CHAPTER 1

Introduction
1.1 Introduction

The phenomenal advances in health awareness, accurate and thorough data review by health and domain authorities, and non-willingness of consumers to tolerate unnecessary serious adverse reactions have contributed to the recent increase in cases of drug recalls from the market (WHO "Safety of Medicines - a Guide to Detecting and Reporting Adverse Drug Reactions - Why Health Professionals Need to Take Action").

A drug recall is a situation where drug product that has been distributed is found to be potentially harmful, and must be pulled from stock and returned to the supplier. Usually, a recall is associated with a defective or contaminated product.

<table>
<thead>
<tr>
<th>GENERIC (BRAND) NAME</th>
<th>ADR REPORTED</th>
<th>YEAR INTRODUCED</th>
<th>YEAR WITHDRAWN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide (Contergan®)</td>
<td>Teratogenic</td>
<td>1957</td>
<td>1961</td>
</tr>
<tr>
<td>Benoxaprofen(Orafl ex ®)</td>
<td>Liver necrosis</td>
<td>1982</td>
<td>1982</td>
</tr>
<tr>
<td>Terfenadine(Seldane ®)</td>
<td>Fatal cardiac arrhythmias</td>
<td>1985</td>
<td>1998</td>
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<tr>
<td>Encainide (Enkaid ®)</td>
<td>Excessive mortality</td>
<td>1987</td>
<td>1991</td>
</tr>
<tr>
<td>Flosequinan (Manoplax ®)</td>
<td>Excessive mortality</td>
<td>1992</td>
<td>1993</td>
</tr>
<tr>
<td>Temafloxacin (Omnifl ox ®)</td>
<td>Haemolytic anemia</td>
<td>1992</td>
<td>1992</td>
</tr>
<tr>
<td>Mibefradil(Posicor ®)</td>
<td>Multiple drug interaction</td>
<td>1997</td>
<td>1998</td>
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<tr>
<td>Bromfenac(Duract ®)</td>
<td>Serious hepatotoxic effect</td>
<td>1997</td>
<td>1998</td>
</tr>
<tr>
<td>Rofecoxib (Vioxx®)</td>
<td>Cardiovascular events</td>
<td>1992</td>
<td>2004</td>
</tr>
</tbody>
</table>

ADR: Adverse Drug Reaction

Recalls can be either voluntary by the manufacturer, or rarely, mandated by The United States Food and Drug Administration (FDA) or Health Canada. Specific information about drug
recalls is issued by FDA and Health Canada and many of the other regulatory agencies like MHRA (UK), PDMA (Japan), EMEA (EU), TGA (Australia) & CDDA (Sri Lanka) etc.

In the practice of pharmacy, it is very important to keep up with drug recalls. Recalls vary in seriousness and in the action that must be taken. Sometimes a drug company will recall only a specific batch or lot. But there are other cases when all batches or lots of a drug are affected. In the U.S., there are three classes of recalls, listed here in order from most serious to least serious:

- **Class I** recalls involve products that are likely to cause serious adverse events (SAEs) or deaths in people who take the drug. For example, a label mix-up on a lifesaving drug would lead to a class I recall. Sometimes a drug will be removed from the market permanently (i.e., withdrawn) following a class I recall. A notable example of a class I recall would be the heparin recall in 2008, which was a result of an over sulfated chondroitin sulfate contamination (Kishimoto et al. 2457-67). The contaminant was associated with allergic reactions and deaths in a number of patients.

- **Class II** recalls are the most frequent and involve products that could cause temporary but reversible effects. In this instance, there is little chance of a serious adverse event in people who are taking the drug. In early 2010 lots of injectable ketorolac were recalled in the U.S., due to the possibility of tiny particles in the vials is an example of a class II recall (Hospira). Another example would be the recent recall of lots of epoetin alfa (Epogen, Procrit) in the U.S. This happened due to an interaction between the drug solution and the glass vials which may have led to tiny flakes of glass (USFDA "Amgen Initiates Voluntary Nationwide Recall of Certain Lots of Epogen® and Procrit® (Epoetin Alfa)"). Particles in any solution that is for intravenous administration have the potential to cause adverse events such as blood clots or allergic reactions. An example in Canada was the recall of a certain manufacturer’s injectable ciprofloxacin as a precautionary measure due to possible contamination.

- **Class III** recalls involve products or specific batches or lots that are unlikely to cause adverse events (AEs) in people who are taking the drug. These types of recalls are usually from packaging issues or malfunctioning delivery devices rather than a problem with/from the actual medication. For example, in 2008 Watson Pharmaceuticals recalled one lot of their fentanyl 75 mcg pain patches due to a small number of patches that were leaking fentanyl gel, potentially
exposing the patient or caregiver to the drug. It is very unlikely a person would have any safety issues from exposure to the gel, unless they ingested it. So the company put a class III recall on the specific lot to test the patches and correct the issue (USFDA "Fentanyl Transdermal System Patch Recall").

Health Canada’s system is similar, with hazard classifications of **Type I**, **II**, and **III** corresponding to FDA’s classifications. This has led to adoption of control mechanisms and various risk management approaches by regulatory authorities.

### 1.2 Pharmacovigilance

The Pharmacovigilance (PV) is the system is one of those risk management & control mechanisms. PV covers legal and humane aspects by emphasizing safety. Pharmacovigilance can be defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects of a drug. In other words, pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of drugs (WHO "Safety of Medicines - a Guide to Detecting and Reporting Adverse Drug Reactions - Why Health Professionals Need to Take Action").

Adverse drug reactions (ADRs) are thought to be the 4th to 6th largest causes of death in the U.S. and are estimated to cause 3-7% of all hospital admissions (Lazarou, Pomeranz and Corey 1200-05). More than half of these ADRs are not recognized by the physicians on admission, and ADRs are responsible for the deaths of 15 out of the 1000 patients admitted (Gandhi et al. 1556-64). Although, in India precise estimates are not available, ADRs causal rank & hospitalization ratio remains more or less the same.

It is needless to say that ADRs must be continuously monitored through a well validated PV program. PV entails a continuous and ongoing process which allows assessing the safety of a medicinal product through its life cycle. PV collects, records, codes Adverse Drug Events (ADEs) & ADRs analyses, assesses the reports, and promotes the safe use of drugs. It is significant to discuss how PV has emerged.
1.2.1 Emergence of Pharmacovigilance

An eye-opening tragedy like Thalidomide urged the importance of drug safety and therefore the need for PV (WHO "The Importance of Pharmacovigilance"). Thalidomide (α-N-[phthalimido] glutarimide) was first synthesized in 1953 by Ciba, a Swiss pharmaceutical firm, and then in 1954 by Kunz, a chemist at Chemie Grünenthal, a German pharmaceutical company (Stephens and Brynner; Eriksson, Björkman and Höglund 365-76; Lenz 203-15). On October 1, 1957, Chemie Grünenthal introduced the drug into the market as a sedative (Lenz 203-15; Stephens and Brynner; Lenz 417-18). Thalidomide lacked the typical addictive properties of barbiturates and produced a natural, calm sleep.

