Review Article

Monitoring Adverse Drug reactions: Milestones achieved

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Abstract

Mankind with its existence requires medicines either to prevent, to get rid of from ailments or to maintain normal health from invaders. The idea of protecting us from adverse drug effects in such a way has come up with the advent of more and more new drug molecules. Need of vigilance is created to justify and verify the desired role of those new and old molecules. In fact, sense of vigilance activities on medicines has gained impetus in pharmaceutical or medical sciences. In such a way Pharmacovigilance now a days is a separate segment in monitoring the Adverse Drug Reactions.

Keywords: Drug, adverse effects, pharmacovigilance

Introduction:

The word "Pharmacovigilance" (henceforth will be written as "PV"), itself conveys some sense of observance or monitoring activities on medicinal products. In fact, consequent upon the heinous tragedy of "Thalidomide- babies" in mid-60's, the word "pharmacovigilance" was first coined by some French pharmacologists/ doctors by conjoining two words Pharmakon (Greek) = medicinal substance, and Vigilia (Latin) = to keep watch. Now this "sense of vigilant activities" raises many questions as to why these vigilance activities are needed on medicines [1]. Even if it is needed, who will be the suitable persons to execute such activities? How, where and when these activities are to be carried out on medicinal products? etc.

Let us try to explore the common curriculum taught under pharmaceutical sciences and examine which discipline may be the suitable and nearest to PV. Under the pharmaceutical sciences we find various disciplines e.g., Drug discovery & Design (medicinal Chemistry, structural biology etc.), Drug Delivery (Pharmaceutics), Drug Action (Pharmacology, Toxicology, Pharmacodynamics / Pharmacokinetics), Clinical Sciences (Efficacy. Adverse effects, drug-drug interaction, bioavailability), Drug Analysis, Pharmaco-economics (Cost effectiveness), Regulatory affairs. Hence, we find that PV being a structured scientific activity, aiming to monitor the risk/benefit ratio of Medicines can be well placed under clinical sciences discipline & medical Pharmacology field. The ultimate objective of PV is to improve patient's safety and thereby maintaining the quality of patient's life, that has important social and commercial implications in a country. The data generated through PV activities also become a treasure trove for further research works in drug discoveries.

In this commentary, I am trying to report the centuries old milestones of PV up to the present day, in order to understand all those historical incidences that have characterized the evolution of PV as the torch bearer in the world-wide drug regulatory affairs and Clinical Sciences. Understanding the tragic events, it's chronologies in the practices of medicines and remedial steps taken consequently, has become the driving force for further progression in PV. The constantly evolving Drug regulatory methodologies including PV activities (outlined in Figure 1) have strengthened the medical fraternity to improve the health care services, to develop pharmacological concepts and also to identify the challenges in coming years to the medical professionals. To summarize, we can say that critical observations on obnoxious, untoward medical incidences during the last couple of centuries lead to the consensus agreement of the scientific community to report such clinical facts through letters, publication in journals, issuing warning-letters to medical professionals and this has been now culminated to the present day ultra-structured, web-based electronic platforms with software driven data-mining facilities across the globe. With the application of Artificial Intelligence, the science and activities of PV is still evolving [2].

