INTRODUCTION

1.1 What is Pharmacovigilance?

Medical science has grown in leaps and bounds since the days of Hippocrates. Modern day pharmaceutical drugs have changed the way diseases are managed and controlled. They have increased life expectancy and improved quality of life for millions of people. However, despite all the benefits, evidence continues to suggest that adverse reactions to medicines are a common, yet often preventable, cause of illness, disability and even death. In some countries adverse drug reactions (ADRs) are ranked among the top 10 leading causes of mortality. In order to prevent or reduce harm to patients and thus improve public health, mechanisms for evaluating and monitoring the safety of medicines in clinical use are vital. In practice this means having in place a well-organized Pharmacovigilance system. Pharmacovigilance in the early 1990s was entirely about monitoring adverse drug reactions and hence was defined as “The detection in the community of drug effects, usually adverse. Pharmacovigilance maybe passive (the collection of spontaneous reports) or active (structured) where patients and prescribers are recruited and surveyed”¹.

However the next decade brought about marked difference in the definition of Pharmacovigilance, no longer Pharmacovigilance was limited to simply monitoring ADRs but its scope was extended and defined as “The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicines-related problems”².
1.2 Evolution of Pharmacovigilance

Once put onto the market, a medicine leaves the secure and protected scientific environment of clinical trials and is legally set free for consumption by the general population. At this point, most medicines will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals. For good reason, therefore, it is essential that new and medically evolving treatments are monitored for their effectiveness and safety under real-life conditions post release. More information is generally needed about use in specific population groups, notably children, pregnant women and the elderly, and about the efficacy and safety of chronic use, especially in combination with other medicines. Experience has shown that many adverse effects, interactions (i.e. with foods or other medicines) and risk factors come to light only during the years after the release of a medicine.

The horrible experiences of the drug thalidomide can be cited to emphasize the point above. Thalidomide had been introduced, and welcomed, as a safe and effective hypnotic and anti-emetic. It rapidly became popular for the treatment of nausea and vomiting in early pregnancy. Tragically, the drug proved to be a potent human teratogen that caused major birth defects in an estimated 10,000 children in the countries in which it was widely used in pregnant women³. It was not until the disaster caused by thalidomide in 1961 that the first systematic international efforts were initiated to address drug safety issues. At that time many thousands of congenitally deformed infants were born as the result of exposure in utero to an unsafe medicine promoted for use by pregnant mothers⁴.
1.3 Magnitude of the problem

During the last decades it has been demonstrated by a number of studies that medicine morbidity and mortality is one of the major health problems which is beginning to be recognized by health professionals and the public. It has been estimated that such adverse drug reactions (ADRs) are the 4th to 6th largest cause for mortality in the USA. They result in the death of several thousands of patients each year, and many more suffer from ADRs. The percentage of hospital admissions due to adverse drug reactions in some countries is about or more than 10%, eg. Norway 11.5%, France 13.0%, UK 16.0%. In addition suitable services to treat ADRs impose a high financial burden on health care due to the hospital care of patients with drug-related problems. Some countries spend up to 15-20% of their hospital budget dealing with drug complications. Beside ADRs, medicine-related problems also include – drug abuse, misuse, poisoning, therapeutic failure and medication errors. There is very limited information available on ADRs in developing countries and countries in transition. However, one may expect that the situation is worse rather than better. This problem is also caused by a lack, in some countries, of legislation and proper drug regulations, including ADR reporting, a large number of substandard and counterfeit products circulating in their markets, a lack of independent information and the irrational use of drugs.

1.4 Need for Pharmacovigilance:

Not everything is known about a medicine when it receives its license for marketing. The merits of a new drug, balancing its beneficial and its untoward effects become established only after sufficient experience has been gained from its use in real practice.
The reasons for the necessity of Pharmacovigilance are:

1. Information on drug safety collected during drug development is incomplete as preclinical drug development processes involve the evaluation of drug safety and efficacy in animal experiments and often it may not be appropriate to extrapolate the results of animal experiments to human.

2. Clinical trials are evaluated for limited duration and limited numbers of carefully selected patients in carefully selected settings and so it is extremely difficult to accurately determine actual efficacy, adverse effects and total risk-benefit ratio under actual clinical setting.

3. Also information is often incomplete or not available on:
   a. Rare but serious reactions
   b. Use of drugs in vulnerable groups (pregnant women, children, geriatric)
   c. Risks of long term, repeated use and drug-drug, drug-food, drug-nutritional supplement interactions

4. At the time of licensing, the drug is exposed to less than 5,000 human subjects. This allows only the most common ADRs to be detected.

