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PHARMACOVIGILANCE: PROCESS OF DETECTION, ASSESSMENT, UNDERSTANDING AND PREVENTION OF ADVERSE EFFECTS: A REVIEW

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INTRODUCTION

Pharmacovigilance is synonymous with *drug safety*. Pharmacovigilance looks for the adverse effects of drugs after the event whilst the phrase 'drug safety' implies a positive approach before any event, almost the reciprocal of pharmacovigilance (Myles D & B Stephens, 2014).

A broad definition of pharmacovigilance is '*the watchfulness in guarding against danger from drugs or providing for drug safety*' (Abenheim L. et. al., 1999). There are many different definitions, some place emphasis on post-marketing activities while others cover both pre and post marketing activities (Stephens, 2004). The definition given by the WHO in 1969 was: *"pharmacovigilance: one means by pharmacovigilance the notification, the registration and the systematic evaluation of the adverse reactions to medicines delivered with or without a prescription"*; this was the earliest reference to "pharmacovigilance" (WHO, 1969). The information on these reactions can be obtained, either by voluntary notifications by general practitioners or from hospitals and centres previously designated (spontaneous pharmacovigilance), or by the application of epidemiological techniques allowing the systematic collection of information from certain sources: hospitals, representative samples of the medical profession, etc. (intensive pharmacovigilance).

The pharmacovigilance cycle starts with the patient, who after taking a drug and then having an adverse event reports it to a health professional who reports it to a national authority (or pharmaceutical company) which investigates it, establishes the full facts, and assesses them before passing it to the WHO monitoring centre. If this new adverse event supports other data to suggest an adverse drug reaction (ADR) then this is a signal *(Signal: an adverse event that prompts an action , but a more formal definition is 'information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial., which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to prompt verificatory action'* (Hauben and Aronson, 2009)). This signal is then followed up and if on the balance of probabilities it is considered an ADR then it is likely to be published and communicated to all those who prescribe drugs, enabling them to use the information for the benefit of future patients. Unless the cycle is completed pharmacovigilance has failed. The thalidomide disaster was a water-shed for drug safety and heralded the beginning of Pharmacovigilance as a new science. It is now well understood the limitation of clinical trials, which cannot generate enough safety information to safeguard the public health. To ensure the safety of new drug product after marketing authorization, there are provisions to continuously monitor the safety of drug as a part of regulatory requirements. Pharmacovigilance emerged after much overlooked area of drug safety, which resulted in the tragic thalidomide disaster at around 1960's (David and Keith, 2007 & Hornbuckle et al., 1999). After that, there has been lots of progress in the drug safety issues.

Pharmacovigilance is all about the safety of drugs in their conditions of normal routine use. It does involve collection and analysis of information about drugs as they are used in a community. No longer is the major focus that of the randomised controlled clinical trial where a well-defined subset of the population is exposed under carefully controlled circumstances to a medicine of interest and followed for a defined duration thereafter. We now enter the area of observational studies with all the problems in interpretation that such studies entail. It is important to realise that the interpretation of

observational data can be much more complex than the interpretation of randomised controlled clinical trials. Such studies are, by their very nature, full of incomplete information and are likely to need careful recognition of confounding, either at the design or analysis stage. Indeed, some such studies cannot be interpreted because of insurmountable problems with bias or other distortions. They fall broadly into three categories:

1. The anecdotal study in which reports of suspected problems are solicited and analysed to see if they can give hints about possible drug-related problems, exemplified by the *spontaneous reporting schemes*.
2. More detailed observational studies, but still without appropriate comparator groups who are not exposed to the medicine of interest, for example *ad hoc follow-up studies.*
3. Controlled studies, including *case–control and cohort studies.*

As long ago as 1987, giving the keynote address on pharmaco-epidemiology and public health policy at the International Society for Pharmaco-epidemiology meeting in Minneapolis, several points were made about this subject which are worthwhile repeating here. These are as follows:

1. It is the duty of pharmaco-epidemiologists to ensure that spontaneous reports of suspected adverse reactions are used wisely in the full knowledge of their substantial limitations.
2. It is our duty as pharmaco-epidemiologists to ensure that other sources of information are available which can be interpreted in a reasonably rapid time frame. Good data in 6 years is no substitute for usable data in 6 months or less.
3. Pharmaco-epidemiology will not prosper if it develops as an intellectual subject which plots the history of why drugs fall from favour. It must be a live and contemporary subject, providing answers to current problems of drug use and drug safety in real time.

These aphorisms are as relevant today as they were when first spoken. They apply across the board to all types of studies. Thankfully we have made progress in the intervening years, albeit not as much as we would have liked (WHO, 2000).

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.

a. Government
b. Industry
c. Hospitals and academia (Egberts and De Konig, 1996)
d. Medical and pharmaceutical associations
e. Poisons information centres
f. Health professionals (Ronald and Elizabeth, 2002 & Routledge, 1998)
g. Patients
h. Consumers
i. Media
j. WHO

Historical Background

Efficacy and not safety of a drug was the early concern in the history of drugs. The thalidomide disaster of 1960's opened the eyes of drug regulators as well as other healthcare professionals to establish a way to ensure drug safety (Lawson, 1997 & WHO, 2002). The mile stone in the drug safety was the publication of chloroform related death in *The Lancet* journal for the first time in 1893 (Lawson, 1997). Onwards, safety of drug became the global concern and different initiatives were taken by different countries to safeguard the public health safety. In 1906, the US Federal, Food and Drug act (US FDA) was passed The Act was amended to control misbranding of ingredients and false advertising clams after the deaths associated with sulphanilamide elixir. There were 107 deaths by the use of diethylene glycol as a solvent for sulphanilamide elixir. Immediately after the tragedy the US FDA act was amended to compulsory premarketing submission of both efficacy and safety data in 1962. The UK Medicines act was enforced in 1968, however, safety monitoring via "yellow card system" was introduced in 1964 (Lawson, 1997). The drug safety issues were globalised, strengthen and systematized after the establishment of World Health Organization (WHO) Programme for International Drug Monitoring in 1968 (Uppsala Monitoring Centre, 2011 and Kulkarni, 1986). The Uppsala Monitoring Centre (UMC) located at Uppsala, Sweden co-ordinates the International Drug Monitoring program. There are 104 official member countries and 33 associate members throughout the world, comprising developed, developing and under-developed country (Kulkarni, 1986).

In India, it was not until 1986 that a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centres, each covering a population of 50 million, was proposed (National Pharmacovigilance Program, 2004). In 1997, India joined hands with the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. Three centres for ADR monitoring were identified, mainly based in teaching hospitals: A National Pharmacovigilance Centre located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi and two WHO special centres in Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh Muslim University). These centres were to report ADRs to the drug regulatory authority of India. The major role of these centres was to monitor ADRs to medicines which are marketed in India. However, they hardly functioned as information about the need to report ADRs and about the functions of these monitoring centres were yet to reach the prescribers and

there was lack of funding from the government. This attempt was unsuccessful and hence, again from the 1st of January 2005, the WHO-sponsored and World Bank-funded National Pharmacovigilance Program for India was made operational (Biswas, 2013).