By 1960, thalidomide was sold by Chemie Grünenthal and its licensees in more than 40 countries and became popular as both a sedative and a morning sickness treatment during pregnancy. Thalidomide was marketed under various commercial names such as Contergan, Distaral, Softenon, Neurosedyn, Isomin, Kedavon, Telargan, and Sedalis (Lenz et al. 1-45).

On November 18, 1961, four years after thalidomide entered the market, Widukind Lenz, a German physician and geneticist, indicated that thalidomide was associated with severe teratogenic malformations. He had observed more than 50 malformed infants whose mothers had taken the drug during pregnancy. In December 1961, an independent confirmation came from William McBride, an Australian obstetrician, who questioned whether thalidomide was responsible for teratogenic malformations (McBride 1358).

The findings of these 2 investigations soon were confirmed by numerous physicians worldwide. As a result, by the end of 1961, thalidomide was taken off the market in most countries. Although they initially contested these findings, they were later convinced that the drug was a powerful teratogen, as nearly 10,000 infants were affected worldwide. Fetal malformations due to thalidomide occurred when a pregnant woman, between days 35 and 49 after the last menstrual period, ingested the drug. A single pill was sufficient to produce teratogenic effects. Fetal malformations included the absence of ears and arms, deafness, phocomelia, defects in the face and palate, and malformations of the gastrointestinal system. Approximately 40% of affected infants died within their first year of life (Rajkumar 899-903).
The Thalidomide disaster raised an issue about clinical safety of marketed medicinal products and initiated the establishment of regulatory bodies at Europe and all over the globe. It was in the interest of general public health that new drugs should be licensed by going through various filtering processes of well-established regulatory authorities before being introduced for clinical use. Learning a lesson from the past incidences, there were certain aims that were put forward to achieve the success of PV.

The Tylenol Case
In October of 1982 Tylenol, the leading pain-killer medicine in the United States at the time, faced a tremendous crisis when seven people in Chicago were reported dead after taking extra-strength Tylenol capsules. It was reported that an unknown suspect put 65 milligrams of deadly cyanide into Tylenol capsules, 10,000 more than what is necessary to kill a human.

The tampering occurred once the product reached the shelves. They were removed from the shelves, infected with cyanide and then returned to the shelves. In 1982, Tylenol controlled 37 percent of its market generating revenue of about $1.2 million and immediately after the cyanide poisonings; it was reduced to seven percent.

Although Johnson & Johnson knew they were not responsible for the tampering of the product, they assumed responsibility by ensuring public safety first and recalled all of their capsules from the market. In fact, in February of 1986, when a woman was reported dead from cyanide poisoning in Tylenol capsules, Johnson & Johnson permanently removed all of the capsules from the market.

Tylenol products were re-introduced containing a triple-seal tamper resistant packaging. It became the first company to comply with the Food and Drug Administration mandate of tamper-resistant packaging. Furthermore, they promoted caplets, which are more resistant to tampering. Thus PV emerged with the goal of focusing more on patient safety (Mitchell 601-18).

1.2.2 Aims of Pharmacovigilance
The safety of a medicinal product is generally evaluated during the clinical development phase. However to enforce drug monitoring with stringent rules, PV plays a vital role in ensuring that
clinicians, together with the patient, have enough information to make a decision when it comes
to choosing a safer drug for treatment. In fact, in order to market or to test a pharmaceutical
product in most countries, adverse event data received by the license holder (usually a
pharmaceutical company) must be submitted to the local drug regulatory authority. Ultimately,
PV is concerned with identifying the hazards associated with pharmaceutical products and with
minimizing the risk of any harm that may come to patients.

- To improve patient care and safety
- To promote rational and safe use of medicines
- To contribute to the assessment of benefit, harm, effectiveness and risk of medicines
- To promote education and clinical training
- To promote effective communication to the public regarding the Adverse effects of the
drug

The aim of establishing a comprehensive PV can only be achieved through all important
components of PV. Let us have a brief look at components of PV.

1.2.3 Components of Pharmacovigilance
Pharmacovigilance is the pharmacological science relating to the collection, collation and
assessment of adverse events, to arrive at an inference; to recommend to a regulatory authority;
besides communicating risks to the health care professionals as well as the general public.

1.2.3.1 Adverse Drug Reactions
Pharmacovigilance heavily focuses on adverse drug reactions, which are defined as any
response to a drug which is noxious and unintended, including a lack of efficacy, which occurs
at doses normally used for the prophylaxis, diagnosis or therapy of a disease, or for the
modification of a physiological function. Medication errors such as overdose, and the misuse
and abuse of a drug, are also of interest as they may result in an ADR. PV mainly deals with
ADRs. Thus, it should be discussed in brief to ensure efficient functioning of PV.

A reaction in contrast to an event is characterized by the fact that a causal relationship between
the drug and the occurrence is suspected. For regulatory reporting purposes, if an event is
spontaneously reported, even if the relationship is unknown or unstated, it meets the definition
of an ADR (ICH).
**Adverse Events**

Adverse events (AEs) are any untoward medical occurrences in patients who were administered a drug and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not considered related to this drug (ICH).

**Seriousness Criteria for AEs**

The most internationally agreed seriousness criteria appear in ICH guideline E2A. A serious adverse event/experience or reaction is any untoward medical occurrence that at any dose: ‘results in death’, is life-threatening, ‘requires inpatient hospitalization or in prolongation of existing hospitalization’, ‘results in persistent or significant disability/incapacity is a congenital anomaly/birth defect’, is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered as serious such as important medical events that may not be immediately life threatening but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse (ICH).

**Unexpected Adverse Drug Reactions**

An ADR whose nature, severity, specificity, or outcome are not consistent with the term or description, as used in the official product information, should be considered unexpected. An ADR with a fatal outcome should be considered unexpected, unless the official product information specifies otherwise. In the absence of special circumstances once the fatal outcome is itself expected, reports involving fatal outcomes should be handled as for any other serious expected ADR in accordance with the appropriate regulatory requirements. In Signal detection Spontaneous ADR reporting plays a vital role (ICH).
1.2.3.2 Spontaneous ADR Reporting

The word “spontaneous” itself suggests that, the instantaneous reporting of ADRs as soon as it took place. Spontaneous ADR reporting schemes depend majorly on the individual reports from healthcare professionals from their clinical suspicion that a drug may have been responsible for an adverse event. In most countries, such reports are centrally collated in a database, which can be used to detect signals of unrecognized toxicity that require confirmation or refutation using other data sources. In recent years, there have been major advances in the use of mathematical approaches to assess whether or not reports of a particular drug-reaction combination is in excess of expectations but which do not depend on drug exposure data which are rarely available.

