Chapter 1

Introduction

"*The farther back you look the farther forward you can see"*

Winston Churchill

After reading this chapter, you should be able to understand and appreciate:
• The genesis and importance of the term 'Pharmacovigilance'.
• The consequences of Adverse Drug Reactions.
• Historical development of safety monitoring programme.
• The sources of data for Pharmacovigilance.
• Aims and Scope of Pharmacovigilance.
• The Minimum Requirements for National Pharmacovigilance System.

Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medicines, biological products, herbals and traditional medicines with a view to identify new information about hazards and preventing harm to patients. The word 'Pharmacovigilance' is derived from the Greek word *pharmakon* meaning drug and the Latin word *vigilare* meaning to keep awake or alert, to keep watch. The word was initially used in France in 1960s and later was perceived as the new name for the old terminology post marketing surveillance (PMS). The Pharmacovigilance term is now used internationally. The World Health Organization introduced the term in 2002 and has been adopted by International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The domain of Pharmacovigilance is not just restricted to PMS but to the entire period of journey of medicines and related products from the pre-approval development to the post approval period.

Safety and efficacy parameters are the prime requirements of evaluation in the process of drug development. While efficacy is important for assessing the usefulness of a testing drug, the safety requirements make it whether to use or not. The possibility that drug use could result in adverse reaction came to the fore rather earlier than did concern about inefficiency. Even, the father of the modern medicine Hippocrates said "Do no harm". There are many quotes which described the importance of safety issues. The two are cited here:

"Cured yesterday of my disease, I died last night of my physician/medicine".

"Go to the Doctor, get your prescription, pay his fees as the doctor has to survive; Go to the Pharmacist, buy your medicine and pay for it, because the pharmacist has to survive; Now go home and throw your medicines because you need to survive".

The quotes are just to emphasize the issues with the use of medicines and they are not to undermine the importance of medicines in everybody's life. The medicines are perhaps the greatest weapon of mankind fighting illnesses, preventing diseases and improving quality of life besides increasing longevity.

The new drugs undergo a significant amount of testing for safety and efficacy in animals and humans through which the effectiveness can be assessed with certainty but the safety issue with less certainty. The clinical trials never tell the whole story of the effects of a drug in all situations. The clinical trials are incomplete studies due to various reasons like limited and selected patients are used; duration of trial is limited; data on special group of patients either not generated or incomplete. The clinical trials can detect only the commonest adverse drug reactions (with more than 1% incidence). The less common adverse drug reactions (with less than 1% incidence) can only be discovered in a long term study in large population. It took decades before the ADRs of Aspirin on gastrointestinal tract became apparent. It also took years to recognise the renal toxicity of phenacetin. This implies the need of continuing drug safety evaluation in post approval period.

The safety study in post approval period is also called post marketing surveillance (PMS). The word surveillance is derived from French terms: *sur* (meaning over) and *veiller* (meaning to watch). The terminology post marketing surveillance first appeared in 1960s and is attributed to Bill

Inman, a medically qualified doctor worked in drug safety issues in UK for long time.

Clinical Trials (CT): *They are human experimentations conducted in order to assess the safety and efficacy of prospective drug. CT is broadly divided into: Pre-approval and post approval studies. Pre-approval studies are divided into Phase – I, Phase – II and Phase – III.*

Phase – I: *is conducted in 20-100 healthy volunteers to determine the tolerable concentration, the route of administration and the initial pharmacokinetic information. It also checks the possible side effects.*

Phase – II: *is conducted in 100-500 patients. It provides information on efficacy, short term tolerability and to determine the dose that best balances between efficacy and safety (tolerability).*

Phase – III: *is conducted in 1000-5000 patients to confirm effectiveness and monitor adverse drug reactions from longer use.*

Based on the three phases of studies, the drug is approved for marketing. The post approval studies, also called Phase – IV or Post Marketing Surveillance, are conducted to identify the undiscovered adverse drug reactions.

With urgent need of novel treatment for diseases like TB, Malaria, and HIV; more and more drug products are expected to be approved on an accelerated and fast track basis. These arrivals are on conditional basis that safety monitoring is to be continued. This situation further necessitates the need of PV system in place to minimise the risk of new treatment.

Consequences of ADRs

Not that all ADRs are very serious but some are definite causes of death, hospitalization, or serious injury. ADRs have two important consequences on the individuals and the health system:

(i) sufferings (including deaths) and prolonged stay at hospital and

(ii) economic impact.