The National Pharmacovigilance Program established in January 2005, was to be overseen by the National Pharmacovigilance Advisory Committee based in the Central Drugs Standard Control Organization (CDSCO), New Delhi. Two zonal centres-the South-West zonal centre (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the North-East zonal centre (located in the Department of Pharmacology, AIIMS, New Delhi), were to collate information from all over the country and send it to the Committee as well as to the Uppsala Monitoring centre in Sweden. Three regional centres would report to the Mumbai centre and two to the New Delhi centre. Each regional centre in turn would have several peripheral centres reporting to it.

The Legislative requirements of PV in India are guided by specifications of Schedule Y of the Drugs and Cosmetics Act 1945. The National Pharmacovigilance Programme (NPP) [Figure 1] was launched by Central Drugs Standard Control Organization (CDSCO) on 23-Nov-2004 which became operational from 01-Jan-2005. However, due to some technical difficulties the NPP was closed in 2008. It was again resurrected as the Pharmacovigilance Programme of India (PVPI) on 14-Jul-2010 (Paliwal and Mehan, 2014).

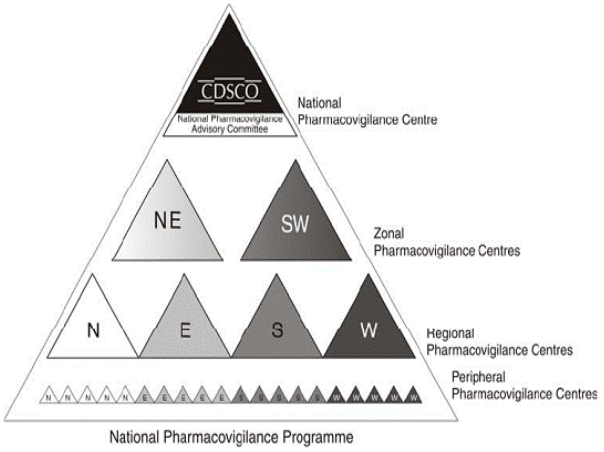

Figure 1: National Pharmacovigilance Program (NPP) of India.

In order to ensure implementation of the programme in a more effective way the National Co-ordination centre (NCC) at AIIMS, New Delhi was shifted to CDSCO in collaboration with Indian Pharmacopoeia commission, Ghaziabad on 15-Apr- 2011 (Paliwal and Mehan, 2014). The Figure 2 shows elements of PVPI. To streamline the growth of the PVPI programme further, the commission has planned to include all medical colleges across the country under its fold. The commission aims to expand PVPI and attain its goal of setting up 350 ADR centers across the country (National Pharmacovigilance programme, 2005). As of December 2014, 120 countries have joined the WHO Programme for International Drug Monitoring, and in addition 28 'associate members' are awaiting full membership while compatibility between the national and international reporting formats is being established (Hauben and Aronson, 2009).

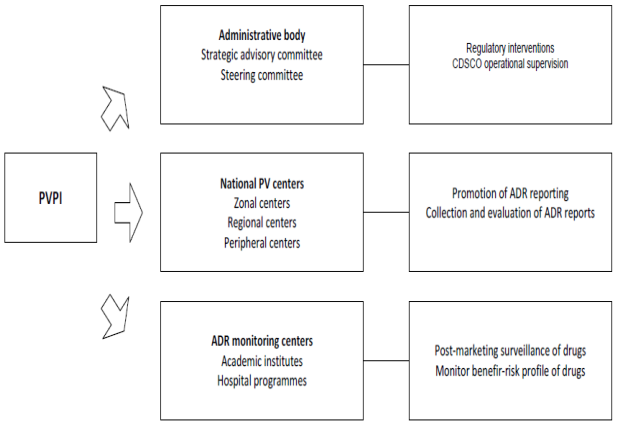

Figure 2: Pharmacovigilance programme of India.

The aim of this review is to provide a summary of the most common methods used in pharmacovigilance to guarantee the safety of a drug. Recent developments in pharmacovigilance as well as future needs are discussed.

Importance of Pharmacovigilance (WHO, 2002)

Pharmacovigilance is an important and integral part of clinical research. Both clinical trials safety and post marketing surveillance are critical throughout the product lifecycle. Pharmacovigilance is still in its infancy in India and there exists very limited knowledge about the discipline.

While major advancements of discipline of pharmacovigilance have taken place in the western countries not much has been achieved in India. There is an immense need to understand the importance of pharmacovigilance and how it impacts the life cycle of a 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.

Pharmacovigilance is not new to India and has in fact been going on from 1998, when India decided to join the Uppsala centre for adverse event monitoring. The importance of pharmacovigilance is withdrawals the regulatory agencies, media; consumers have become more aware about the benefit and risks of medicines. Spontaneous reporting of adverse drug reaction and adverse events is an important tool for gathering the safety information for early detection. In recent years many Indian companies are increasing the investment in research and development and are enhancing their

capacity to develop and market new drugs with their own research efforts.

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 placed for the first time on the market in USA, Europe, and Japan or somewhere in the world and its subsequent availability in India has decreased considerably. As a result, for such drugs the long term safety data is not available and the time of their marketing in India. This is clear by the fact that all the high profile drugs that have been recently withdrawn were available in Indian market. In such cases, the Indian regulatory agencies cannot count on the experience of other market to assess benefit risk balance of a drug (Zhengwu, 2009).

There by stressing the importance of developing their own adequately designed pharmacovigilance system in India. For an effective pharmacovigilance system to be functional and efficient, all the stake holders need to be alert and attentive throughout the life cycle of a medicinal product in the market. The office of the Drugs Controller General of India (DCGI) has been making sincere attempts for the implementation the National Pharmacovigilance Programme (NPP) in India. To full fill the pharmacovigilance obligations for its marketed products, as per regulations, a generic company in India is mainly to carry out the following activities. Collection monitoring and reporting of spontaneous adverse reactions, including expedited reporting of serious unexpected adverse reactions and preparations. Pharmacovigilance help to prevent adverse drug effects: Medical science has grown in leaps and bounds since the days of Hippocrates. Modern day pharmaceutical drugs are really life saves. They have increased life expectancy and improved the quality of life for millions of people. But there is the other side of the coin as well; these drugs sometimes have very adverse effects that can even be life threatening (Kumanan et al., 2010).

There is a need to monitor the effects of drugs before and after it's successfully tested and launched in the market. Pharmacovigilance involves the monitoring and assessing the quality of drugs, detection and preventing of any adverse effects of drugs. Pharmacovigilance involves evaluating information provided by health care providers, pharmaceutical companies and patients in order to understand the risk and benefits involved with a particular drug. Pharmaceutical companies spend millions of dollars and a considerably long time in developing new drugs.

They again spend a lot of money in conducting clinical trials before the drugs are approved and launched in the market. It is recognized that information technology (IT) has entered and transformed the world of health care and clinical medicine in which the work of doctors and the care of patients proceed with higher quality, efficiency and lower costs. It is also no secret that IT has merged in to clinical safety practice and sparks the creation of worldwide pharmacovigilance systems for safety signal detection.

The IT transformative force and health it, adoption have fundamentally changed the conduct of clinical research, practice of medicines and medicinal safety monitoring. In today's world pharmacovigilance pushes new boundaries and it is no longer sufficient to simply report adverse events along with efficacy and quality requirements.