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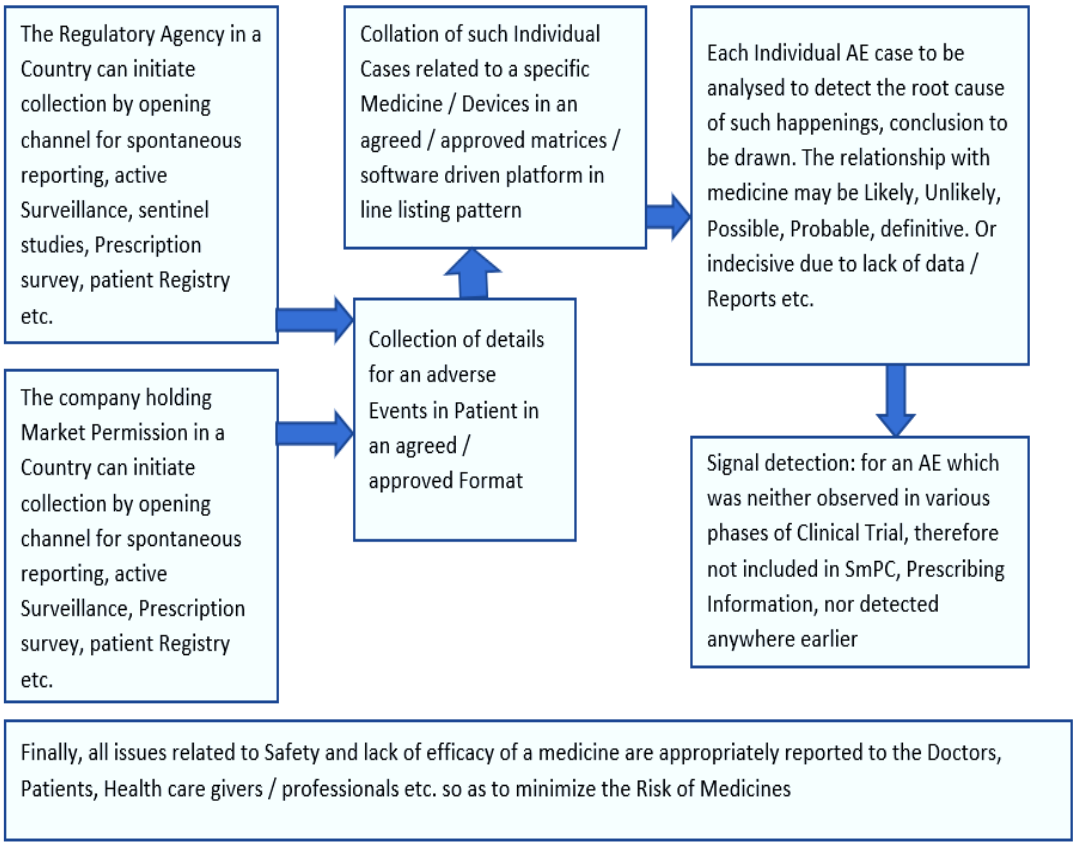

Figure 1. Outline of pharmacovigilance activities.

Historical Perspectives:

All medicines can cause unwanted symptom (side effects). Such medicines may be a prescription drug, over-the-counter (OTC) medicines or complementary medicines including Vitamin formulations and herbal preparations that are dispensed by naturopaths and clinical practitioners of other system of medicinal products (e.g. Unani, Siddha, Ayurveda, Tibetan, Chinese etc). It has been reported that around 230,000 Australians are admitted to hospital every year because of problems with their medicines, including side effects. While most side effects can be managed, some can be very serious and may lead to death. Consistent Pharmacovigilance activities is therefore very important in the best interests to wisely manage medicines for a patient.

By digging out the historical facts, it is found that way back on 29th Jan 1848, (almost 173 years back), a young girl (Ms. Hannah Greener) in the northern England died after receiving chloroform as anesthetic before removal of an infected toenail. By that time, Sir James Simpson had discovered chloroform ($CHCl_3$) to be a safer and powerful anesthetic, and he introduced it in clinical practice. The root cause analysis of that reported death case was done, but could not come to a conclusion what caused Hannah's death. With our current knowledge, this can be predicted that a lethal arrhythmia or pulmonary aspiration happened to her and that lead to her unfortunate Death.

The application of anesthesia before surgery resulted in other deaths and the then clinician raised alerts that lead to public furors about the safety of anesthesia. The Lancet Journal established a commission to look into this problem. The commission insisted that the English doctors in England and its colonies to report deaths caused by the anesthesia. The results were published in "The Lancet" (1893). This was probably the first example of giving significance to the reporting of adverse incidences occurring from the treatment by a medical product.

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On 30th June 1906, the United States Federal Food and Drug Act was signed by the then President of America Mr Roosevelt and published for the public to maintain the Government order that "drugs" must be pure and contamination free. Furthermore, in 1911, the US-FDA enacted prohibition for promotion of false therapeutic indications of drugs. Nevertheless, in 1937,

Sulfanilamide elixir tragedy engulfed the USA- citizens with 107 deaths. The investigation outcome pinpointed the presence of "diethyl glycol (DEG)" as the solvent in the Elixir.
The manufacturing company in USA was not aware about the toxicity of this solvent. Consequently, in 1938 the Federal Food, Drug and Cosmetic Act was promulgated with an overhauling objective to renovate the public health system in USA. This new system of medicine regulation enacted that, before market approval of medicinal products there should be prior demonstration of its safety aspects and also the factory premises to be inspected.
The above mentioned untoward, noxious incidences in the history of medical science in different geographical areas within a gap of little lesser than a century taught us the need of robust Drug-Regulation for a medicinal product to be launched in clinical practices and whatsoever be the adverse outcome there is always a need for reporting for betterment of the situation.