ADRs are one of the leading causes of morbidity and mortality.

In USA, 700,000 emergency department visits and 120,000 hospitalizations are due to ADEs annually. USD 3.5 billion is spent on extra medical costs of ADEs annually. At least 40% of costs on ambulatory (non-hospital settings) Adverse Drug Events management are estimated to be preventable. In UK, some studies showed that the prevalence of hospital admission resulting directly from adverse drug

reactions was over 5% and adverse drug reactions accounted for 0.15% of deaths among all admissions. Worldwide on an average 3 to 5% of hospital admissions are attributed to ADRs and 0.32 to 6.7% is the incidence of serious and fatal adverse drug reactions out of total ADRs in hospital patients. Due to poor reporting culture much reliable data from India is not available. However, one study from a south Indian hospital [http://www.ncbi.nlm.nih.gov/pubmed/14762985] reported that 3.7% of the hospitalised patients experienced an ADR, 0.7% of the admissions were due to ADRs and 1.8% had a fatal ADR. The average cost of managing an ADR was reported to be ₹ 690/-.

The safety information obtained helps the drug regulating authority to advice on labelling changes to restricting its availability to completely banning the product. Many drugs have been withdrawn from the world market because of actual or perceived safety concern. An estimated one third was withdrawn within two years of launch and a half within five years. Having learnt the importance of safety monitoring of medicines beyond the clinical trials, it may be appropriate to know how the system of safety monitoring has evolved over the years. This is divided into two periods: pre-thalidomide and post thalidomide period.

Pre-Thalidomide Period

The thalidomide disaster changed the world's outlook towards medicines' safety and the world became wiser and started monitoring the medicines in use. This has been a milestone in safety monitoring programme. But there have been records of toxicity caused by the medicines even much before the thalidomide tragedy. Here are few examples of drug safety records that are reported prior to thalidomide: The death of a person during the routine anaesthesia with chloroform in 1848 in north–east England was identified as an episode of ventricular fibrillation. Chloroform was just introduced a year earlier into clinical practice and was known to be better than ether as the former produced less nausea and vomiting. Because of continuing concerns of the public and the profession about the safety of anaesthesia, the Lancet set up a commission which invited doctors in Britain and its colonies to report anaesthesia related deaths. This was viewed as the forerunner of a system of reporting adverse events; the first suspicion that drug might be involved in causing aplastic anaemia was aroused by Labbi and Langlois in 1919 which is around 30 years after the first description of the disease.

In 1934, the role of a drug in the aetiology of agranulocytosis was suggested for the first time.

Though the recording or documenting of toxic effects of medicines has a long history, even in USA there was no assurance of safety and effectiveness of medicines till 1930s. The manufacturers were not in obligation to disclose the contents on the label. The legislation of 1906, Pure Food and Drug Act, was meant just to ensure the purity and consistency of food and drugs and also to ensure the clear and accurate identification of active ingredients. The Act was silent on safety and efficacy. Until 1938, the drugs could still be useless and/or dangerous as long as the label listed the ingredients in a correct manner.

Story of Sulfanilamide Elixir: In 1937, a remedy of sore throat called sulfanilamide elixir manufactured by a small factory in Tennessee was found to be the cause of 107 deaths. As the drug was not soluble in water, it was difficult to form a paediatric preparation. The company, ignorant of toxic aspects of the new solvent, dissolved drug in diethelene glycol. The product had not been adequately tested for safety.

USFDA seized the entire stock before causing further deaths. FDA acted not because the drug was not safe. Safety was not an issue as it was not the requirement (1906 regulation). The FDA acted because the preparation had been mislabelled. Technically an elixir had to contain some quantity of ethyl alcohol and it had none. This was in violation of the law.

But the incident made America to make regulation not only to ensure the safety of the drug but also of the whole product.

Following the sulfanilamide elixir issue, there was demand for better legislation for ensuring safety or against the unsafe drugs. In December 1937, US Congress passed the legislation that had been stalled for several years. This new legislation called Federal Food, Drug and Cosmetic (FDC) Act had taken effect in 1938. This Act necessitated the requirement of demonstration that new drugs were safe before they could be marketed commercially.

Post-Thalidomide Period

A direct consequence of thalidomide disaster that occurred in several countries outside USA, the US Government had amended the FDC Act, known as Kefeuver–Harris Amendment of 1960. As a result of this

amendment, the drug companies were required to prove that new drugs were effective as well as safe. The safety was not a matter of concern till this time. The physicians were instructed through a federal programme called MedWatch to report to the FDA any instance of adverse effect resulting from use of new drug by their patients.