Regulators are demanding proactive surveillance programs that include comprehensive risk management plans and signal detection/ analysis throughout a clinical products life cycle.

a. This addresses what exactly is pharmacovigilance?
b. What do we know of its benefits and risks?
c. What challenges are out there preventing its wide spread usage?
d. What does the future hold for pharmacovigilance in worldwide medicine?

It is now generally accepted that part of the process of evaluating drug safety needs to happen in the post marketing phases through judgment as to whether and how this might happen lies with the regulators. The stronger the national systems of pharmacovigilance and adverse drug reaction (ADR) reporting, the more likely reasonable regulatory decisions will be made for the early release of new drugs with the promise of therapeutic advances. Careful safety monitoring is not restricted, however to new drugs or to significant therapeutic advances. It has a critical role to play in the introduction of generic medicines, and in review of the safety profile of older medicines already available as well, where new safety issues may have arises. While spontaneous reporting remains a corner stone 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 are unable to determine the frequency of an ADR attribution to a product or its safety in relation to a comparator.

More systematic and robust epidemiological methods that take in to account the limitations of spontaneous reporting or post marketing studies are required to address these key safety questions. They need to be incorporated in to post marketing surveillance programs. This includes the use of pharmaco-epidemiologic studies (Deepa, 2008).

These activities are under taken with the goal of identifying adverse events and understanding to the extent possible, their nature, frequency and potential risk factor. Pharmacovigilance in principle involves the identification and evaluation of safety signals. Safety signal refer to a concern about an excess of adverse

events compared to what would be expected to be associated with products use.

Signals can arise from post marketing data and other sources, such as pre clinical data and events associated with other products in the same pharmacological class. Pharmacovigilance is particularly concerned with adverse drug reactions. Many other issues are also relevant to pharmacovigilance science are substandard medicines, medication errors, lack of efficacy reports, use of medicines for indications that are not approved and for which there is inadequate scientific basis, case reports of acute and chronic poisoning, assessment of drug related mortality, abuse and misuse of medicines, adverse interactions of medicines with chemicals, other medicines and food.

Aim of Pharmacovigilance (WHO, 2004)

a. Improve patient care and safety in relation to the use of medicines, all medical and Para medical interventions.
b. Research the efficacy of drug and by monitoring the adverse effects of drugs right from the lab to the pharmacy and then on for many years.
c. Pharmacovigilance keeps track of any drastic effects of drugs.
d. Improve public health and safety in relation to the use of medicines.
e. Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost effective) use.
f. Promote understanding, education, clinical training in pharmacovigilance and its effective communication to the public.

These processes involved in the clinical development of medicines. 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. In some cases as few as 500 subjects, and rarely more than 5000, will have received the product prior to its release (WHO, 2006).

For good reason, therefore it is essential that new and medically still 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.

Glossary of Terminologies (IPC, 2005)

Absolute risk
Risk in a population of exposed persons; the probability of an event affecting members of a particular population (e.g. 1 in 1,000). Absolute risk can be measured over time (*incidence*) or at a given time (prevalence).

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.

Adverse (Drug) Reaction (ADR)
A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. (WHO, 1972). "A response to a medicinal product which is noxious and unintended."

Association
Events associated in time but not necessarily linked as cause and effect.

Attributable risk
Difference between the risk in an exposed population (*absolute risk*) and the risk in an unexposed population (*reference risk*). Attributable risk is the result of an absolute comparison between outcome frequency measurements, such as incidence.

Biological products
Medical products prepared from biological material of human, animal or microbiologic origin (such as blood products, vaccines, insulin).

Causal relationship
A relationship between one phenomenon or event (A) and another (B) in which A precedes and causes B. In pharmacovigilance; a medicine causing an adverse reaction.

Causality assessment
The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction. Causality assessment is usually made according established algorithms.

Caveat document
The formal advisory warning accompanying data release from the WHO Global ICSR Database: it specifies the conditions and reservations applying to interpretations and use of the data.

Cem-Flow
Software developed by UMC for collection and analysis of data in Cohort Event Monitoring.

Clinical trial
A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion (ADME) of the products with the objective of ascertaining their efficacy and safety.

Cohort Event Monitoring
Cohort Event Monitoring (CEM) is a prospective, observational study of events that occur during the use of medicines, for intensified follow-up of selected medicinal products phase. Patients are monitored from the time they begin treatment, and for a defined period of time.

Compliance
Faithful adherence by the patient to the prescriber's instructions.

Control group
The comparison group in drug-trials not being given the studied drug.

Critical terms
Some of the terms in WHO-ART are marked as 'Critical Terms'. These terms either refer to or might be indicative of serious disease states, and warrant special attention, because of their possible association with the risk of serious illness which may lead to more decisive action than reports on other terms.

Data mining
A general term for computerised extraction of potentially interesting patterns from large data sets often based on statistical algorithms. A related term with essentially the same meaning is 'pattern discovery'. In pharmacovigilance, the commonest application of data mining is so called disproportionality analysis, for example using the Information component (IC).

De-challenge
The withdrawal of a drug from a patient; the point at which the continuity, reduction or disappearance of adverse effects may be observed.

Disproportionality analysis
Screening of ICSR databases for reporting rates which are higher than expected. For drug- ADR pairs, common measures of disproportionality are the Proportional Reporting Ratio (PRR), the Reporting Odds Ratio (ROR), The Information Component (IC), and the Empirical Bayes Geometrical Mean (EBGM). There are also disproportionality measures for drug-drug-ADR triplets, such as Omega (Ω).

Effectiveness/risk
The balance between the rates of effectiveness of a medicine versus the risk of harm is a quantitative assessment of the merit of a medicine used in routine clinical practice. Comparative information between therapies is most useful. This is more useful than the efficacy and hazard predictions from pre-marketing information that is limited and based on selected subjects.

Efficacy
The ability of a drug to produce the intended effect as determined by scientific methods, for example in pre-clinical research conditions (opposite of hazard).

Epidemiology
The science concerned with the study of the factors determining and influencing the frequency and distribution of disease, injury and other health-related events and their causes in a defined human population for the purpose of establishing programs to prevent and control their development and spread.

Essential medicines
Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness.

Excipients
All materials included to make a pharmaceutical formulation (e.g. a tablet) except the active drug substance(s).

Formulary
A listing of medicinal drugs with their uses, methods of administration, available dose, dosage forms, side effects, etc, sometimes including their formulas and methods of preparation.

Frequency of ADRs
In giving an estimate of the frequency of ADRs the following standard categories are recommended:
Very common* > 10%
Common (frequent) >1% and <10%
Uncommon (infrequent) >0.1% and < 1%
Rare >0.01% and <0.1%
Very rare* <0.01%
* *Optional categories*

Generic (multisource product)
The term 'generic product' has somewhat different meanings in different jurisdictions. Generic products may be marketed either under the non-proprietary approved name or under a new brand (proprietary) name. They are usually intended to be interchangeable with the innovator product, which is usually manufactured without a license from the innovator company and marketed after the expiry of patent or other exclusivity rights.

Harm
The nature and extent of actual damage that could be caused by a drug. Not to be confused with risk.

Herbal medicine
Includes herbs, herbal materials, herbal preparations and finished herbal products.