The methods yield similar results unless the numbers of cases are small, but it is important to note that their aim is to separate a signal from background noise and provide an indication of the strength of the signal. However they do not prove that an association is causal. There is also the so called “Weber effect” which refers to the observation that reporting is much more frequent for newly licensed drugs and declines over time. Comparisons of new drugs with older drugs of the same class are thus complicated by the time factor. Additionally, if the ADR is rare, then there may be a considerable lag time in the detection of the reaction, which relies on the accumulation of a sufficient number of cases to provide a signal (ICH). (Signal- a causal relationship or a pair between a drug and adverse reaction associated with it when statistically calculated from a particular database).

Once a signal has been detected which is considered to be sufficiently strong and is potentially important clinically, a detailed evaluation is necessary. This involves assessing the clinical data and any other relevant data including pre-clinical data, mechanistic studies, clinical trials and post-marketing studies. The key issues to be considered in the assessment are causality, frequency, clinical implications and preventability with a particular focus on identifying the information required to confirm or refute the signal. If existing data are inadequate, new research from basic science through clinical investigation to pharmaco-epidemiological studies may be required.

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Following factors can improve the existing Spontaneous ADR reporting by surpassing its limitations.

- Regionalization
- Combination with DIC-activities
- Retrieval of additional information
- Access to all relevant pre- and post-marketing information
- Access to detailed drug utilization data
- Standardized Assessment of causality and seriousness
- Simulation

Sound knowledge and training about methodology of Spontaneous ADR Reporting should be given to all professionals who are supposed to report in a manner to surpass biases. A systematic approach should be established by setting up strict regulations. The general awareness about importance of Spontaneous ADR Reporting needs to be spread. To overcome the delay in reporting the reporting system should be channelized and the reporting centers must be distributed in large numbers throughout the country for solving the issue.

**Role of Spontaneous Reporting**

Spontaneous Reporting covers all drugs used of all populations. The 13/18 of the most important ADRs before 1982 has been ‘signaled’ for the first time by Spontaneous Reporting. More than 50% of all ‘alert’ black boxes in the Physician’s Desk Reference (PDR) are derived from Spontaneous Reporting. Spontaneous ADR Reporting plays a vital role for understanding epidemiological issues, educating ADRs for better communication (ICH).

Spontaneous Reporting provide the highest volume of information at the lowest maintenance cost, and have proven their value in the early detection of patient safety issues related either to the products themselves or to their use. Most important function of the spontaneous reporting
Limitations of Spontaneous Reporting

Following factors influences the Spontaneous ADR reporting:

1. Spontaneous ADR reporting is a voluntary system, which has lots of ifs, and buts associated with it and lead towards the greatest limitation of this system.
2. Another limitation is that the reporting is done by various professionals like physicians, pharmacists and nurses which may raise a problem of bias in the reporting system.
3. The submission of Spontaneous ADR reports at various levels like Physicians, MAHs, and Regional or Zonal centers may lead to the issues of bias in reporting.
4. Lack of training or knowledge of the person who is reporting may turn into inadequate data which could be in deficit of a fruitful outcome.

Improvisation in Spontaneous Reporting Systems

The Spontaneous ADR Reporting can be strengthened by: regionalization of data received, combining DIC activities, upgrading information collecting format to retrieve additional information, enabling access to pre & post marketing information and drug utilization data. With more precise assessment of casualty & seriousness and stimulation of data collected. The sound knowledge and training about methodology of Spontaneous ADR reporting should be given to all professionals who are supposed to report in a manner to surplus biases. A systematic approach should be established by setting up strict regulations. The general awareness about importance of Spontaneous ADR reporting needs to be spread. To overcome the delay in reporting the reporting system should be channelized and the reporting centers must be distributed in large numbers for solving the issue as like Yellow Card Scheme by MHRA (Davis and Coulson 786-88).

1.2.3.3 Individual Case Safety Reports (ICSRs)

Individual case safety reports communicate genuine clinical concerns from observant health professionals. As they are based on actual patients in the real world clinical practice, their collection and analysis increase the chance to discover ADRs that are due to drug–drug interaction, affecting patients with certain medical predispositions or that belong to patient
subgroups that tend to be excluded from pre marketing clinical trials, such as children or pregnant women (Hasford ; Edwards 138-41).

Much of the information on these reports can be originally provided as free text, some of which is later encoded as structured information upon database entry. Trained personnel at pharmaceutical companies or at national authorities usually do this. The encoding of observed ADR incidents in terms of standardized terminology is a critical part of the preprocessing. One potential pitfall is the risk of misinterpretation when someone who has never actually met the patient performs the ADR encoding. Variation in coding across regions and time periods may lead to systematic differences that can affect subsequent data analysis.

A general problem is that several ADR terms are often applicable to a given incident. Thus, exploratory analysis focusing on single ADR term may fail to include all relevant reports—a phenomenon which has been referred to as ‘signal fragmentation’ (Purcell 63-64). While in the follow-up of specific issues, this can be remedied by specifying groups of relevant ADR terms for the issue of interest; it is not obvious how such strategies can be easily automated for routine exploratory analysis.

Individual case safety reports refer to suspected ADR incidents and some adverse events observed in association with drug prescription will in reality be coincidental, due to concomitant medication or natural progression of the underlying disease. There may also be variation in the propensity to report suspected ADRs during the life-span of a drug and in response to any attention to suspected drug safety issues in the public or scientific media. The categories of health professionals who are allowed to submit reports also differ over time and between regions. Some countries allow only medical doctors to submit reports, whereas others accept reports from medical nurses and pharmacists as well. In addition, some countries encourage direct consumer reporting. Unsurprisingly, the propensity to report suspected ADRs of different types varies considerably between different categories of reporters (Savage).

An important characteristic of individual case safety report submission is that separate reports sometimes have a common origin and therefore cannot be considered as independent pieces of information (Finney 387–93). This may distort automated knowledge discovery and mislead clinical review. The most obvious cause of non-independent reports is report duplication, where
a single suspected ADR incident results in several reports. More subtle examples include groups of reports provided by the same health professional, reports from the same clinical study (sometimes mislabeled as spontaneous reports) or separate reports for the same patient at different points in time. If single individuals are responsible for encoding large numbers of reports, this may also induce superficial similarity between reports.