5. At least 30,000 people are required to be treated with a drug to be sure not to miss at least one patient with an ADR which has an incidence of 1 in 10,000 exposed individuals.

6. There are differences among countries in the occurrence of ADRs and other drug related problems. This may be due to differences in:
   a. Diseases and prescribing practices
   b. Genetic, diet, traditions of the people
   c. Drug distribution and use including indications dose and availability
d. The use of traditional and complementary drugs which may pose specific toxicological problems, when used alone or in combination with other drugs.

Data derived from within the country or region may have greater relevance and educational value and may encourage national regulatory decision-making. Information obtained in one country (e.g. the country of origin of the drug) may not be relevant to other parts of the world, where circumstances may differ. Therefore, drug monitoring is of tremendous value as a tool for detecting ADRs and specifically in relation to counterfeit and substandard quality products. It helps ensure that patients obtain safe and efficacious products. Thus, post-marketing surveillance is important to permit detection of less common, but sometimes very serious ADRs.$^{11}$

1.5 Aims of Pharmacovigilance

Events such as the thalidomide tragedy highlight the extreme importance of effective drug monitoring systems for all medicines. The principal aims of Pharmacovigilance programmes 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
• Promote understanding, education and clinical training in Pharmacovigilance and its effective communication to health professionals and the public.$^{12}$
1.6 Role of Pharmacovigilance in regulation of medicines

Robust regulatory arrangements provide the foundation for a national ethos of medicine safety, and for public confidence in medicines. To be effective, the scope of drug regulatory authorities needs to go further than the approval of new medicines, to encompass a wider range of issues relating to the safety of medicines, namely:

- Clinical trials
- The safety of complementary and traditional medicines, vaccines and biological medicines
- The development of lines of communication between all parties which have an interest in medicine safety, ensuring that they are able to function efficiently and ethically, particularly at times of crisis

In order to achieve their respective objectives, Pharmacovigilance programmes and drug regulatory authorities must be mutually supporting. On one hand, Pharmacovigilance programmes need to maintain strong links with the drug regulatory authorities to ensure that the latter are well briefed on safety issues in everyday clinical practice, whether these issues are relevant to future regulatory action or to concerns that emerge in the public domain. On the other, regulators need to understand the specialized and pivotal role that Pharmacovigilance plays in ensuring the ongoing safety of medicinal products\textsuperscript{11}.

1.7 Partners in Pharmacovigilance

The management of the risks associated with the use of medicines demands close and effective collaboration between the key players in the Pharmacovigilance. Sustained commitment to such collaboration is vital if the future challenges in Pharmacovigilance are to be met and if the discipline is to continue to develop and flourish. Those
responsible must jointly anticipate, describe and respond to the continually increasing demands and expectations of the public, health administrator policy officials, politicians and health professionals. However, there is little prospect of this happening in the absence of sound and comprehensive systems which make such collaboration possible. The constraints typically include lack of training, resources, political support, and especially scientific infrastructure. Understanding and tackling these are an essential prerequisite for future development of the science and practice of Pharmacovigilance. 

1.8 Pharmacovigilance in a country’s national drug policy

The provision of good quality, safe and effective medicines and their appropriate use is the responsibility of national governments. The establishment of a national medicine regulatory agency and a designated centre for the study of adverse reactions are central to the achievement of these functions. Multidisciplinary collaboration is of great importance, in particular, links need to be forged between various departments of the ministry of health and also with other stakeholders, such as the pharmaceutical industry, universities, nongovernmental organizations (NGOs) and professional associations having responsibility for education on rational use of medicines and pharmacotherapy monitoring.

1.9 World Health Organization (WHO) Programme for International Drug Monitoring

As a means of pooling existing data on ADRs, WHO’s Programme for International Drug Monitoring was started in 1968. Initially a pilot project was started in 10 countries with established national reporting systems for ADRs. The network has since expanded
significantly as more countries worldwide developed national Pharmacovigilance centers for the recording of ADRs. Currently, 86 countries participate in the programme, which is coordinated by WHO together with its collaborating centre in Uppsala, Sweden. The collaborating centre is responsible for maintaining the global ADR database, Vigibase. At present the database contains more than three million ADR reports. The WHO Collaborating Centre analyses the reports in the database to:

- Identify early warning signals of serious adverse reactions to medicines
- Evaluate the hazard
- Undertake research into the mechanisms of action to aid the development of safer and more effective medicines

Through an advisory committee, WHO plays an important role in the provision of expert advice on all matters relating to the safety of medicines. The Committee also exists to facilitate consistent policies and action among member countries and to advise those who may be concerned about action taken in another country. The success of WHO’s International Drug Monitoring Programme is entirely dependent on the contributions of National Pharmacovigilance Centers. Such centers provide an essential pool of experience and competence which has been instrumental in the continuous development of the WHO programme and of Pharmacovigilance as a whole. Ideally every country should have a Pharmacovigilance centre.