Homeopathy
Homeopathy is a therapeutic system which works on the principle that 'like treats like'. An illness is treated with a medicine which could produce similar symptoms in a healthy person. The active ingredients are given in highly diluted form to avoid toxicity. Homeopathic remedies are virtually 100% safe.

Information component (IC)
The Information component (IC) measures the disproportionality in the reporting of a drug- ADR pair in an ICSR database, relative to the reporting expected based on the overall reporting of the drug and the ADR. Positive IC values indicate higher reporting than expected. The IC has also been implemented on electronic health records, to detect interesting temporal relationships between drug prescriptions and medical events.

Incidence
Number of new cases of an outcome which develop over a defined time period in a defined population at risk.

Individual Case Safety Report (ICSR)
A report that contains 'information describing a suspected adverse drug reaction related to the administration of one or more medicinal products to an individual patient'.

MedDRA
MedDRA is the Medical Dictionary for Regulatory Activities. WHO-ART, the WHO Adverse Reactions Terminology, is now mapped to MedDRA.

Medical error
"An unintended act (either of omission or commission) or one that does not achieve its intended outcomes."

Member countries
Countries which comply with the criteria for, and have joined the WHO Programme for International Drug Monitoring.

National Pharmacovigilance centres
Organisations recognised by governments to represent their country in the WHO Programme (usually the drug regulatory agency). A single, governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyse and give advice on all information related to drug safety.

Odds
Probability of an occurrence *p* divided by the probability of its non-occurrence (1 - *p*).

Odds ratio
Ratio of the *Odds* in a given population and the *Odds* in another population.

Omega (Ω)
A measure of disproportionate reporting for drug-drug-ADR triplets in ICSR databases, designed to highlight potential signals of drug- drug interactions. Just like the more established disproportionality measures for drug-ADR pairs, Ω is based on a contrast between the observed and expected number of reports. A positive Ω indicates higher reporting than expected.

OTC (Over the Counter) medicine
Medicinal product available to the public without prescription.

Pani-Flow
Software developed by UMC for collection and analysis of data in relation to vaccinations in a pandemic situation.

Periodic Safety Update Report (PSUR)
A systematic review of the global safety data which became available to the manufacturer of a marketed drug during a specific time period. Produced in an internationally agreed format.

Pharmacoepidemiology
Study of the use and effects of drugs in large populations.

Pharmacology
Study of the uses, effects and modes of action of drugs.

Pharmacovigilance
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug- related problem.

Phocomelia
Characteristic deformity caused by exposure to thalidomide in the womb, also very rarely occurring spontaneously. Meaning: limbs like a seal.

Phytotherapy
Western-style, scientific treatment using plant extracts or materials.

Placebo
An inactive substance (often called a sugar pill) given to a group being studied to compare results with the effects of the active drug.

Polypharmacy
The concomitant use of more than one drug, sometimes prescribed by different practitioners.

Post-marketing
The stage when a drug is generally available on the market.

Predisposing factors
Any aspect of the patient's history (other than the drug) which might explain reported adverse events (genetic factors, diet, alcohol consumption, disease history, polypharmacy or use of herbal medicines, for example).

Pre-marketing
The stage before a drug is available for prescription or sale to the public.

Prescription Event Monitoring (PEM)
System created to monitor adverse drug events in a population. Prescribers are requested to report all events, regardless of whether they are suspected adverse events, for identified patients receiving a specified drug. Also more accurately named *Cohort Event Monitoring*.

Prescription Only Medicine (POM)
Medicinal product available to the public only on prescription.

Prevalence
Number of existing cases of an outcome in a defined population at a given point in time.

Prophylaxis
Prevention or protection.

Rational drug use
An ideal of therapeutic practice in which drugs are prescribed and used in exact accordance with the best understanding of their appropriateness for the indication and the particular patient, and of their benefit, harm effectiveness and risk.

Re-challenge
The point at which a drug is again given to a patient after its previous withdrawal - also see *de-challenge*.

Record linkage
Method of assembling information contained in two or more records, e.g. In different sets of medical charts, and in vital records such as birth and death certificates. This makes it possible to relate significant health events that are remote from one another in time and place.

Reference risk
Risk in a population of unexposed persons; also called baseline risk. Reference risk can be measured over time (*incidence*) or at a given time (*prevalence*). The unexposed population refers to a reference population, as closely comparable to the exposed population as possible, apart from the exposure.

Regulatory authority
The legal authority in any country with the responsibility of regulating all matters relating to drugs.

Relative risk
Ratio of the risk in an exposed population (*absolute risk*) and the risk in an unexposed population (*reference risk*). Relative risk is the result of a relative comparison between outcome frequency measurements, e.g. incidences.

Risk
The probability of harm being caused; the probability (chance, odds) of an occurrence.

Serious Adverse Event or Reaction
A serious adverse event or reaction is any untoward medical occurrence that at any dose:

a. results in death
b. requires inpatient hospitalisation or prolongation of existing hospitalisation
c. results in persistent or significant disability/incapacity
d. is life-threatening

Side effect
Any unintended effect of a pharmaceutical product occurring at normal dosage which is related to the pharmacological properties of the drug.

Signal
Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. The publication of a signal usually implies the need for some kind of review or action.

Summary of Product Characteristics (SPC)
A regulatory document attached to the marketing authorization which forms the basis of the product information made available to prescribers and patients.

Spontaneous reporting
System whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.

Traditional medicines
Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.

Unexpected adverse reaction
An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug.

Vigi-Base
The name of the WHO Global ICSR Database.

Vigi-Flow
Vigi-Flow is a complete ICSR management system created and maintained by the UMC. It is web-based and built to adhere to the ICH-E2B standard. It can be used as the national database for countries in the WHO Programme as it incorporates tools for report analysis, and facilitates sending reports to Vigi-Base.

Vigi-med
Share point based conferencing facility, exclusive to member countries of the WHO Programme for International Drug Monitoring for fast communication of topical pharmacovigilance issues.

Vigi-Mine
A statistical tool within Vigi-Search with vast statistical material calculated for all Drug- ADR pairs (combinations) available in Vigi-Base. The main features include the disproportionality measure (IC value) stratified in different ways and useful filter capabilities.

Vigi-Search
A search service for accessing ICSRs stored in the Vigi-Base database offered by the UMC to national pharmacovigilance centres and other third-party inquirers.

Vigi-Access
This database allows you to browse and view data on suspected side-effects from various medicinal products (also known as suspected adverse drug reactions ("ADRs")).

WHO-ART
Terminology for coding clinical information in relation to drug therapy. WHO-ART is maintained by UMC.

WHO Drug Dictionary (WHO DD)
The WHO Drug Dictionary is an international classification of drugs providing proprietary and non-proprietary names of medicinal products used in different countries, together with all active ingredients.

Classification of Adverse Drug Reactions
The following classification introduced by Rawlin & Thompson in 1991. Is the most frequently and commonly used as (Ferner and Aronson 2010).