It is in the roots of pharmaceutical development that the full safety profile of a new medicinal product will not be known at the time it is introduced to the general public. Because randomized clinical trials are limited in both the types and numbers of patients exposed, continued safety monitoring of drugs is in the interest of patients, regulatory authorities and pharmaceutical companies. PV and all drug safety issues are relevant for everyone whose life is touched in any way by medical interventions.

An inherent problem in pharmacovigilance is that most case reports concern suspected adverse drug reactions. Adverse reactions are rarely specific for the drug, diagnostic tests are usually absent and a rechallenge is rarely ethically justified. In practice, a few adverse reactions are ‘certain’ or ‘unlikely’; most are somewhere in between these extremes, i.e. ‘possible’ or ‘probable’. In an attempt to solve this problem many systems have been developed for a structured and harmonised assessment of causality. For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g., stroke, pulmonary embolism).

Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with long-term follow-up, are usually needed to assess causality in such instances. The analyses of drug-related AEs presented by applicants are usually based on assessments made by investigators at the time of an event, are highly dependent on information about the side effect profile of the drug available at the time of the study (e.g., what is in the investigator’s brochure), and are not informed by awareness of the entire safety database. These analyses are generally not expected to provide much useful information in assessing causality.

The contents of pharmacovigilance discussed above contribute to effective functioning of PV system. This PV system applies certain methods to accomplish the PV study. Let us have a glance at PV study methodologies.
1.2.4 Pharmacovigilance Study Methodology

PV studies are planned in a manner to generate fruitful data as its outcome. As, mentioned earlier the outcome from PV studies may be very handy for “Signal detection” and conclude that the drug is safe to use clinically or not. The best method to address a specific situation can vary depending on the product, the indication, the population being treated, and the issue being addressed. The method chosen can also depend on whether an identified risk, potential risk, or missing information is the issue & whether signal detection, evaluation or safety demonstration is the main objective of study. When choosing a method to address safety concerns, a sponsor should employ the most appropriate design.

Carefully designed and conducted pharmacoepidemiological studies, specifically observational (non-interventional, non-experimental) studies, are important tools in PV. In observational studies, the investigator “observes and evaluates results of ongoing medical care without 'controlling' the therapy beyond normal medical practice”. Before the observational study that is part of a PV Plan commences, a protocol should be finalized. Experts from relevant disciplines should be consulted. It is recommended that the protocol be discussed with the regulatory authorities before the study starts. It is also suggested that the circumstances in which a study should be terminated early be discussed with regulatory authorities and documented in advance. A study report after completion, and interim reports if appropriate, should be submitted to the authorities according to the milestones within the Pharmacovigilance Plan.

It is recommended that the sponsor follow good epidemiological practice for observational studies and also internationally accepted guidelines, such as the guidelines endorsed by the International Society for Pharmacoepidemiology. In some of the ICH regions, local laws and guidelines also apply to the design and conduct of observational studies and should be followed. The highest possible standards of professional conduct and confidentiality should always be maintained and any relevant national legislation on data protection followed. The PV study designs are mentioned as follows:

1.2.4.1 Case-Control Study Designs

Case-control are a type of epidemiological study designs which are used to identify factors that may contribute to a medical condition by comparing subjects who have that abnormal condition which serves as 'cases' with patients who do not have that particular abnormal condition and
serve as 'controls' (BMJ). Case-control studies are comparatively inexpensive and can be carried out by small teams or individual researchers in single facilities with more structured approach. Two eminent examples are studies which exhibit the association between aspirin and Reye’s syndrome and the evaluation of Diethylstilbestrol (DES) and breast cancer in the offspring of mothers who took DES in pregnancy (Moynihan et al. 1645-50; CDC). The final results of these studies present a risk in the outcome associated with the exposure under study-expressed as odds ratio. A nested case control study affords the ability to quantify absolute risk while taking advantage of inherent efficiency of the case-control designs.

1.2.4.2 Cohort Studies

A Cohort study is a form of longitudinal study used in medicine and social science. A cohort is defined as a group of people who share a common characteristic or experience within a defined period (e.g., are born, leave school, lose their job, are exposed to a drug or a vaccine, etc.). Thus a group of people who were born on a day or in a particular period, say 1983, form a birth cohort. The comparison group may be the general population from which the cohort is drawn from, or it may be another cohort of people thought to have had little or no exposure to the substance under investigation, but otherwise similar. Alternatively, subgroups within the cohort may be compared with each other.

Cohort studies can be conducted prospectively, but such studies are usually expensive and time consuming. Retrospective cohort studies can be conducted within large existing databases, providing the advantage of the cohort study design and the efficiencies inherent in the studies using existing records. The advantage of cohort study data is the longitudinal observation of the individual through time, and the collection of data at regular intervals, reducing recall error. However, cohort studies are expensive to conduct, sensitive to attrition and take a long time to generate useful data.

Case-control studies are particularly useful to confirm a safety signal relating to rare event (less than 1/1000). Cohort studies are useful when the outcome has not been identified or when multiple outcomes are of interest. Both case-control and cohort studies can be conducted within large existing databases, assuming the required information is available.
An example of an epidemiologic question that can be answered by the use of a cohort study is: does exposure smoking correlate with outcome lung cancer. Such a study would recruit a group of smokers and a group of non-smokers (the unexposed group) and follow them for a set period of time and note differences in the incidence of lung cancer between the groups at the end of this time. The groups are matched in terms of many other variables such as economic status and other health status so that the variable being assessed, the independent variable (in this case, smoking) can be isolated as the cause of the dependent variable (in this case, lung cancer).

In this example, a statistically significant increase in the incidence of lung cancer in the smoking group as compared to the non-smoking group is evidence in favor of the hypothesis. However, rare outcomes, such as lung cancer, are generally not studied with the use of a cohort study, but are rather studied with the use of a case-control study (Mann and Andrews 7-10).
1.2.4.3 Randomized Controlled Trials

In this method of study, a group of patients is divided into two or more in strictly random order; one group is exposed and other is not exposed, so that the outcomes cannot be compared. The method is of great importance because random assignment of treatment removes some of the biases possible in observational studies. It is however, of only limited use as a pharmacoepidemiological tool because most serious ADRs are relatively uncommon; randomized controlled trials (RCT) used in such contexts can, therefore, become unmanageably large and expensive. Nevertheless, it is sometimes not practical or ethical to perform RCTs to answer a clinical question. To take our example, if we already had reasonable evidence that smoking causes lung cancer then persuading a pool of non-smokers to take up smoking in order to test this hypothesis would generally be considered quite unethical (Doll).