1.10 Pharmacovigilance: An Indian context

Major percentage of the disease population is borne by the developing world including India. Here there are too many drugs and irrational combinations, aggressive marketing and high reliance on traditional systems of medicines leading to no data on ADRs that
may occur due to interactions between the established medicines and traditional, herbal medicines jeopardizing the safety of the patients.

While major advancements in the area of Pharmacovigilance have taken place in the developed western countries, not much has been achieved in India. Pharmacovigilance is not new to India and has been around from 1998 when India decided to join the WHO’s Uppsala Monitoring Centre for adverse event monitoring\(^\text{15}\). However, there is an immense need to understand the importance of Pharmacovigilance and how it impacts the life cycle of a medicinal product. This will enable integration of good Pharmacovigilance practice in the process and procedures to help ensure regulatory compliance and enhance clinical trials safety and post marketing surveillance.

Further India is becoming a hub for clinical research activities due to its large population, high enrolment rate and low cost. Moreover, the lag period when a drug is introduced for the first time on the market in USA, Europe, etc. and its subsequent availability in India has decreased considerably. As a result, for such drugs the long term safety data is not available at the time of their marketing in India. This is clear by the fact that several high profile drugs that have been recently withdrawn worldwide were available in Indian market. In such cases, the Indian regulatory agencies cannot count on the experience of other markets to assess risks and benefits of drugs made available in Indian markets, thereby stressing the importance of developing an adequately designed Pharmacovigilance system in India.
1.11 Pharmacovigilance in public health care programmes

The monitoring of medicine safety in India where there is no mature and adequate regulatory or safety monitoring system in place, especially in remote areas with little or no health care surveillance or infrastructure, is a matter of great concern. The problems are apparent in situations that involve the use of medicines for treatment of specific diseases, for example, tropical diseases such as malaria, leishmaniasis and schistosomiasis, and for the treatment of HIV/AIDS and tuberculosis. In some settings several disease control initiatives involving the administration of medicines to large communities are being implemented within the same population with little knowledge of, or regard to, how these various medicines could interact with each other. Pharmacovigilance should be a priority for a country like India with public health disease control programmes.

The ready availability of safer and more effective medicines of good quality inspires confidence and trust among patients. For this to be achieved it is necessary for information about drug safety programmes to be easily available to the public so that the central role of the patient in the rational and safe use of medicines is understood.

1.12 Costs to society of drug-related problems

When considering the cost of disease to society, ADRs and what is spent on detecting, preventing and managing them need to be included in the analysis. As pharmaceuticals become an increasingly prominent item in health budgets, and reliance is increasingly placed on physicians for controlling costs and curtailing their prescribing practices, Pharmacovigilance has growing importance in addressing health costs\(^1\).
The management of HIV/AIDS in developing countries like India is illustrative of these issues. Within the debate over drug prices and intellectual property rights there are in addition important concerns regarding widespread use of potentially toxic medicines in developing countries with poor resources. Antiretroviral treatment regimens commonly involve two or three potentially toxic agents. Monitoring safety and efficacy in this situation involves regular laboratory testing of liver function, hematology, viral resistance by CD4 cell count and viral load. Furthermore, treatment of the serious and not uncommon adverse effects of such treatment, which include dermatological, hepatic, hematological, metabolic and neurological disturbances, adds even further to the health budget.

1.13 Training of healthcare professional and health care workers

Healthcare professionals and healthcare workers are unaware of the importance of the Pharmacovigilance which is indicated by the fewer number of studies that are being carried out in this area, resulting in incomplete and insufficient data about possible adverse drug reactions in Indian population.

Safety monitoring of medicines in common use should be an integral part of clinical practice. The degree to which clinicians are informed about the principles of Pharmacovigilance, and practice according to them, has a large impact on the quality of health care. Education and training of health professionals and healthcare workers in medicine safety would serve to enhance effective patient care\textsuperscript{17}. 
1.14 Important role of Active Surveillance

While spontaneous reporting remains a cornerstone of Pharmacovigilance in the regulatory environment, and is indispensable for signal detection, the need for more active surveillance has also become increasingly clear. Without information on utilization and on the extent of consumption, spontaneous reports do not make it possible to determine the frequency of an ADR attributable to a product, or its safety in relation to certain parameters\textsuperscript{18}.

More systematic and robust epidemiological methods that take into account the limitations of spontaneous reporting are required to address these important safety questions and need to be incorporated into post-marketing surveillance programmes.