1. Dose related or Augmented. Common related to pharmacological action of drug, predictable .e.g., haemorrhage seen with warfarin. Respiratory depression with opiates, bradycardia with beta blockers and hypotension with antihypertensive.
2. Non dose related or Bizarre Uncommon, unpredictable, not related to pharmacological action of the drug e.g.; phocomelia with thalidomide tragedy which revolutionized the monitoring to ensure safe and effective use of medicine; CV effects with cox-2 inhibitors, vaginal cancer in young women with stilbestrol, penicillin hypersensivity, malignant hyperthermia
3. Dose & time related or Chronic Uncommon, related to cumulative dose e.g.; HPA axis suppression by corticosteroids, Benzodiazepine dependence
4. Time-related or Delayed Uncommon, usually dose related. Delayed onset e.g.; teratogens, carcinogenesis, tardive dyskinesia.
5. Withdrawal or End of use Uncommon. Occurs soon after drug is stopped e.g.; opiate withdrawal syndrome.
6. Unexpected failure of therapy or Failure. Common, dose-related, often caused by interactions with other drugs e.g.; Decreased oral contraceptive effectiveness when used with anti-tuberculosis medication.

Ferner and Aronson have proposed a comprehensive mechanistic classification of adverse drug effects in 2010. This classification called as EIDOS is based upon five elements which are:

1. The Extrinsic chemical species (E) that initiates the effect;
2. The Intrinsic chemical species (I) that it affects;
3. The Distribution (D) of these species in the body;
4. The (physiological or pathological) Outcome (O); and
5. The Sequela (S), which is the adverse effect.

This classification EIDOS, describes the mechanism by which an adverse effect occurs; it complements the DoTS classification of adverse effects (based on clinical pharmacology), which takes into account the following:

1. Dose responsiveness;
2. Time course; and
3. Susceptibility factors.

Together, these two classification systems, mechanistic and clinical, comprehensively delineate all the important aspects of adverse drug reactions; they should contribute to areas such as drug development and regulation, pharmacovigilance, monitoring therapy, and the prevention, diagnosis, and treatment of adverse drug effects (Pirmohamed, 2004).

Understanding ADR-Causality is of great significance for any efficient PV-programme anywhere. Some definitions and explanations are given below. Relationship between drug and an adverse event may be graded as follows: (Policy For Reporting Adverse Drug Reactions, 2002, Meyboom and Royer, 1992, & Edwards and Biriell, 1994). It is the probability that an ADR is

due to a drug and refers to individual cases and the assessment of what a healthcare professional would call clinical likelihood that the ADR was due to the drug. The relationship of an AE to the study drug is graded as follows:

(a) None: The AE is definitely not associated with the study drug administered.

(b) Remote: The temporal association is such that the study drug is not likely to have had an association with the observed event.

(c) Possible: This causal relationship is assigned when the AE: (i) follows a reasonable temporal sequence from study drug administration; (ii) could have been produced by the participant's clinical state or other modes of therapy administered to the participant.

(d) Probable: This causal relationship is assigned when the AE: (i) follows a reasonable temporal sequence from study drug administration; (ii) abates upon discontinuation of the study drug; (iii) cannot be reasonably explained by known characteristics of the participant's clinical state. The essential distinctions between 'Probable' and 'Possible' are that in the latter case there may be another equally likely explanation for the event and/or there is no information or uncertainty with regard to what has happened after stopping.

(e) Definitely related: This causal relationship is assigned when the AE: (i) follows a reasonable temporal sequence from study drug administration; (ii) abates upon discontinuation of the study drug; and (iii) is confirmed by reappearance of the adverse event on repeat exposure (re-challenge).

WHO-UMC Causality Categories are as follows:

1. **Certain (**Event definitive**);**
2. **Probable/ Likely (**Unlikely to be attributed to disease or other drugs**);**
3. **Possible (**Could also be explained by disease or other drugs);
4. **Unlikely (**relationship improbable but not impossible),
5. **Conditional/Unclassified (**More data for proper assessment needed**)** and
6. **Unassessable /Unclassifiable (**Data cannot be supplemented or verified**)** (WHO-UMC system).

The US Food and Drug Administration (FDA) has released its latest list of drugs to monitor based on potential signs of serious risks or new safety information identified in the agency's Adverse Event Reporting System (AERS).The quarterly watch list released on February 8, 2011, consists of 13 drugs that treat a wide range of conditions, including cough, angina, diabetes, cancer, and bipolar disorder. The FDA is studying the 13 drugs to determine whether they are causally linked to the possible risks reported through AERS from July to September 30, 2010. The drugs are considered pharmacologically innocent until proven guilty. According to the FDA physicians should not stop prescribing these drugs, nor should patients stop taking them. Among the 13 drugs are Lithium citrate, Lopinavir/Ritonavir oral solution & Pioglitazone HCl. According to the article, Lopinavir/Ritonavir has been associated with serious adverse events in neonates, Pioglitazone with rhabdomyolysis & Lithium citrate with Brugada syndrome (a hereditary syndrome that causes sudden unexpected cardiac death in apparently healthy young males) (AERS, 2011).

Methods used in Pharmacovigilance

The activities undertaken in the name of pharmacovigilance can be roughly divided into three groups: regulatory, industry, and academia. Regulatory pharmacovigilance is driven by the aim to provide drugs with a positive benefit-harm profile to the public. Some of the problems related to regulatory post-marketing surveillance will be discussed in this context, followed by a description of the methods used to detect new ADRs and a discussion of the pros and cons of each method.

Clinical Trial Data Insufficient to Evaluate Drug Risk

The main method currently used to gather information on a drug in the pre-marketing phase is to conduct a clinical trial. Pre-marketing clinical trials can be divided into three phases. Phase III studies are often double blind randomised controlled trials; these are considered to be the most rigorous approach to determining whether a cause-effect relationship exists between a treatment and an outcome. However, when it comes to monitoring the safety of a drug, this study design is not optimal. Due to the limited number of patients participating, it is generally not possible to identify ADRs that occur only rarely. The relatively short duration of clinical trials makes it difficult to detect ADRs with a long latency. Another limitation of clinical trials is the population in which a drug is tested. The characteristics of the participants do not always correspond to the characteristics of the population in which it will later be used; consequently, it may be difficult to extrapolate the results obtained from clinical trials to the population at large (Gross et al. 2002). This is especially true for the elderly, for women or for people belonging to a minority ethnic group (Heiat et. al., 2002 and Zarin et. al. 2005).

In order to study rare ADRs, ADRs with a long latency and ADRs in specific populations, careful monitoring of the drug in the post-marketing phase is essential. Post-marketing studies can be descriptive or analytical. Descriptive studies generate hypotheses and attempt to describe the occurrence of events related to drug toxicity and efficacy. Analytical studies test hypotheses and seek to determine associations or causal connections between observed effects and particular drugs, and to measure the size of these effects. Descriptive studies are widely used in post-marketing surveillance because they are able to generate hypotheses that will become starting points for analytical studies (Wardell et. al., 1979). Two forms of descriptive studies-spontaneous reporting and intensive monitoring will be discussed here. Analytical studies can be conducted using a variety of approaches, including

case-control studies, cohort studies and clinical trials. In order to be able to conduct retrospective cohort and case–control studies, data which have been collected in a reliable and routine manner needs to be available. To provide an example of such studies, we describe here two European databases frequently used for analytical studies, the General Practitioners Research Database (GPRD) in the UK and the PHARMO Record Linkage System in the Netherlands.