Large simple trials have become more common over last decade in evaluating safety and efficacy in special circumstances, such as vaccine and development, hormone replacement therapy and treatments for common cardiovascular conditions. This becomes a mammoth task to conduct PV system effectively. Hence, various partners of PV system contribute at different stages to ensure the precise conclusion of PV study (Mann and Andrews 7-10).

1.2.5 Partners of Pharmacovigilance

There should be a link between wide ranges of partners in the practice of drug safety monitoring. Constant alliance and commitment are vital if, the future challenges in PV are to be met and the discipline is to continue to develop and flourish.

1.2.5.1 The WHO Team

The WHO is a globally working organization for the betterment of mankind and health related issues. WHO runs the Adverse Drug Reaction Monitoring Program, which take care of clinical safety related issues of any drug.

The Quality assurance and safety medicines team of WHO is responsible for providing guidance and support to countries on drug safety matters. The team is part of the Department of Essential Drugs and Medicines Policy, within the WHO Health Technology and Pharmaceuticals cluster. WHO works towards fulfilling this mission by providing global guidance on essential drugs and medicines, and working with countries to implement national

1.2.5.2 World Database - Uppsala Monitoring Centre (UMC)
The Uppsala Monitoring Centre (UMC) was established in the year 1978 located at Sweden. The UMC manages the international database of ADR reports received from National Centers (Olsson 1-10). The UMC database is known as VigiBase™. The services provided by VigiBase are utilized by a Pharmaceutical industry to collect data related to their product from all part of the globe. UMC also provides the services of Signal Detection, and updating PSUR data. The signal detection in PV is performed by statistical approaches like sophisticated Bayesian confidence propagation neural network (BCPNN) program created in 1998, which ensures earlier alert signals than previous methods (Uppsala).

The effectiveness of this system depends on:
- The size of the database
- The quality of the reports received from the contributing centers
- The timeliness of such reporting
- An active and reliable reporting culture within participating countries

1.2.5.3 Hospitals and Academia
The efforts of clinical pharmacology and pharmacy departments around the world have resulted in the development of PV as a clinical discipline, a number of medical institutions have developed adverse reaction and medication error surveillance systems in their clinics, wards and emergency rooms. The expansion of scientific knowledge in drug safety is attributable to the greater awareness and academic interest in this field. Academic centers of pharmacology and pharmacy have played an important role through teaching, training, research, policy development, clinical research, ethics committees (institutional review boards) and the clinical services they provide. In many medical institutions, particularly in the developed world, ADR monitoring is recognized as an essential quality assurance activity (Bate et al. 315-21).

1.2.5.4 Professionals
The success or failure of any spontaneous reporting system depends on the active participation of reporters. Originally physicians were the only professionals invited to report as judging
whether disease or medicine causes a certain symptom by exercising the skill of differential diagnosis. It was argued that accepting ADR reports from physicians only, would ensure high quality information and minimize the reporting of unrelated, random associations. Studies have shown, however, that different categories of health professionals will observe different kinds of drug related problems (Moore 1-7; Hall et al. 173-75).

1.2.5.5 Patients

Only a patient knows the actual benefit and harm of a medicine taken. Observations and reports made by a health professional will be an interpretation of a description originally provided by the patient, together with objective measurements. Some believe strongly that direct patient participation in the reporting of drug related problems will increase the efficiency of the PV system and compensate for some of the shortcomings of systems based on reports from health professionals’ only.

1.2.6 Legal Basis for Pharmacovigilance

Pharmaceutical companies have a responsibility to make the use of their medicines as effective and as safe as possible. Hence, companies need to conduct effective pharmacovigilance throughout the life cycle of all medicinal products, so that accurate, well-informed and up-to-date information is provided to physicians, pharmacists and patients. In addition, companies must keep regulatory authorities informed with regard to the ongoing safety profiles of their products so that the authorities can fulfill their own obligations to protect public health.

Each company should collect safety data on all of its products, from all available sources on a worldwide basis, and have appropriate evaluation and reporting mechanisms in place. However, the current diversity of regulatory requirements for reporting adverse drug reactions (ADRs) results in different authorities requesting that information from the same source be presented according to different inclusion criteria, formats and time intervals.

Despite the best efforts of the Council for International Organizations of Medical Sciences (CIOMS) and the International Conference on Harmonization (ICH), it is evident that effort put into compliance with diverse ADR reporting requirements draws resources away from the medical evaluation of safety signals. Thus, a single set of standards for the worldwide communication of safety information is still required in order to facilitate a shift in emphasis
away from the administration of safety data towards more cost-effective identification and evaluation of important safety signals (Stephens, Talbot and Waller 376-82).

1.2.6.1 Council for International Organizations of Medical Sciences (CIOMS)
CIOMS is a non-governmental organization established in 1949 by the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO), primarily to act as a forum for capturing and disseminating opinion on new developments in biology and medicine, as well as in exploring their social, ethical, moral, administrative and legal implications.

In 1986, CIOMS initiated the ‘CIOMS I’ Working Group with the objective of standardizing expedited ADR reporting requirements. Subsequent CIOMS working groups have addressed a variety of safety-related topics, as follows:

I. International reporting of adverse drug reactions
II. Harmonization of data elements for electronic ADR reporting
III. International reporting of periodic drug-safety update summaries
IV. Guidelines for preparing core clinical-safety information on drugs
V. Benefit–risk balance for marketed drugs: evaluating safety signals
VI. Current challenges in pharmacovigilance: pragmatic approaches
VII. Safety monitoring and evaluation during clinical trials

Groups I–VI have completed their activities and, with the exception of CIOMS Ia, have published their recommendations as CIOMS reports; CIOMS VI activities are ongoing. Each CIOMS Working Group report represents a significant milestone in pharmacovigilance. Groups I, III and VI have contributed significantly to the harmonization of international ADR reporting requirements, and are described further below-

CIOMS I –International Reporting of Adverse Drug Reactions
The CIOMS I group was formed with the objective of developing an internationally acceptable method for manufacturers to report post-marketing ADRs rapidly and effectively to regulatory authorities. The group comprised individuals from regulatory authorities and pharmaceutical companies and issued its final report in 1990.
The final report of the CIOMS I group contains several recommendations relating to conventions and definitions, report content and format. In due course, this established the CIOMS I form for worldwide expedited reporting. CIOMS reports should be filed once they contain the following minimum standard of information:

- an identifiable source
- a specific patient
- a suspected drug
- a suspected reaction

Manufacturers should submit completed CIOMS I forms to regulatory authorities within working days after initial receipt of information, thereby allowing companies sufficient time to collect reasonably detailed information on a case before notification and reducing the need for follow-up reports (Faich, Castle and Bankowski 133-38).