Dr. Frances Kathleen Oldham Kelsey, a pharmacologist in USFDA, prevented the entry of thalidomide into USA market by not approving it. She insisted the need of further studies despite of its approval in UK and other countries. She received commendable appreciation for preventing thalidomide disaster in USA which would have otherwise caused the birth of thousands of armless and legless children. In 1962, she was awarded with President's award for Distinguished Federal Civilian Service from President John F. Kennedy. In 2010 the FDA honoured Kelsey by naming one of their annual awards after her and she was the first recipient.

In UK the Committee on Safety of Drugs (CSD) was formed in 1963. The next year in 1964, it had introduced the Yellow Card system (YCS) with a letter circulated to all doctors urging to report promptly the details of any untoward condition in a patient that might be the result of drug treatment. The YCS is a prepaid system even working today got its name from the colour of the original document used for reporting ADRs. The Medicines and Healthcare Products Regulatory Agency (MHRA) is

responsible for ensuring safety and effectiveness of drugs. Committee on Safety of Drugs was replaced by the terminology Committee on Safety of Medicines (CSM) in 1970. Again in 1970, this was replaced by Commission on Human Medicines (CHM).

Again, it was felt by World Health Organization (WHO) to have an international system for monitoring adverse reaction to drugs (ADRs) based on the data from national centres. After a pilot study in USA, an international database was established at Geneva, WHO head quarter, in 1971. The base for international monitoring system was moved to Uppsala, Sweden, in 1978. Since then, Uppsala Monitoring Centre (UMC) has been managing the primary aspects of expanding worldwide Pharmacovigilance network of more than 180 countries covering approximately 99% of the world's population. UMC is the WHO collaborating Centre for international drug monitoring. India joined the WHO programme in 1998. The Pharmacovigilance Programme of India launched in 2010 has grown leaps and bounds. India has contributed 3.6 % of the total report to the UMC's VigiBase database (as of 2023-2024). This makes India as 4th largest contributor of ICSRs (Individual Case Safety Reports), USA being on the top. The National Coordination Centre, Indian Pharmacopoeia Commission, has achieved the status of WHO Collaborating Centre. The recent initiative of World Health Organization to make the safety database accessible to all would be helpful promoting safe medications.

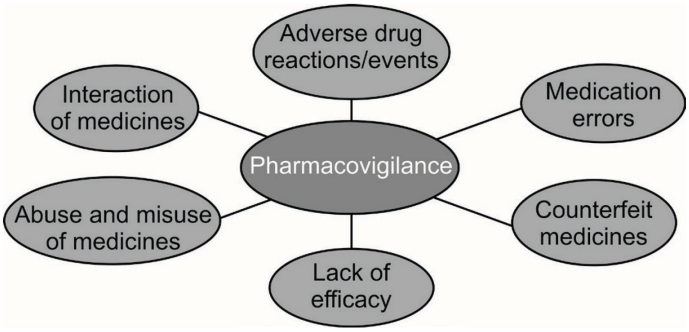
Minimum Requirements for a Functional National PV System:

1. A National PV Centre with designated at least one full time staff, stable basic funding, clear mandates, well defined structure and roles, and collaborating with WHO Programme for International Drug Monitoring;
2. The existence of a National Spontaneous Reporting System with a National Individual Case Safety Report (ICSR) form;
3. The existence of a National Database or System for collating and managing ADR reports;
4. The existence of National Advisory Committee who should be able to provide technical assistance on causality assessment, risk assessment, risk management, case investigation and where necessary take up management and crisis communication; and
5. The existence of a clear communication strategy for routine and crisis communication.

[Source: The Global Fund to Fight AIDS, TB, and Malaria; and WHO]

Scope of Pharmacovigilance

The scope of PV has expanded and can be diagrammatically presented [WHO Pharmacovigilance Indicators, WHO, 2015]



Methods in Pharmacovigilance

The Pharmacovigilance data (ADRs reports) comes primarily from spontaneous reporting (also known as volunteering reporting) by the healthcare professionals. This type of reporting is dependent on the initiative and motivation of the potential reporters, the healthcare professionals. These reports are called "individual case safety report (ICSR)". Another issue with the voluntary reporting that doctors may worry that the adverse effects they report may be seen as the result of their bad practice which may not only leave them open to criticism but also to litigation.