Spontaneous Reporting

In 1961, a letter from the Australian physician WG McBride was published in Lancet. In this letter, he shared his observation that babies whose mothers had used thalidomide during pregnancy were born with congenital abnormalities more often than babies who had not been exposed to thalidomide in uterus (McBride, 1961). In the years to come it became evident that thousands of babies had been born with limb malformations due to the maternal use of thalidomide. In order to prevent a similar disaster from occurring, systems were set up all over the world with the aim of regulating and monitoring the safety of drugs.

Spontaneous reporting systems (SRS) were created, and these have become the primary method of collecting post-marketing information on the safety of drugs. The main function of SRS is the early detection of signals of new, rare and serious ADRs. A spontaneous reporting system enables physicians and, increasingly more often, pharmacists and patients to report suspected ADRs to a pharmacovigilance centre (Van et. al., 2004, Van et. al., 2004 and Van et. al. 2005). The task of the pharmacovigilance centre is to collect and analyse the reports and to inform stakeholders of the potential risk when signals of new ADRs arise. Spontaneous reporting is also used by the pharmaceutical industry to collect information about their drugs. By means of a SRS it is possible to monitor all drugs on the market throughout their entire life cycle at a relatively low cost. The main criticism of this approach is the potential for selective reporting and underreporting (Eland et. al., 1999).

In a review article, Hazell and Shakir investigated the magnitude of underreporting in SRS and determined that more than 94% of all ADRs remain unreported (Hazell and Shakir, 2006). Under reporting can lead to the false conclusion that a real risk is absent, while selected reporting of suspected risks may give a false impression of a risk that does not exist. However, underreporting and selective reporting can also been seen as advantages. Because only the most severe and unexpected cases are reported, it is easier to detect new signals of ADRs because the person reporting the reaction has already pinpointed what may be a new safety issue. Against this background, the system should perhaps be called 'concerned reporting' instead of spontaneous reporting, seeing as those reporting the issues are highly selective of what they are reporting (Edwards, 1999). With a SRS, it is not possible to establish cause-effect relationships or accurate incidence rates; it is also not possible to understand risk factors or elucidate patterns of use. Although critics say that spontaneous reporting is not the ideal method for monitoring the safety of drugs, it has proven its value throughout the years. Eleven products were withdrawn from the UK and U.S. markets between 1999 and 2001. Randomised trial evidence was cited for two products (18%) and comparative observational studies for two products (18%). Evidence from spontaneous reports supported the withdrawal of eight products (73%), with four products (36%) apparently withdrawn on the basis of spontaneous reports only. For two products, the evidence used to support their withdrawal could not be found in any of the identified documentation (Clarke et. al., 2006).

Data Mining in Spontaneous Reporting

In the past, signal detection in spontaneous reporting has mainly occurred on the basis of case-by-case analyses of reports. In recent years, however, data mining techniques have become more important. The term ‘data mining’ refers to the principle of analysing data from different perspectives and extracting the relevant information. Algorithms are often used to determine hidden patterns of associations or unexpected occurrences-i.e. signals-in large databases. Although the methodology of the various data mining methods applied in pharmacovigilance differ, they all share the characteristic that they express to what extent the number of observed cases differs from the number of expected cases (Hauben et. al., 2005).

Several approaches of data mining are currently in use. Proportional reporting ratios (PPRs), compare the proportion of reports for a specific ADR reported for a drug with the proportion for that ADR in all other drugs. The calculation is analogous to that of relative risk. Using the same information, it is also possible to calculate a ‘reporting odds ratio’ (Puijenbroek et. al., 2003).

The Bayesian confidence propagation neural network (BCPNN) method is used to highlight dependencies in a data set. This approach uses Bayesian statistics implemented in a neural network architecture to analyse all reported ADR combinations. Quantitatively unexpectedly strong relationships in the data are highlighted relative to general reporting of suspected adverse effects. The WHO Collaborating Centre for International Drug Monitoring uses this method for data mining (Bate et. al., 2002). A related approach is the Multi-Item Gamma Poisson Shrinker (MGPS) used by the FDA for data mining of their spontaneous report’s database. The MGPS algorithm computes signal scores for pairs, and for higher-order (e.g. triplet, quadruplet) combinations of drugs and events that are significantly more frequent than their pair-wise associations would predict (Szarfman et. al., 2005). All data-mining approaches currently cannot distinguish between associations that are already known and new

associations. Moreover, clinical information described in the case reports is not taken into account; consequently, there is still the need for a reviewer to analyse these events.

Intensive Monitoring

In the late 1970s and early 1980s a new form of active surveillance was developed in New Zealand (the Intensive Medicines Monitoring Programme) and the UK (Prescription Event Monitoring). These intensive monitoring systems use prescription data to identify users of a certain drug. The prescriber of the drug is asked about any adverse event occurring during the use of the drug being monitored. These data are collected and analysed for new signals. The methodology of these intensive monitoring systems have been described in depth elsewhere (Mackay, 1998; Mann, 1998; Coulter, 1998).

The basis of intensive monitoring is a non-interventional observational cohort, which distinguishes it from spontaneous reporting because the former only monitors selected drugs during a certain period of time. Through its non-interventional character, intensive monitoring provides real world clinical data involving neither inclusion nor exclusion criteria throughout the collection period. It is unaffected by the kind of selection and exclusion criteria that characterise clinical trials, thereby eliminating selection bias. Another strength of the methodology is that it is based upon event monitoring and is therefore capable of identifying signals for events that were not necessarily suspected as being ADRs of the drug being studied. Intensive monitoring programmes also enable the incidence of adverse events to be estimated, thus enabling quantification of the risk of certain ADRs. This approach, however, also has recognised limitations. The proportion of adverse effects that go unreported to doctors is unknown. The studies also produce reported event rates rather than true incident rates. This is the same for all studies based on medical record data, including computer databases and record linkage. There is no control group in standard intensive monitoring studies, and the true background incidence for events is therefore not known (Coulter, 2000). Although the intensive monitoring methodology was developed more than 20 years ago, this methodology has received renewed interest in the last years. In the European Commission consultation 'Strategy to better protect public health by strengthening and rationalising EU pharmacovigilance' intensive monitoring is mentioned as one tool that can improve the pharmacovigilance system (Shakir, 2007).

Database Studies

In order to test a hypothesis, a study has to be performed. The study can be conducted using a variety of methods, including case–control studies and cohort studies. The limitations of these methods include power considerations and study design. In order to be able to conduct retrospective cohort and case–control studies, data which have been collected in a reliable and routine fashion needs to be available. The General Practice Research Database (GPRD) and the PHARMO Record Linkage System, which will be described in further detail in the following sections, were chosen here because they represent two different types of European databases. Other database- and record linkage systems are available for research purposes in both Europe and in North America (EUCEI, 2007).

General Practice Research Database

Virtually all patient care in the UK is coordinated by the general practitioner (GP), and data from this source provide an almost complete picture of a patient, his illnesses and treatment. In any given year, GPs, who are members of the GPRD, collect data from about 3 million patients (about 5% of the UK population). These patients are broadly representative of the general UK population in terms of age, sex and geographic distribution. The data collected include demographics (age and sex), medical diagnoses that are part of routine care or resulting from hospitalisations, consultations or emergency care, along with the date and location of the event. There is also an option of adding free text, referral to hospitals and specialists, all prescriptions, including date of prescription, formulation strength, quantity and dosing instructions, indication for treatment for all new prescriptions and events leading to withdrawal of a drug or a treatment. Data on vaccinations and miscellaneous information, such as smoking, height, weight, immunisations, pregnancy, birth, death, date entering the practice, date leaving the practice and laboratory results, are also collected.