**CIOMS II – International Reporting of Periodic Drug-Safety Update Summaries**
The CIOMS II Working Group was convened with the objective of developing a model periodic safety update report (PSUR) that could serve as the basis for harmonizing international approaches to periodic reporting, and it issued its final report in 1992. The CIOMS II Working Group established well-recognized standards for PSURs that have progressed through the European Union (EU) and ICH processes dealing with this topic (Ebbers et al. 217-26).

**CIOMS V – Current Challenges in Pharmacovigilance: Pragmatic Approaches**
The CIOMS V Working Group was convened to consider practical proposals on a wide range of issues concerning pharmacovigilance and ADR reporting, including unresolved issues from previous CIOMS Working Groups, and it issued its final report in 2001. The CIOMS final report in 2001 addressed several issues to bring programmatic approach in PV right from sources of ICSRs like: from consumer, published internet or available on internet. To establish effective case management practices like: clinical evaluation of cases and to access patient & reporter identifiability; to generate accurate summary reporting time & frequency; to determine & utilize population exposure data like; PSURs & exposure data sources & technical consideration; to implement clinical safety reporting regulation by overviewing of current regulation & recommending change (CIOMS Current Challenges in Pharmacovigilance: Pragmatic Approaches: Report).
The International Conference on Harmonization (ICH)

The ICH is a unique project bringing together regulatory authorities from three regions (EU, USA and Japan) with experts from the pharmaceutical industry. The process involves discussion of scientific and technical aspects of product registration, leading to recommendations that facilitate the harmonization of requirements for product registration, thereby reducing the need to duplicate effort during the development of new medicinal products.

The terms of reference of the ICH were defined as follows:

- Provide a forum for constructive dialogue between regulatory authorities and the pharmaceutical industry regarding differences in the technical requirements for product registration in the EU, USA and Japan.
- Identify areas where modifications in technical requirements or greater mutual acceptance of R&D procedures could lead to more economical use of resources without compromising safety.
- Recommend practical ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for registration.

Co-sponsors of the ICH are the European Commission (EC), European Federation of Pharmaceutical Industries and Associations (EFPIA), Ministry of Health, Labour and Welfare (MHLW), Japan, Japan Pharmaceutical Manufacturers Association (JPMA), Food and Drug Administration (FDA), USA, and Pharmaceutical Research and Manufacturers of America (PhRMA).

In addition, the International Federation of Pharmaceutical Manufacturers’ Associations (IFPMA) provide the ICH secretariat, and the WHO, European Free Trade Association and Canada have provided observers to the process. IFPMI encourage a global policy environment that is conducive to medicines innovation, both therapeutic and preventive, for the benefit of people around the world. They promote and support principles of ethical conduct and practices voluntarily agreed upon, as exemplified by the IFPMA Code of Practice. Clinical drug safety-related topics have been addressed at several ICH meetings, primarily in association with expedited and periodic reporting requirements as well as developing standards for the electronic communication of clinical safety data.
All of the countries except Kenya and Turkey have a pharmacovigilance center or unit responsible for carrying out the activities related to ADR monitoring, pharmacovigilance and PMS studies. These units are mainly concerned with the collection of spontaneous and suspected ADR reports that have to be submitted on expedite basis. All other reports like non-serious ADRs, etc. need not be submitted on an expedite basis but should be properly archived and made available as and when requested by the regulatory authority (Giaquinto).

All these reports are then sent to the WHO ADR Monitoring Centre at Uppsala, Sweden, which helps to update the world pool of information on this topic.

Table 1.2: Current status of PV in selected countries (Yadav S4-S9)

<table>
<thead>
<tr>
<th>Countries status</th>
<th>Australia</th>
<th>Brazil</th>
<th>India</th>
<th>Jordan</th>
<th>Kenya</th>
<th>Malaysia</th>
<th>Singapore</th>
<th>South Africa</th>
<th>Turkey</th>
<th>Ukraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is an ADR reporting system present?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Date of commencement</td>
<td>1968</td>
<td>2001</td>
<td>2003</td>
<td>2001</td>
<td>-</td>
<td>1993</td>
<td>1997</td>
<td>-</td>
<td>2000</td>
<td>-</td>
</tr>
<tr>
<td>Regulatory body</td>
<td>ADRAC</td>
<td>NDMC,</td>
<td>NPAC</td>
<td>JPC</td>
<td>MADRC</td>
<td>PVU</td>
<td>NADEMC</td>
<td>SPC</td>
<td>MCC</td>
<td>MoH</td>
</tr>
<tr>
<td>ADR responsible for</td>
<td>PVU</td>
<td>NDSMC</td>
<td>MCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADR control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Related legislation</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Guidelines available</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Official forms</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>ADR Reporting responsibilities of the following</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MoH (mandatory)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Others (mandatory)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Validation and follow-up of ADR reports by the MoH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigation reporting time for spontaneous ADRs</td>
<td>≤15 days</td>
<td>≤15 days</td>
<td>≤15 days</td>
<td>≤15 days</td>
<td>≤15 days</td>
<td>≤15 days</td>
<td>≤15 days</td>
<td>≤15 days</td>
<td>≤15 days</td>
<td>≤15 days</td>
</tr>
<tr>
<td>PMS studies conducted</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Reporting between submission of application and grant of license</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Reporting of non-serious ADRs</td>
<td>No</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Reporting to the WHO centers (mandatory)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
</tbody>
</table>

The details mentioned in Table no. 1.2 clearly indicate a PV system & its existence across world. Now, let us focus on the Indian PV system. These partners of PV system ensure the success of PV study. The role of PV system has to be clearly established in for the success of
PV study. Let us discuss these roles of PV (Hornbuckle, Wu and Fung 1117-24; WHO "Consumer Reporting of Adrs").

1.2.7 Role of Pharmacovigilance
PV itself is such a vast field that it covers all the effective areas covering patient safety. PV has a vital role in drug regulation, in clinical research, in post marketing studies, and in international health.

1.2.7.1 Pharmacovigilance - in Drug Regulation
The issues with which drug regulatory authorities have to contend besides the approval of new medicines include:

- Clinical trials
- Safety of complementary and traditional medicines, vaccines and biological medicines
- Developing lines of communication between all parties with an interest in drug safety and ensuring that they are open and able to function efficiently, particularly at times of crisis.

Regulators understand that PV plays a specialized and pivotal role in ensuring ongoing safety of medicinal products. PV programs need to be adequately supported to achieve their objectives. A new medicine must pass three hurdles before its approval by the national drug regulatory authority. Sufficient evidence is required to show the new drug to be, of good quality, effective, and, safe for the purpose or purposes for which it is proposed.