In 50's – 60's, the biggest tragedy in the history of allopathic medicinal system happened to be reported that shook the world. One West German pharmaceutical company M/s Chemie Grünenthal GmbH developed "Thalidomide" in the 1950s, originally intended as a sedative or tranquiliser. Thalidomide was soon promoted for treating a wide range of other conditions, including colds, flu, nausea and morning sickness in pregnant women. The researchers at the company, during animal testing, found that it was virtually impossible to give lethal dose of the drug (based on the LD50 test) to the test animals. Largely, based on this, the drug was deemed to be harmless to humans. Thalidomide was licensed in July 1956 for over-the-counter (OTC) sale (no doctor's prescription was needed) in Germany. With its growing popularity more and more pharmaceutical companies started producing and marketing the drug under license from M/s Chemie Grünenthal. By the end of -1950s, approximately, 14 pharmaceutical companies were marketing "Thalidomide" in 46 countries under at least 37 different trade names.

In 1958, thalidomide was produced in the United Kingdom by M/s Distillers Company (Biochemicals) Ltd, under the brand names Distaval, Tensival, Valgraine and Asmaval. Their advertisement also claimed that Distaval can be given with complete safety to pregnant women and nursing mothers without adverse effect on mother or child.

An Australian doctor William McBride, in 1961, first time proposed the link between thalidomide and its impact on limb development of foetus in mother's womb. 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. He made this public by publishing a letter in "The Lancet". In a Paediatric Convention in Germany Dr. Lenz also presented a correlation between malformations of baby's limbs and thalidomide and this was published in a German Journal (Welt am Sonnatag). These facts on congenital malformations of babies by ingestion of thalidomide during pregnancy, were further reinforced in a retrospective study (1973). With the growing outcry from other areas, the drug was formally withdrawn by M/s Chemie Grünenthal GmbH on 26 November 1961. Within few short years that thalidomide was available, its estimated that over 10,000 babies were affected by the drug worldwide. Around half died within months of being born and others survived with defective limb formation (Phocomelia). In 1968 M/s Chemie Grünenthal GmBH was brought to trial in Germany. The company settled the case out of the court and arrangements were made to compensate German victims. No one was found guilty of any crimes. In the same year, in the UK the British distributor, M/s Distillers Company, also reached a compensation settlement with the UK victims of the drug.
Under these horrifying situations in Europe, Australia it was remarkable that in USA, the Thalidomide tragedy was averted. The credit went to Dr. Francis Rhodham Kelsey who was the then working as reviewer for the discovery document of medicines. As Reviewing Medical Officer in US-FDA office her principal duty was to review new drug applications and that was a legal requirement for approval of any drug in USA. Dr. Kelsy got the first assignment of reviewing the application for THALIDOMIDE submitted to US-FDA office by the German Company. By that time the drug was already available in dozens of countries around the world. Dr. Kelsey, did not bent upon the pressure created by the company and refused to approve the application because of its inadequate evidence.
The company continued to send in what they believed was proof of thalidomide's safety, but Dr. Kelsey adamantly insisted on scientifically reliable evidence, which she felt the application profoundly lacked. Approximately a year later, the researchers in Germany and Australia the doctors started hue & cry about the possible link between thalidomide to phocomelia (severe birth defects—hands and feet projecting directly from the shoulders and hips) [3-4].

Pharmacovigilance Now:

The European Commission (EU) defines the term "PV" as the "Process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines".

World Health organization (WHO) defines the same term "PV" as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem".

All chemical origin medicines, biological origin monoclonal antibody-based medicines and vaccines have revolutionized the prevention, treatment, mitigation and diagnosis of diseases and disorders in human being and animal. Nevertheless, all such medicinal products always carry the potential RISK factors that lead to occurrences of undesirable and / or unexpected side effects, in addition to their expected benefits.

In this era, before approval of any medicinal product in a country a battery of tests including clinical trials on human subjects are carried out to evaluate the safety and efficacy of such products. However, the clinical trial process involves studying the medicinal products in a relatively small number of selected individuals for a short period of time. Moreover, during such pre-approval clinical trials there remains very little scope for concomitant usages of other drugs on the trial subjects. Therefore, the drug-drug interactions often remain unexplored during such trials. Certain side effects may only emerge once these products have been used by a heterogenous

population, including people with other concurrent diseases, and over a long period of time. Post-marketing surveillance is seamless activity that primarily protects the public from the ill-effects of medicines. The continuous PV- activities (also called Post Market surveillance) enables the Country's drug Regulatory agencies to modify various regulatory Documents e.g. Prescribing information (PI), Patient Information Leaflet, Risk Management Plan.

The Thalidomide related phocomelia babies shook the entire medical professionals' communities around the world. In particular, this tragedy brought a drastic change in the Drug regulatory activities and enforced the World Medical Association (WMA) to take cognizance of introducing Drug monitoring Systems.