In addition to spontaneous reporting of adverse drug reactions, there are systems/methods to have active surveillance. Usually, the academic scientists or hospitals or industries contribute significantly by active follow up after treatment. The events may be detected by asking patients directly or screening patients' records. The cohort event monitoring is the most comprehensive method. The active surveillance is also a part of pharmacoepidemiolgy which is defined as the science of investigating the effects of drugs already in the market in large group of population.

Irrespective of the source of data, the reports are analysed for assessing their association with the drug(s) called causality assessment. They are useful in detecting a signal, a notice of an early concern about possible drug safety problem. Detecting signals is one of the primary objectives of Pharmacovigilance. The Pharmacovigilance data provides evidence for making regulatory decisions based on strengthened signals.

Pharmacovigilance Programme aims to:

- Improve patient care through ensuring safety of medicines;
- Improve public health through ensuring safe use of medicines;
- Help in assessment of benefit, harm, effectiveness and risk of medicines;
- Promote understanding, education, and training on Pharmacovigilance to ensure safe use of medicines [Reducing or minimising medicine use related harm].

Conclusion

Pharmacovigilance aims at getting the best outcome from a drug treatment. Though no one wants to harm patients, unfortunately many medicines harm the patients sometimes. Good Pharmacovigilance will identify the risks in the shortest possible time after the medicine is marketed and will help to establish/identify risk factors. The Pharmacovigilance information would allow intelligent and evidence based prescribing with potential for preventing many adverse reactions. This would ultimately ensure optimum therapy at a lowest cost to each patient and the health system.

Dr. Marie Lindquist, Director of Uppsala Monitoring Centre, compares the Pharmacovigilance activities with observational skills of the Sherlock Homes. With his attention to every detail and its meaning and implication help Sherlock to analyze the situation in logical way and solve the mystery. She quotes Sherlock "when you have eliminated the impossible, whatever remains, however improbable, must be the truth".

Pharmacovigilance Practice requires handling and managing huge volume of data with increasing data complexity. The drug safety industries are looking for solutions to reduce case processing costs without compromising the need of regulatory requirements and quality of information. Artificial Intelligence (AI) and the Cloud Technology offer a solution. The AI will do the work that once only humans could do. The future of PV will depend on automation and machine learning. The system must be geared up before embracing this new change which is inevitable.

While the safety of the medicines and the related products are of prime importance to all stakeholders: manufacturers, health professionals and the patients, falsely attributing a harmful effect to a medicine, or a treatment, causes a lot of damage which can be difficult to reverse. The reported causal relationship between the MMR (Measles, Mumps and Rubella) vaccination and autism influenced the patients rejecting the

vaccine. MMR vaccine was introduced in UK in 1988 as a replacement of individual vaccines. Following the study reported in the Lancet in 1998 on the possible link between the autism and MMR vaccine raised an alarm among the parents. This impacted the higher prevalence of measles in the UK. There were 2,016 confirmed cases of measles in England and Wales in 2012, the highest total for 18 years. However, one of the biggest studies of all - a 2002 paper examining the records of 537,303 children born in Denmark - also showed no link between MMR and autism [http://www.bbc.co.uk/news/health-22173393 accessed on 19 October 2013].

Key Messages

- The word 'pharmacovigilance' is originated in France in 1960 from Greek word 'pharmakon' [meaning drug] and Latin word 'vigilare' [meaning to keep watch].
- Though pharmacovigilance originally intended for safety monitoring of approved medicines (post-marketing surveillance), now it includes the safety monitoring for the entire period of life cycle inclusive of pre- approval and post- approval period.
- Pre-approval clinical trials cannot detect all adverse drug reactions but only the common ones with more than 1% incidence. Hence, there is a need of post-marketing surveillance when medicines are used by large section of the population.
- Though all adverse drug reactions are equally harmful affecting human health, they are one of the leading causes of morbidity and mortality worldwide.
- Safety information (Adverse drug reaction reports) collected in pharmacovigilance programme helps the regulatory authority (Government) to take appropriate action ranging from advices on labelling change to restricting availability to completely banning a product.
- Following Thalidomide disaster of 1960s, the countries had initiated programme on safety monitoring including the International drug monitoring by WHO. At present over 180 countries are participating in WHO's programme covering approximately 99% of the world's population.
- India's National Pharmacovigilance Programme is coordinated by Indian Pharmacopoeia Commission.
- Pharmacovigilance aims to ensure safe and optimum therapy.

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