Whereas the first two criteria must be met before any consideration can be given to approval, the issue of safety is less certain. Safety is not absolute, and it can be judged only in relation to efficacy, requiring judgment on the part of the regulators in deciding on acceptable limits of safety. There is a possibility that rare yet serious adverse events will not be detected in the pre-registration development of the drug. For example, fatal blood dyscrasia occurring in 1 in 5,000 patients treated with a new drug is only likely to be recognized after 15,000 patients have been treated and observed, provided that the background incidence of such a reaction is zero or a causal association with the drug is clear. (This arbitrary ‘rule of three’ is based on the experience that for any given adverse effect approximately threefold the number of patients need to be
treated and observed for the side effect to become manifest and reliably linked with the drug assuming a background incidence of zero of the effect being observed.)

For drug regulators, the changing trends over recent years in the conduct of clinical trials present special and urgent challenges, particularly in ensuring that the rights and health of patients and their communities are protected. Safety monitoring during clinical trials is now recognized as one of the major concerns for new drug development, which is currently being addressed by a Council for International Organizations of Medical Sciences (CIOMS) working group. The CIOMS is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949 (Yao et al. 94-106).

Three main topics that are being addressed are: a) the collection of adverse experience information; b) the assessment and monitoring of clinical data; and c) the reporting or communication of clinical data.

Once research into new drugs is in the post-marketing stage (Phase IV studies), safety may be monitored to comply with the conditions of registration, particularly when there are unresolved concerns. This may lead to improved and more rapid changes in labeling or even withdrawal of a new drug from the market (Sasich, Lurie and Wolfe). Routine application of principles of good clinical practice that ensure patient safety and strict compliance with prescribed regulatory requirements would substantially improve standards of clinical trials (Lancet 1123).

### 1.2.7.2 Pharmacovigilance – in Post-Marketing Surveillance

It is now generally accepted that part of the process of evaluating drug safety needs to happen in the post-marketing phase, if important innovations are not to be lost in an unduly restrictive regulatory net. In a developing country, these latter considerations are likely to be more important than the benefits a novel therapeutic entity might bring to an already pressed health service. While spontaneous reporting remains a cornerstone of PV 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 a comparator (Meyboom et al. 429-47).
More systematic and robust epidemiological methods that take into account the limitations of spontaneous reporting are required to address these important safety questions. They need to be incorporated into post-marketing surveillance programs. There are other aspects of drug safety that have been rather neglected until now, which should be included in monitoring latent and long-term effects of medicines. These include:

- Detection of drug interactions
- Measuring the environmental burden of medicines used in large populations
- Assessing the contribution of ‘inactive’ ingredients (excipients) to the safety profile
- Systems for comparing safety profiles of similar medicines
- Surveillance of the adverse effects on human health of drug residues in animals, e.g. antibiotics and hormones.

A more difficult question is whether PV has resulted in inappropriate removal from the market of potentially useful medicines as a result of misplaced fears or false signals. The CIOMS report on benefit-risk assessment of medicines after marketing has contributed to a more systematic approach to determining the merit of available medicines. Systematic medical and prescription record linkage, with drug utilization studies, would contribute to greater accuracy. This is a responsibility that falls outside the strict traditional terms of reference of national PV centers (CIOMS "Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals").

1.2.7.2 Pharmacovigilance - in Clinical Practice

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 PV, and practice according to them, has a large impact on health care quality. Education and training of health professionals in drug safety, exchange of information between national centers, the co-ordination of such exchange, and linking clinical experience of drug safety with research and health policy, all serve to enhance effective patient care. National programs for PV are perfectly placed for identifying research necessary for better understanding and treatment of drug-induced diseases. Drug safety monitoring is an essential element for the effective use of medicines and for high quality medical care. PV is a clinical discipline in its own right – one that contributes to an ethos of safety and serves as an indicator of the standards of clinical care practiced within a country. Healthcare practitioners are in a position to make good use of their patients’ positive and negative experiences of treatment to contribute to medical science and to an improved understanding of disease and of the medicines (Meyboom et al. 374-89).
The significance of PV in clinical practice has been such impactful & eye-catchy that, so many drugs have been recently withdrawn from the market. Eg: Rofecoxib. Table 1 enlists drugs which have been forced for recall from the market.

This directed the foundation of an effective PV system in India also. The Indian perspective of PV is discussed below.

![Figure 1.1: National pharmacovigilance program](image)

CDSCO: Central Drugs Standard Control Organization, New Delhi

UMC: Uppsala Monitoring Center in Sweden

### 1.2.8 Pharmacovigilance: Indian Perspective

The PV in India is in need of an hour because, of increasing trend of outsourced clinical trials and new researches going on in clinical field. In India, PV system is still in its dormant stage but it is not a newly coined term. The initiation took place in 1986 when a formal ADR monitoring system consisting of 12 regional centers, each covering a population of 50 million, was proposed for India (Kulkarni 110-13). However, under the name of development, nothing much took place until in 1997 when India joined the World Health Organization (WHO) Adverse Drug Reaction Monitoring Program based in Uppsala, Sweden. Three centers for ADR monitoring were identified, mainly based in teaching hospitals as follows:

1. National Pharmacovigilance Centre located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi,
2. KEM Hospital and,

3. JLN Hospital, Aligarh Muslim University, Aligarh.

All these centers were to report ADRs to the drug regulatory authority of India and to monitor ADRs related with medicines marketed in India. Practically speaking, they hardly functioned as information about the need to report ADRs and the functions of these monitoring centers 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 Programme (NPP) for India was made operational (CDSCO). The NPP had three broad objectives as follows:

1. Short-term objective was to foster a reporting culture,
2. Intermediate objective was to involve a large number of healthcare professionals in the systems in information dissemination and,
3. The long-term objective is for the program to be a benchmark for global drug monitoring.

The NPP functions in the upward direction as shown in the Figure 1. The purpose of the program is to collate data, analyze it and use the inferences to recommend informed regulatory interventions, besides communicating risks to healthcare professionals and the public.

1.2.8.1 Effective factors of Pharmacovigilance for Indian Regulatory System

The success of any pharmacovigilance system including an Indian system depends upon the following factors:

- Public awareness on need to report suspected ADRs.
- Government support and well-defined policies with proper financial assistance.
- Presence of national coordinator and an advisory committee.
- Trained healthcare workers.
- Quality control of laboratories.
- Free and open communication between public and the policy makers.
- Ability to have free flow of information, i.e. inquiries, feedback, etc.
Having considered the problems and challenges facing the development of a robust pharmacovigilance system for India, we would like to make the following proposals (Biswas, P and Biswas, A. K., 1540–47).

1. Building and maintaining a robust pharmacovigilance system
The DCGI should invite experienced private firms to help, train and set up the pharmacovigilance system to combat the problems of inexperience and shortage of trained personnel.