A recent review of protocols using GPRD data showed that the database is used for pharmacoepidemiology (56%), disease epidemiology (30%) and, to a lesser degree, drug utilisation, pharmacoeconomics and environmental hazards. There have been over 250 publications in peer-reviewed journals using the GPRD (Strom, 2005; Gelfand et. al., 2005; Parkinson et. al., 2007).

Pharmo

In the early 1990s, the PHARMO system of record linkage as developed in The Netherlands. PHARMO links community pharmacy and hospital data within a specific region on the basis of patient birth date, gender and GP code. The system now includes drug-dispensing records from community pharmacies and hospital discharge records of about 2 million people in the Netherlands. The data collection is longitudinal and goes back to 1987. More recently, PHARMO has also been linked to other data, such as primary care data, population surveys, laboratory and genetic data, cancer and accident registries, mortality data and economic outcomes. The system has well-defined denominator information that allows incidence and prevalence estimates and is relatively cheap because existing databases are used and linked. The PHARMO database is

used for follow-up studies, case–control studies and other analytical epidemiological studies for evaluating drug induced effects. In the past the database has been used for studies on drug utilisation, persistence with treatment, economic impact and ADRs (Wood and Martinez, 2004; Leufkens and Urquhart 2005).

Future Perspectives

On a regulatory level, progress has been made during the past few years. However, the results of these changes have yet to become apparent and, therefore, it has not yet been proven if these developments have contributed to better pharmacovigilance conduct. In order to further prove pharmacovigilance as a science, it is essential that academia develops new methods which can strengthen the current system.

Pharmacovigilance as we know it today has been about detecting new ADRs and, if necessary, taking regulatory actions needed to protect public health—for example, by changing the summary of product characteristics (SPCs) or withdrawing the drug from the market. Little emphasis has been put into generating information that can assist a healthcare professional or a patient in the decision-making process of whether not to use a drug. The gathering and communication of this information is an important goal of pharmacovigilance. Active surveillance is necessary to receive information about the safety of a drug at an early stage. When developing new methods for active post-marketing surveillance, one has to bear in mind the importance of being able to gather information in a timely manner. Spontaneous reporting has indeed been shown to be a useful tool in generating signals, but the relatively low number of reports received for a specific association makes it less useful in identifying patient characteristics and risk factors that will contribute to the occurrence of an ADR in a certain person.

This information is essential when it comes to a healthcare provider recommending whether or not a particular patient should use the drug in question. Furthermore, when facing an ADR, questions that patients as well as the treating physician can ask are: will this ADR disappear?; how long will it take before it does?; what treatment is needed? None of the main methods used today in post-marketing surveillance can provide an answer to these questions. It is therefore important to develop methods that can follow a patient using a particular drug over time, as the information gathered using such methods will enable such questions to be answered. Pharmacogenetics could play a role in identifying individual risk factors for the occurrence of certain ADRs (Sturkenboom, 2007).

The role of the patient is gradually changing. From being a person with little knowledge and little power, the present day patient is highly informed about his disease and wants to participate actively in his treatment. As mentioned earlier, in some countries the importance of patients as a source of information about ADRs has been acknowledged. In these countries, patients have the option of reporting ADRs via the spontaneous reporting system. This patient empowerment will continue and, in the future, pharmacovigilance has to concentrate on this group as a source of information in addition to the more traditional groups, such as the health professionals.

The field of pharmacovigilance has made a tremendous journey since it was recognised in the early 1960s after the thalidomide disaster. Recent events, such as the withdrawal of aprotinin and the questioning of the safety of rosiglitazone, show that it is a topic that lies close to people's hearts. In the past few years there has been a major push in trying to change the existing pharmacovigilance systems in order to meet the demands of the future. Scientific underpinning of pharmacovigilance is needed to ensure that it will develop as a scientific discipline and thereby contribute to the innovation needed in this field. The pharmacovigilance of tomorrow must be able to identify new safety issues without delay. If we succeed herein, patient's confidence in drugs will return. Furthermore, pharmacovigilance methods must also be able to describe which patients are at risk of developing an ADR and what the course of the ADR is. One approach to doing this would be to use patients-more than has been done up to now-as a source of information; this approach would be consistent with the growing patient involvement in drug safety.

WHO - UMC & INDIA

The WHO Program for International Drug Monitoring provides a forum for WHO member states that includes India to collaborate in the monitoring of drug safety. Within the Program, individual case reports of suspected adverse drug reactions are collected and stored in a common database, presently containing over 3.7 million case reports. Since 1978 the Uppsala Monitoring Center (UMC) in Sweden has carried out the Program. The Uppsala Monitoring Center is responsible for the collection of data about adverse drug reactions from around the world, especially from countries that are members of the WHO including India. Member countries send their reports to the Uppsala Monitoring Center where they are processed, evaluated and entered into the WHO International Database. When there are several reports of adverse reactions to a particular drug this process may lead to the detection of a signal – an alert about a possible hazard communicated to member countries. These ADR reports are assessed locally and may lead to action within the country. Through membership of The WHO International Drug Monitoring Program, a country can know if similar reports are being made elsewhere. (The European Union also has its own scheme). India is a country with a large patient pool and healthcare professionals, yet ADR reporting is in its infancy (Anonymous, 1990; Dworkin et. al., 2003).

The National Pharmacovigilance Program (NPP) was launched on November 23, 2004 by the Government of India to collect ADR reports across the country and create awareness about pharmacovigilance. So far very few reports have been sent to UMC's Vigibase, which is relatively a less figure considering the number of health care professionals in country. 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 drugs. These medicines are used by various patients for different diseases these people 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 different brands of 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 that have also to be monitored through pharmacovigilance (Driessen and Reimann, 1992). In some cases, adverse drug reaction of certain medicines might occur only in one country's or region's citizens. To prevent all undue physical, mental and financial suffering by patients, pharmacovigilance proves to be an important monitoring system for the safety of in a country with the support of doctors, pharmacists, nurses and other health professionals. All the regions of the world have their own particular pharmacovigilance system, though based on WHO guidelines. Pharmacovigilance system in Europe is coordinated by the European Medicines Agency (EMA) and conducted by the National Competent Authorities (NCAs). The EMA maintains and develops the pharmacovigilance database comprising all suspected serious adverse drug reactions observed in the European region. Here, the pharmacovigilance system is called Eudra Vigilance and contains separate but similar databases of human and veterinary reactions. It can be said that the information obtained from reports about adverse drug reactions promote drug safety on a local and national level (Bamigbade et. al., 1997). These reports are entered into the national adverse drug reaction database and analyzed and justifying the whole pharmacovigilance system.

