinal ulcers [7].

In 1961, a big change of European Pharmacovigilance happened following the tragedy of Thalidomide. Dr. McBride, an Australian doctor, wrote a letter to the editor of the Lancet Journal, in which he suggested a connection between congenital malformation of babies and thalidomide. In fact, he observed that the incidence of congenital malformations of babies (1.5%) had increased up to 20% in women who had taken thalidomide during pregnancy [8]. At the same time, during a Pediatric Convention in Germany Dr. Lenz suggested a correlation between malformations and thalidomide and his suspect was published in a German Journal (Welt am Sonntag) [9]. In 1973, a retrospective study showed the correlation between the congenital malformations of babies and the ingestion of thalidomide during pregnancy [10]. In USA, the tragedy of thalidomide was not observed, because Dr. Kelsey showed strong doubts about the safety of thalidomide during pregnancy [3]. The tragedy of thalidomide brought to light many problems and critical issues, in particular, the reliability of animal tests, the behavior of the industrial company, and the importance of monitoring the drugs after their marketing. In particular, this tragedy changes the system of Pharmacovigilance, because the spontaneous reporting of adverse drug reactions became systematic, organized, and regulated. This letter

already contained all of the elements needed to generate a spontaneous reporting and to establish a cause-effect relationship between the adverse event and the drug (Fig. 2) [11]. In 1964, the "Yellow card" (YC) was structured in the UK. YC is a specific form to compile a spontaneous report of drug toxicity [12]. In USA (1962), the amendment, requiring safety and efficacy data of drugs before premarketing submission, was approved. As a result of this amendment, the safety data have to include also teratogenicity test in three different animals [3]. In Europe (1965), the disaster of thalidomide stimulated the development of a European legislation with the EC Directive 65/65 [13]. In 1966, a pilot study of Boston Collaborative Drug Surveillance Program started. It was the first group to conduct epidemiologic researches to quantify the potential adverse effects of drugs utilizing in-hospital monitoring and had an essential role in the development and application of methods in drug epidemiology [14]. In 1968, the WHO Programme for International Drug Monitoring was instituted and ten members participated in this program (Australia, UK, USA, Germany, Canada, Ireland, Sweden, Denmark, New Zealand, and Netherlands). Italy participated in this program in 1975 [15]. Many studies of observed adverse drug reactions were conducted between 1968 and 1982 [1]. In 1992, the European Society of Pharmacovigilance (ES0P) was funded, turned into the International Society of Pharmacovigilance (ISOP) .The aims of this society were to promote Pharmacovigilance, and enhance all aspects of the safe and proper use of medicines [16]. In 1995, the European Medicines Agency (EMA) was set up [17]. In 2001, EudraVigilance was funded. It is the official European database for managing and analyzing information on suspected adverse reactions to medicines which have been authorized for the market or being studied in European clinical trials [18]. A major change in European Pharmacovigilance was observed with the new legislation (Directive 2010/84/EU), in 2012 [18]. The main changes in the new legislation were [19]:

- Modification of the definition of adverse drug reactions (ADR);
- Greater involvement of patients and citizens in Pharmacovigilance activities;
- Strengthening of the Eudravigilance database containing reports of suspected reactions reported by all EU Member States;
- Increasing transparency and timeliness of important information on Pharmacovigilance problems;
- Obligation of "additional monitoring" for the products contained in the specific list kept by the EMA;
- Possibility to impose further safety and/or efficacy studies on the certificates of marketing authorization at the time of granting the trust;
- Establishment within the EMA of the Pharmacovigilance Risk Assessment Committee (PRAC