Stevens-Johnson syndrome/toxic epidermal necrolysis is a rare, mucocutaneous disorder most often caused by a reaction to certain drugs

The spontaneous reporting of adverse drug reactions (ADR) became systematic, organized, and regulated. I am trying below the events that were adopted by various regulatory agencies in Europe and USA

- "Yellow card" (YC) was framed and introduced by MHRA in the UK. This specific form was made available to all pharmacies and elsewhere to facilitate spontaneous reporting of drug toxicity and compilation of the same at MHRA level.

- In USA (1962), the Kefauver-Harris amendment was brought into Federal Food, drugs and Cosmetics Act requiring safety and efficacy data of drugs at premarketing submission. This amendment also ensured that the safety data should include teratogenicity test in three different animals.

- In Europe (1965), the disaster of thalidomide stimulated the development of a European legislation with the EC Directive 65/65.

- 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.

- 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.
- Many studies of observed adverse drug reactions were conducted between 1968 and 1982.

- In 1992, the "European Society of Pharmacovigilance (ESoP)" was funded, and later that 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.

- In 1995, the European Medicines Agency (EMA) was set up.
- 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.

- A major change in European Pharmacovigilance was observed with the new legislation (Directive 2010/84/EU), in 2012. The following changes have been incorporated in EMA;

1) Modification of the definition of adverse drug reactions (ADR);
2) Greater involvement of patients and citizens in PV-activities;
3) Strengthening of EudraVigilance database containing reports of suspected reactions reported by all EU Member States;
4) Increasing transparency and timeliness of important information on Pharmacovigilance problems;
5) Obligation of "additional monitoring" for the products contained in the specific list kept by the EMA;
6) Possibility to impose further safety and/or efficacy studies on the certificates of marketing authorization at the time of granting the trust;
7) Establishment within the EMA of the Pharmacovigilance Risk Assessment Committee (PRAC) [1].

The most noteworthy change is the new definition of ADR: "A response to a medicinal product which is noxious and unintended". In fact, this definition is now covering any adverse event following the use of a medicine including the medication errors and off-Label uses of Medicines i.e., out of the terms agreed in the marketing authorization, including the misuse and abuse of the medicinal product.

This new legislation also facilitated development of Good Pharmacovigilance Practices (GVP).

In India the ADR monitoring system was started with 4-regional Nodal authorities in 1995, Later on 2014, the new National co-ordination Center (NCC) was created at Indian Pharmacopoeia Commission (IPC), Ghaziabad. This NCC is operating through 300 ADR monitoring Centres (Called AMC) across the country, established in various medical colleges in Pharmacology Department.

CDSCO being the national Drug Regulatory agency under the aegis of Min. of Health and Family welfare, Govt. of India primarily has the mandate of regulating safety, Efficacy and Quality if "drugs" (including medical devices) as defined in Section 3 (b) (i-iv) in the drugs act 1940. Under this mandate, while approving "New Drugs" the DCG(I) put conditions that PSUR to be submitted to CDSCO every 6-months for first 2-years and then annually for another 2-years. Accordingly, the CDSCO accepts all PSUR from the companies for the newly approved Medicines and review the same for circulation of such reports to all State Drugs Controllers, national Medical Commission and to the companies. The Signal reports generated by PVPI at IPC are also referred to CDSCO for

further review and taking regulatory action appropriately [6-14].

References

1. Pharmacovigilance Risk Assessment Committee: PRAC strategy on measuring the impact of Pharmacovigilance activities. 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/01/WC500199756.pdf.
2. Routledge P. 150 years of pharmacovigilance. Lancet. 1998; 351:1200–1201.
3. FDA Consumer Magazine. https://www.fda.gov/downloads/AboutFDA/WhatWeDo/History/Origin/ucm125604.doc (1981).
4. Food and Drug Administration (FDA). History. https://www.fda.gov/AboutFDA/WhatWeDo/History/.
5. ICH guideline. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf.
6. YellowCard. https://yellowcard.mhra.gov.uk/monitoringsafety/.
7. Council Directive 65/65/EEC. http://www.echamp.eu/eu-legislation-and-regulation-documents/directive_65-65-eec__-__consolidated_version.pdf.
8. Boston Collaborative Drug Surveillance Program. http://www.bu.edu/bcdsp/.
9. WHO Pharmacovigilance. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/.
10. ISoP - ESOP/ISoP History. http://isoponline.org/about-isop/esopisop-history/.
11. EMA History. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us /general/general_content_000628.jsp.
12. EudraVigilance history. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/ general/general_content_000633.jsp. Accessed 22 Dec 2017.
13. Directive 2010/84/EU. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf.
14. EMA Pharmacovigilance. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001819.jsp&mid=WC0b01ac05800241de.