Risk Management Plans (RMPs)

RMP is defined as, "a set of PV activities and interventions designed to identify, characterize, prevent or minimize risks related to a medicinal product, including the assessment of effectiveness of those activities and interventions". In accordance to new legislation, RMP should be risk proportionate and needs to be submitted for all new products. The authorized products require RMP if there are issues affecting the risk benefit balance. The new legal requirement states that "EMA and MS's shall monitor the outcome of risk minimisation measures contained in the RMPs" (GVP Module V).

Signal Detection

The GVP clearly sets out the concept of signal detection, validation, prioritization, evaluation and communication. The MAHs needs to have documented processes for signal detection in accordance with the level of reports received and portfolio of medicinal products. It may include individual case review, statistical analysis or a combination of both (GVP Module IX).

Periodic Safety Update Reports (Addendum to Clinical Reports and PSURs)

The concept of Addendum to the Clinical Overview reports has been expanded and these reports should include a benefit/risk evaluation in renewal applications. The PSURs will not be required for generic and traditional herbal medicinal products. However, CAs can request PSURs for these products on the basis of various safety concerns. In addition, PSUR is replaced with Periodic Benefit Risk Evaluation Report (PBRER) and MAHs shall submit PBRERs/PSURs containing summaries of data relevant to benefits and risks of the product. The new features of the PBRER are (GVP Module VII):

a. Focus on benefit and risk
b. Emphasis on analysis and evaluation, in reference to active substance
c. Focus on cumulative data, with no case line listings (no individual case line listings, no tables of listed vs. unlisted)
d. The submission frequency is determined by drug’s risk profile

Pharmacovigilance in India

It is related to the surveillance of drugs once they are released for use in the community (post marketing surveillance) and relies on voluntary reporting, prescription monitoring, medical records and statistical studies in the population. Since very few new drugs were discovered in India and hardly any new drug was launched for the first time in India in the past, there was no major compulsion to have a strong Pharmacovigilance system to detect adverse reactions of marketed drugs. The experience from the markets where the drug was in use for several years before introduction in India, was used by the Companies and the Regulatory Agencies to assess the safety parameters and take corrective actions , such as the withdrawal or banning of the drug in question. With the Indian Companies" capacity to develop and market new drugs out of their own research efforts, it is important that adequate Pharmacovigilance standards are introduced to monitor adverse reactions of products, first launched in India.

Continuous monitoring of their effects, side effects, contraindications and outright harmful effects which can result in a high degree of morbidity and in some cases, even mortality, is essential to maximize benefits and minimize risks. No degree of care and caution at the pre-clinical and clinical testing stages can guarantee absolute safety, when a drug is marketed and prescribed to large

populations across the Country and outside. Because clinical trials involve several thousand patients at most; less common side effects and adverse drug reactions are often unknown at the time a drug enters the market. Even very severe adverse drug reactions, such as liver damage, are often undetected because study populations are small. Post marketing pharmacovigilance uses tools such as data mining and investigation of case reports to identify the relationships between drugs and adverse drug reactions. The drug regulatory agencies have the responsibility of having a well-established pharmacovigilance system to monitor adverse reactions of drugs. During the drug development phase and later during the life time of a marketed drug (WHO, 2000). Pharmacovigilance is fastest emerging as an important approach for the early detection of unwanted effects of the drugs and to take appropriate regulatory actions if necessary. This may ensure the safer use of drugs (Egberts et. al., 1996).

Historically, Indian market has always, except in very few cases, seen the launch of only products, which have been earlier approved and marketed in U.S.A., Western Europe or Japan. Until now, the time lag between the first marketing of a new drug in a foreign country and India has been on an average around 4 years, and hardly any new drug was introduced for the first time in India. In that kind of scenario, it was not too critical that there was in place a system of pharmacovigilance in India, since reports of side-effects from outside India would have helped our regulatory agencies to assess the rationale of continuing the drug in the Indian market. Thus in the past, action on marketed drugs has been triggered on the basis of reports on the harmful effects of drugs marketed abroad. In a few cases, drugs, which have been banned or withdrawn in foreign markets, were allowed to be kept in the market in India. For example, Chloramphenicol, Phenyl Butazone, Clioquinol, Phenformin, Cisapride, all continue to be prescribed in India on the basis of a conscious decision by the Regulatory Agency that the benefit to risk ratio is in favour of the former (Egberts et. al., 1996).

The evolution of a new Patent regime in the Indian Pharmaceutical Industry (the Post-2005 scenario) as a consequence of India being a founder member of WTO, and her obligations under Trade Related Intellectual Property Rights and Services (TRIPS), makes it incumbent that India can no longer copy patented products and market them without license from the innovator company. The leading Indian companies realizing the compulsions of the new regime have already initiated investments of substantial resources for the discovery and development of new drugs needed for both Indian and International markets. This in turn means that during the coming years Research and Development by the Indian Pharmaceutical companies will hopefully lead to new drugs based on pre-clinical and clinical data generated mostly in India. In such cases, the Indian regulatory agencies cannot count on the experience of other markets to assess the incidence and prevalence of adverse reactions from drug usage, and therein lies the importance of a properly designed pharmacovigilance system in India. For an effective Pharmacovigilance system to be functional and efficient all the stakeholders need to be alert and attentive throughout the lifetime of the drug in the market (NPP, 2005).

Hemovigilance Program of India

Hemovigilance systems, depending upon the country, are governed either by regulators (e.g., France, Germany, Switzerland), blood manufacturers (e.g., Japan, Singapore, South Africa), medical societies (e.g., Netherlands, UK), or public health authorities including regulators (e.g., Canada) (PHS, 2009). Member states of the European Union have to implement hemovigilance program with reporting to a Central Office as per the commission directive (CDEP, 2005; Faber, 2004; Faber, 2004). Among the Asian countries, a well established hemovigilance system is lacking and there is paucity of data on hemovigilance data except for Japan, which has published a report on adverse reactions (Jain and Kaur, 2012).

A Hemovigilance program as an integral part of pharmacovigilance program of India at a national level has been launched on December 10, 2012 with a road map of 5 years, i.e., year 2012–17, with four phases, i.e., initiation phase, expansion and consolidation phase, expansion and maintenance phase, and optimization phase. A core group to coordinate the activities of hemovigilance between the medical colleges and National Coordinating Centre at IPC has been constituted. Furthermore, an advisory committee has also been constituted to:

a. Finalize hemovigilance—Transfusion Reaction Reporting Form (TRRF) to be introduced in the country.
b. Give expert opinion for collection, collation, and analysis of hemovigilance data and development of the software for the same.
c. Monitor the functioning and quality of the data collected by the Adverse Transfusion Reaction Reporting Centres, i.e., ADR Monitoring Centres of PvPI.
d. Develop training modules and guidelines for implementation of hemovigilance program under PvPI, and
e. Develop a roadmap for linking hemovigilance program under PvPI with International Hemovigilance Network.

Initially, 60 medical colleges that are already enrolled under pharmacovigilance program of India have been brought under the ambit of this program. This number will be increased to a total of 90 medical colleges by March 2013. Hemovigilance program has been launched with the following objectives:

1. Monitor transfusion reactions
2. Create awareness among health care professionals

3. Generate evidence based recommendations
4. Advise Central drugs standard control organization (CDSCO) for safety related regulatory decisions
5. Communicate findings to all key stakeholders
6. Create national and international linkages (Akanksha et. al., 2013).

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