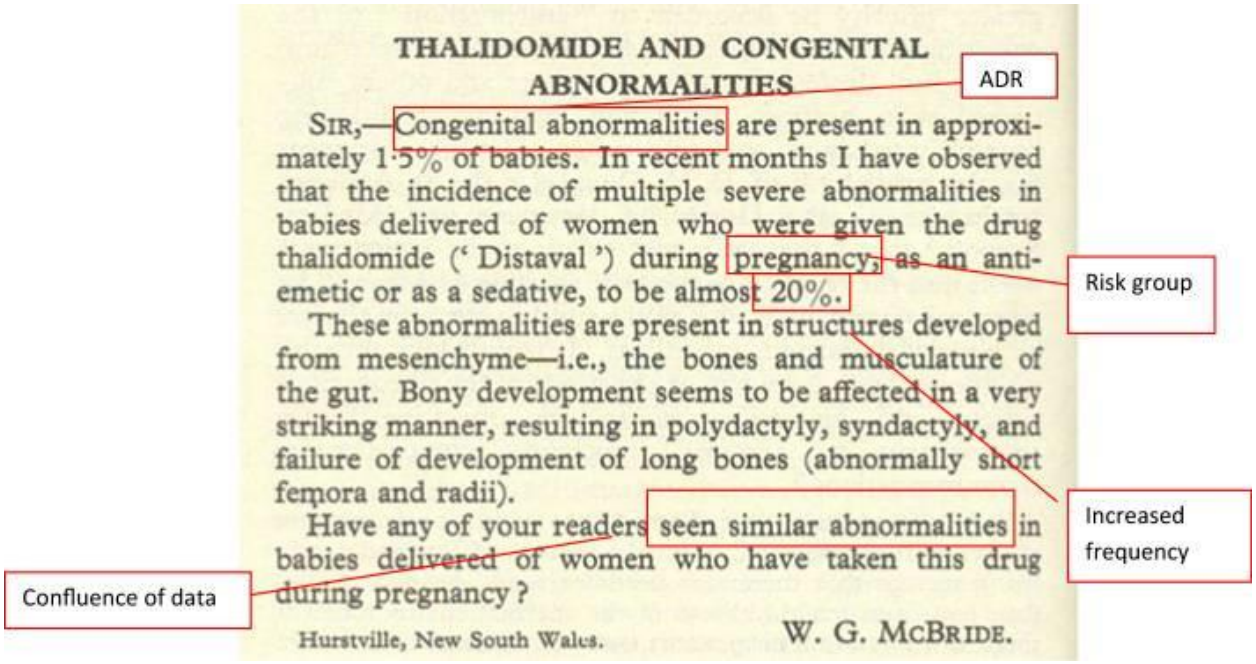

Figure: 2 McBride's letter and important elements for generating spontaneous reporting

In particular, the most relevant change consists in the new definition of ADR: "A response to a medicinal product which is noxious and unintended". In fact, with this definition were covering any adverse event following the use of a medicine, also medication errors and uses outside the terms of the marketing authorization, including the misuse and abuse of the medicinal product.

Furthermore, the new legislation set-up measures to facilitate the performance of PV, called the Good Pharmacovigilance Practices (GVP). The guideline on GVP is divided into two categories: modules covering major Pharmacovigilance processes and product- or population-specific considerations. This last category is available for vaccines and biological medicinal products. In this guideline there are also special chapters dedicated to special areas, namely pregnancy and breast-feeding (P III) and geriatric population (P V) [20].

In November 2017, the new EudraVigilance format was launched; in particular, the marketing authorizations will have extended access to the EudraVigilance database to support the fulfillment of their Pharmacovigilance obligations. These obligations include the continuous monitoring of EudraVigilance data and the communication of validated signals to the Agency and national regulatory authorities, as outlined in Commission Implementing Regulation (EU) N. 520/20121 [17]

The specific aims of Pharmacovigilance are to:

• improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions,

• improve public health and safety in relation to the use of medicines

• contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use, and

• promote understanding, education and clinical training in Pharmacovigilance and its effective communication to the public.

Pharmacovigilance has developed and will continue to develop in response to the special needs and according to the particular strengths of members of the WHO Programmer and beyond. Such active influence needs to be encouraged and fostered; it is a source of vigor and originality that has contributed much too international practice and standards.

Absolute risk

Risk in a population of exposed persons; the probability of an event affecting members of an event affecting member of a particular population. Absolute risk can be measured over time (incidence) or at a given time (Prevalence) .

Active surveillance

Systematic follow-up of groups of subjects exposed to a specific product or groups with a specified diagnosis.

Adverse event (AE) : Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Synonym: adverse experience

ADVERSE DRUG REACTION (ADR)

A response which is noxious and unintended, and which occurs at does normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.(WHO,1972).An adverse drug reactions, country to an adverse event, is characterized by the suspicious of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.

Adverse drug reactions: importance

- Adverse effect on patient quality of life.
- Admission to hospitals or attendance in primary health center
- Length of hospital stay gets increased
- Cost of patient care gets increased
- Patient may lose confidence in their treating doctor
- Adverse reactions may mimic disease and result in unnecessary investigations and /or delay in treatment procedures

Types of adverse drug reactions

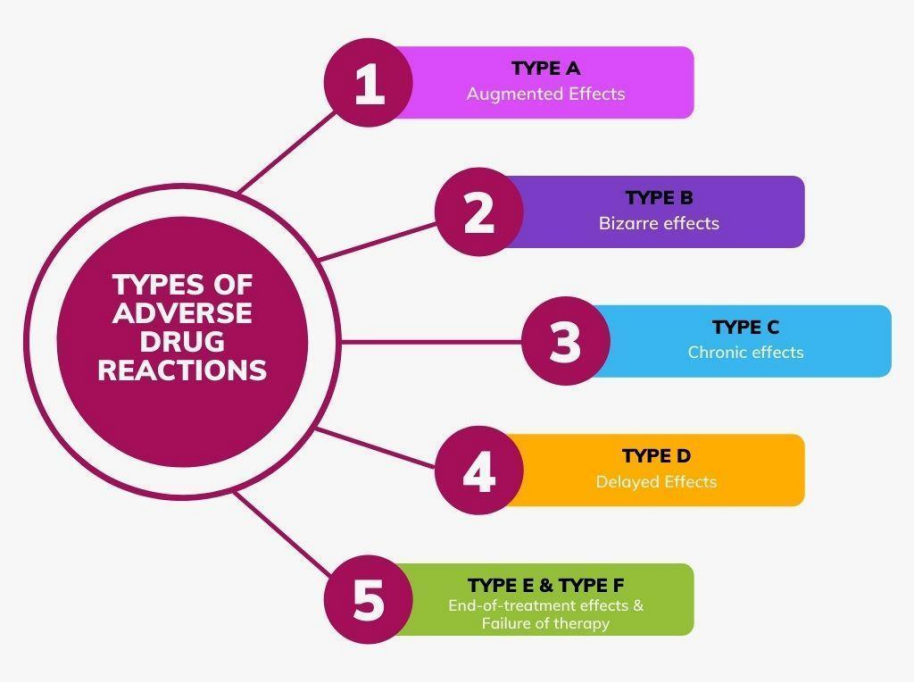

Figure 3: Adverse Drug Reactions: Pharmaguideline

Type A (Augmented) : This is the commonest type (up to 70%) of ADR which is predictable by pharmacological mechanisms.

E.g: Hypotension by beta-blockers.

These type of adverse drug reactions are dose dependent hence forth severity increases with dose such ADRs are preventable in most part by slow introduction of low dosages. Sometimes referred to as Type I ADRs.

Type B (Bizzare) : This type of ADR is not expected from the known pharmacological mechanisms.

E.g : Hepatitis caused by halothane, aplastic anaemia caused by chloramphenicol , neuroleptic malignant syndrome caused by some anesthetics and antipsychotics. Such ADRs are unrelated to dose. Sometimes referred to as Type 2 ADRs.

Type C (Continuous drug use) : This type of ADR occurs as a result of continuous drug use. Such type of ADR may be irreversible, unexpected, unpredictable.

E.g. : Tar dive dyskinesias by antipsychotics , dementia by anticholinergic medications

Type D (Delayed): This type of ADR is characterized by the delayed occurrence even after the cessation of treatment.

E.g. : Corneal opacities after thioridazine, opthalmopathy after chloroquine , or pulmonary / peritoneal fibrosis by methyserzide.

Type E (End of dose):

This type of ADR is usually characterized by withdrawal reaction. Such ADRs occur typically with the depressant drugs,

E.g., Hypertension and restlessness in opiate abstainer, seizures on alcohols or benzodiazepines withdrawal; first dose hypotension caused by alpha-blockers (prazosin) or ACE inhibitors.

Type F (Failure of therapy): This type of ADR results from the ineffective treatment,

E.g., accelerated hypertension because of inefficient control. This may also be called as lack of efficacy.,

PHARMACOVIGILANCE METHODS

Pharmacovigilance method can be categorized as:

- **Passive Surveillance**
- Spontaneous reporting
- Case series
- **Stimulated Reporting**
- **Active Surveillance**
- Sentinel Sites
- Drugs event monitoring
- Registries
- **Comparative Observational Studies**
- Cross sectional study (survey)

- Case-control study
- Cohort study
- Targeted Clinical Investigations
- Descriptive Studies
- Natural history of disease
- Drug utilization study

Pharmacoepidemiology are also used as tools in Pharmacovigilance for generating initial suspicious (Hypothesis generation method) or testing hypotheses (Hypothesis testing methods) about changes in adverse effect profiles of medicines. The details of these two methods are provided as below:

Hypothesis – generating method

- Spontaneous ADR reporting
- Prescription event monitoring (PEM)

Hypothesis-generating studies, with a recently marked drug, aim to provide unexpected ADRs.

Hypothesis- Testing method

- Case-control studies
- Cohort studies
- Randomized controlled trails

Hypothesis testing studies aim to prove whether any suspicious that may have been raised are justified.

ADVERSE DRUG REACTION

At a normal dose sometimes the given medications may harm the patients which are called **Adverse Drug Reactions (ADR).**[21] Adverse drug reaction is different from side effect. The evaluation of ADRs is most critical in the field of Pharmacovigilance.

Concerning marketed remedies, a suitable definition of an adverse drug reaction is as follows:

1. **Unlisted/unexpected adverse drug reaction** An adverse reaction is the nature or harshness of drug which is not reliable with the proper product data available at the time of clinical trials. Company is needed help during investigators brochure for an unapproved drug.Brief summary of drug data sheet for an official product.

2. **Listed / expected adverse drug reaction**

The information about ADR like nature or severity and specificity of the drug is already recorded.[22]

ADVERSE DRUG REACTIONS REPORTING

When the adverse reaction to drugs is potentially serious or clinically important, all health care workers including doctors, pharmacists, nurses and other health experts are requested to clarify it. It is necessary to report an adverse drug reaction to Pharmacovigilance.

SPONTANEOUS REPORTING SYSTEM

1. Regionalization

2. Repossession of further data

3. Access to all important pre and post marketing information

4. Detailed drug utilization data.

5. Standardized Evaluation of causality and significance

6. Encouragement

Documentation of ADRs

The Pharmacovigilance curriculum conveyed worldwide motivate that all suspected drug related adverse events should be outlined. It takes interests on reports of the following:

(A) Every adverse effect suspected or occurred by new drugs and drugs of current issue

(B) Documentation of various drugs that cause ADRs, which include death, life-threatening conditions, disability, hospitalization and congenital abnormalities

The significant adverse reaction of any drug should be notified within seven days. The other facts related to adverse events should be informed within eight days. (Bates et al. 1995: Classen et al 1997). The ADR form can be collected through any Pharmacovigilance centre. After reviewing the form, the centre forwards it to the regional centre and after that, it is propelled to the zonal centre (Goldman 1998: Palaian et al. 2006: Ravi Shankar et al. 2010). The details are then statistically inspected and forwarded to WHO-Uppsala Monitoring committee (UMC).[23]

The purpose of this document is:

- To present the case for the importance of Pharmacovigilance
- To record its growth and potential as a significant discipline within the medical science.
- To describe its impact on patient welfare and public health.

Monitoring of ADRS

ADR monitoring is the practice of continuously monitoring the undesirable effects caused using any drug. Pharmacovigilance plays an imperative impersonation in monitoring ADRs.[24]

It is inherent for pharmaceutical regulators to screen their pharmaceutical products in the market and record if any suspected adverse reactions are identified. ADRs can occur by use of various pharmaceutical products, herbal drugs, cosmetics, medical devices, biological etc. Introducing this monitoring procedure intends at warranting that patients to receive safe and beneficial medicinal products.{Karch and Lasanga 1997}.

If any of the adverse events are not stated, it may result in noxious and serious effects of remedial products. Thus properly conducting ADR monitoring programs will help to reduce the harmful effects of therapeutic products.

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.[24]

Serious Adverse Event

A serious adverse event (SAE) in human drug trials are defined as any untoward medical occurrence that is caused at any dose

(a) Results in death

(b) Is life threatening

(c) Require in-patient hospitalization

(d) Prolongation of existing hospitalization

(e) Causes congenital anomaly/birth defect.[25] Investigators in human clinical trial are obligated to report these events in clinical study reports. Research suggests that these events are often inadequately reported in publicly available reports.[26]

Pharmacovigilance in India

India has more than half a million qualified doctors and 15,000 hospitals having a bed strength of 6,24,000. It is the fourth largest producer of pharmaceuticals in the world. It is emerging as an important trial hub in the world. Many new drugs are introduced in our country. Therefore, there is a need for a vibrant Pharmacovigilance system in the country to protect the population from the potential harm that may be caused by some of these new drugs. Clearly aware of the enormity of task the Central Drugs Standard Control Organization (CDSCO) has initiated a well structured and highly participative National Pharmacovigilance program. It is largely based on the recommendations the WHO document titled "safety monitoring of medicinal products-Guidelines for setting up and running a Pharmacovigilance centre".[27]

The specific aims of Pharmacovigilance programmers are to:

• Contribute to the regulatory assessment of benefit, harm, effectiveness encouraging their safe, rational and effective use (including cost effective use).

• Improve patient care and in relation to use medicine and all medical and Para medical interventions.

• Improve public health and safety in relation to use of medicines

• Promote understanding, education and clinical training in Pharmacovigilance and its effective communication to the public.

Future aspects of Pharmacovigilance in India

With more and more clinical trials and other clinical research activities being conducted in India, there is an immense need to understand the importance of Pharmacovigilance and how it impacts the life cycle of product. Given this situation, the DCGI should act quickly to improve Pharmacovigilance so as to integrate good Pharmacovigilance practice in to the processes and procedures to ensure regulatory compliance and enhance clinical trial safety and post marketing surveillance. A properly working Pharmacovigilance system is essential if medicines are to be used safely. It will benefit all parties including health care professionals, regulatory authorities, pharmaceutical companies and the consumers. It helps pharmaceutical companies to monitor their medicines for risk and to devise and implement effective risk management plans to save their drugs in difficult circumstances.

The following proposals must be followed

• Building and maintaining a robust Pharmacovigilance system

• Making Pharmacovigilance reporting mandatory and introducing Pharmacovigilance inspections

• High-level discussions with various stake holders

• Strengthen the DCGI office with trained scientific and medical assessors for Pharmacovigilance

• Creating a single country specific adverse event reporting form to be used by all

• Creating a clinical trial and post marketing data base for SAEs/ SUSARs / and ADRs for signal detection and access to all relevant data from various stake holders

• List all new drugs/ indications by maintaining a standard data base for every pharmaceutical company

• Education and training of medical students, pharmacists and nurses in area of Pharmacovigilance.

• Collaborating with Pharmacovigilance organizations in enhancing drug safety with advancements in information technology there has been the emergence of new opportunities for national and international [28]

• Building a network of Pharmacovigilance and pharmacoepidemiologists in India.

Developments

• Drug safety information must serve the health of the public.

• Education in the appropriate use of drugs, including interpretation of safety information, is essential for public at large, as well as for health care providers.

• All the evidence needed to assess and understand risks and benefits must be openly available.

• Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected impartially evaluated and made accessible to all.

• Innovation in drug safety monitoring needs to ensure that emerging problems are promptly recognized and efficiently deals with and that information and solutions are effectively communicated.

AIMS OF PHARMACOVIGILANCE

The aims of Pharmacovigilance are

• The identification and quantification of previously un-recognized adverse drug reaction (ADR

• The identification of sub-groups of patients at particular risk of ADRs (the risk relating to dose, age, gender and underlying disease).

• The continued monitoring of a safety of a product, throughout the duration of it use, to ensure that its risks and benefits remains acceptable. This includes safety monitoring following significant newly approved indications.

• The comparative adverse drug reaction profile of products within the same therapeutic class.

• The detection of inappropriate prescription administration.

• The further elucidation of a product pharmacological/toxicological properties and the mechanism by which it produces adverse drug reactions.

• The detection of significant drug-drug interactions between new products and co-therapy with agents already established on the market, which may only be detected during widespread use.[29] In short, Pharmacovigilance aims to improve patient care and safety, public health, assessment of benefit, harm, effectiveness and risk of medicines promote understanding, education and clinical training.

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. 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.[30] 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.[30]

STEPS IN PHARMACOVIGILANCE PROGRAMME

1. Finding the risk of a drug
2. Clinical trials
3. Pharmacoepidemiological study
4. Case report
5. Developing case series
6. Analysis of case series
7. Use of data mining to identify product- event combination
8. Spontaneous reporting.

ACTIVITIES IN PHARMACOVIGILANCE OPERATIONS

Case Registry

• Triage

• Registry

• Enrollment

Processing

• Data Entering

• Coding

• Labelling

Medical Review

• Serious Case Medical Review

• Non Serious Listing Review

• Aggregate Report Review

Aggregate Reports

• Analysis and Creation of IND/NDA Reports

• Analysis and Creation of Pader Reports

• Analysis and Creation of Psur & Bridge Reports

PARTNERS IN PHARMACOVIGILANCE

A complex and vital relationship exists between wide ranges of partners in the practice of drug safety monitoring. Sustained collaboration and commitment are vital if future challenges in Pharmacovigilance are to be met in order to develop and flourish.

• Government

• Industry

• Hospital and academia [31]

• Poison information centers

• Health professionals [32,33]

• Patients

• Consumers

• Media

• WHO

CONCLUSION

Pharmacovigilance is the only way to ensure drug safety throughout the lifecycle. It is very much crucial as the clinical trials have limitation to detect the rarer and very rarer ADRs .The knowledge and information available about the safety of each drug is very extensive. To protect public health, it is important that medicines regulators make appropriate decisions. Health care professional main report on ADRs. However, there represent great interest under reporting takes place worldwide. It major challenge of today. In spite of those limitation, the spontaneous

reporting system remains as a most widely most widely used method to report ADRs and is able to generate single of rare and very rare type of ADRs. If all the health care professionals take ADR reporting as an ethical obligation and major responsibility, we can make our world safer than what it is today. Every reporting by health care professionals is important, even though focus on the serious unlabelled types of ADRs is more important. There are significant effects on the Pharmacovigilance to make it more functional after the concept has emerged and day by day we are getting closer to destiny. It is our responsibility to ensure well functioning of Pharmacovigilance system. ADR reporting should be viewed by healthcare professional as a very important responsibility rather than an additional clinical burden aimed at ensuring safer use of drugs worldwide.

REFERENCES

1. Routledge P. 150 years of Pharmacovigilance. *Lancet.* 1998;351:1200–1201. doi: 10.1016/S0140-6736(98)03148-1. [PubMed] [CrossRef] [Google Scholar]

2. Commission on Ana esthetics. Lancet. 1893; i:629–38.

3. Woolf AD. The Haitian diethylene glycol poisoning tragedy: a dark wood revisited. *JAMA.* 1998;279:1215–1216.doi: 10.1001/jama.279.15.1215. [PubMed] [CrossRef] [Google Scholar]

4. FDA Consumer Magzine. https://www.fda.gov/downloads/AboutFDA/WhatWeDo/History/Origin/ucm125604.doc (1981). Accessed 22 Dec 2017.

5. Food and Drug Administration (FDA). History. https://www.fda.gov/AboutFDA/WhatWeDo/History/. Accessed 22 Dec 2017.

6. Douthwaite AH. Some recent advances in medical diagnosis and treatment. *Br Med J.* 1938;1:1143. doi: 10.1136/bmj.1.4038.1143. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

7. Levy M. The epidemiological evaluation of major upper gastrointestinal bleeding in relation to aspirin use. In: Kewitz H, Roots I, Voigt K, editors. *Epidemiological concepts in clinical pharmacology.* Berlin: Springer; 1987. pp. 100–104. [Google Scholar]

8. McBride WG. Thalidomide and congenital abnormalities. Lancet. 1961; ii:1358.

9. Lenz W, Knapp K. Foetal malformations due to Thalidomide. *German Med.* 1962;7:253–258. [Google Scholar]

10. Kajii T, Kida M, Takahashi K. The effect of thalidomide intake during 113 human pregnancies. *Teratology*. 1973;8:163–166.doi: 10.1002/tera.1420080208. [PubMed] [CrossRef] [Google Scholar]

11. ICHguideline. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf. Accessed 22 Dec 2017.

12. YellowCard. https://yellowcard.mhra.gov.uk/monitoringsafety/. Accessed 22 Dec 2017.

13. Council Directive 65/65/EEC. http://www.echamp.eu/eu-legislation-and-regulation-documents/directive_65-65-eec__-__consolidated_version.pdf. Accessed 22 Dec 2017.

14. Boston Collaborative Drug Surveillance Program. http://www.bu.edu/bcdsp/. Accessed 22 Dec 2017.

15. WHOPharmacovigilance. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/. Accessed 22 Dec 2017.

16. I Sop - ESOP/I Sop History. http://isoponline.org/about-isop/esopisop-history/. Accessed 22 Dec 2017.

17. EMAHistory. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000628.jsp. Accessed 22 Dec 2017.

18. EudraVigilancehistory. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000633.jsp. Accessed 22 Dec 2017.

19. Directive 2010/84/EU. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf. Accessed 22 Dec 2017.

20. EMAPharmacovigilance. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001819.jsp&mid=WC0b01ac05800241de. Accessed 14 Mar 2018.

21. Joerg H. Basic principles of Pharmacovigilance and data sources.

22. Sachdev Y. Pharmacovigilance: safety matters, Indian pharmacology. February 2008; 40.

23. Hall et al. 1995; Horbuckle et al. 1999; Tuntti and Neuroren 2002.

24. Moore N (2001). The role of clinical pharmacologist in management of ADRs. Drug safety, 211(1): 17.

25. The importance of Pharmacovigilance; safety monitoring of medical products, Geneva, WHO, 2002.

26. J.P Loannidis, J Lau. Completeness of safety reporting in randomized trials: an evaluation of seven medical areas. JAMA, 2001; 285(4): 437-443.

27. P.Biswas, A. K. Birwa's setting standards for proactive Pharmacovigilance in India: the way forward. Indian Journal of pharmacology, 2007; 39: 124-128.

28. Ronaldd M, Elizabeth BA.

29. Moore N. The role of clinical pharmacologist in the management of ADRs. Drug safety, 2001;24(1):17.

30. Hall M, Mc Cormack P, Arthur N, Feely J. The spontaneous reporting of ADRs by nurses. British journal of clinical pharmacology, 1995; 40: 173-175.

31. Horn buckles K, WUH-H, Fung MC. Evaluation of spontaneous adverse event of reports by primary reporter a 15 year review (1983-1997). Drug information journal of clinical pharmacology, 1995; 40: 173-175.

32. Consumer reporting ADRs. WHO drug information, 2000; 14: 211-215.

33. Egberts GPG Smulderes M, De Konig FHP et al. Can ADRs be detected earlier? A comparision of reports by patients and professionals. British Medical Journal, 1996; 313: 530531.