2. Making pharmacovigilance reporting mandatory and introducing pharmacovigilance inspections
The Government of India's Health Ministry will need to pass a law and make pharmacovigilance reporting mandatory. This should be valid not only for the MNCs operating within India but also for the Indian pharmaceutical companies. A department for Pharmacovigilance Inspections should be incorporated within the DCGI with the view of starting inspections in all pharmaceutical companies operating in India. All pharmaceutical companies should be instructed to maintain and submit to the DCGI the Summary of Pharmacovigilance System document operating within the company, which would serve as the base for future pharmacovigilance inspections.

3. High-level discussions with various stakeholders
A high-level discussion with various stakeholders, i.e., Ministry of Health and Family Welfare (MHW), Indian Council of Medical Research (ICMR), Medical Council of India (MCI), Pharmacy Council, Nursing Council, Dental Council, Pharmaceutical Companies, Consumer Associations, Nongovernmental Organizations (NGOs) and Patient Groups should be initiated in order to make them aware of how the DCGI is planning to improve and develop a robust system in pharmacovigilance.

4. Strengthen the DCGI office with trained scientific and medical assessors for Pharmacovigilance
Intensive training should be given in all aspects of pharmacovigilance to officials working within the pharmacovigilance department of the DCGI and in the peripheral, regional and zonal centers. This should be an ongoing activity with training scheduled twice a year.
5. Creating a single countrywide specific adverse event reporting form to be used by all
A single countrywide specific adverse event reporting form needs to be designed, which should not only be used by the National Pharmacovigilance Centers, but also by all registered hospitals (both private and government), teaching hospitals, Drug Information Centers and pharmacies throughout the country. It should also be made available to all primary healthcare centers (PHCs) in rural areas and all practicing general practitioners and physicians.

6. Creating a clinical trial and post-marketing database for SAEs/SUSARs and ADRs for signal detection and access to all relevant data from various stakeholders
Full complete data should be made available to the DCGI and to the various stakeholders from the date of first registration of the clinical trial in the India. This data should comply with consolidated standards of reporting trials (CONSORT) guidelines including overall benefit-risk profile of the product.
Current standards of safety reporting as outlined in Schedule Y and information about all AEs and ADRs per study arm should be systematically included as well as detailed description of cases with previously unknown AEs/ADRs and the reasons for study withdrawals.
For drugs already in the market, type and frequency of all adverse events (serious and non-serious) should be submitted in periodic safety update reports (PSURs) and also added to the summary of product characteristics (SPCs).

7. List all new drugs/indications by maintaining a standard database for every pharmaceutical company
A list should be maintained by the regulatory authorities and pharmaceutical companies for all new drugs/indications in the database. All new issues need to be put under heightened surveillance. Pharmaceutical companies in these circumstances should have meetings set up with the DCGI to outline their risk management plan (RMP) for the safety issues in question and describe how they would put effective strategies in place to mitigate them.

8. Education and training of medical students, pharmacists and nurses in the area of pharmacovigilance
There are several courses conducted by various organizations focusing in clinical research, but to date there is no course relevant to pharmacovigilance in the country. The various stakeholders including the MCI should incorporate a pharmacovigilance syllabus within the pharmacology and medicine curricula so that proper theoretical and practical training can be imparted to
physicians. Similarly, nurses and pharmacists should also be trained in pharmacovigilance so that they are able to recognize ADRs and develop a culture of reporting ADRs in the future.

9. Collaborating with pharmacovigilance organizations in enhancing drug safety
With advancements in information technology (IT), there has been the emergence of new opportunities for national and international collaborations that can enhance post-marketing surveillance programs and increase drug safety. The Uppsala Monitoring Center (UMC) is an example of an international collaboration to establish a harmonized post-marketing surveillance database. The system is based on the exchange of adverse reaction information among national drug monitoring centers in 80 countries. The information is transferred, stored and retrieved in a timely and secure way through the internet. The UMC database collectively contains over four million records with a large number of data fields. A similar database can be built for the DCGI with the help of experienced private firms from the safety data received from clinical trials and post-marketing surveillance.

10. Building a network of pharmacovigilance and pharmacopeidemiologists in India
A core group of experts will need to be formed which will have representatives from MNCs, Indian pharmaceutical companies and personnel from the regulatory authority (DCGI).

11. Interaction with the IT sector in building a robust pharmacovigilance system for India
Software programs developed can be used for collection and analyses of data sets, determining trends of drug usage in various disease areas, compliance, medication errors and drug interactions leading to ADRs.

1.2.8.2 National Pharmacovigilance Advisory Committee (NPAC)
The NPAC consists of 16 members committee appointed by Government. Of India and oversees the functioning of NPP. The NPAC also takes the pain to assess PV data collected from different Zonal, Regional and Peripheral centers of India and also forwards this data to the WHO database at UMC in Sweden (Adithan 347). The CDSCO is initiating a country-wide Pharmacovigilance program under the aegis of DGHS, Ministry of Health & Family Welfare, and the Government of India. The program shall be coordinated by the National Pharmacovigilance Centre at CDSCO. The National Centre will operate under the supervision of the NPAC to recommend procedures and guidelines for regulatory interventions.
1.2.8.3 The National Pharmacovigilance Centre (NPC) at Central Drug Standard Control Organization (CDSCO)

1. NPC monitors the adverse drug reactions of medicines in order to identify previously unexpected adverse drug reactions or indicate that certain reactions occur more commonly than previously believed. These reports are also submitted to the WHO International Drug Monitoring Programme for international collaboration on drug safety.

2. Reviews Periodic Safety Update Reports (PSURs) submitted by pharmaceutical companies. PSURs are submitted every 6 monthly for the first 2 years of marketing in India, and annually for the subsequent 2 yrs.

3. Maintains contacts with international regulatory bodies working in PV and exchanges information on drug safety.

4. Assess the regulatory information relating to safety in order to determine what action, if necessary, needs to be taken to improve safe use. The Advisory Committee makes recommendations on product label amendments, product withdrawals and suspension.

5. Provides information to end-users through adverse drug reaction news bulletins, drug alerts and seminars.

*Figure 1.2: Role of national pharmacovigilance center

*ADR: Adverse Drug Reactions, PSUR: Periodic Safety Update Reports, PV: Pharmacovigilance

The NPAC and CDSCO play an important role in the smooth functioning of NPP. The Figure 2 explains the activities and responsibilities of individual centers like PPC (Peripheral Pharmacovigilance Centre), RPC (Regional Pharmacovigilance Centre) and ZPC (Zonal Pharmacovigilance Centre) which come under NPP. The strict regulations are necessary to overview the proper functioning of each individual PV center. The exchange of information is
necessary between NPC and UMC for effectiveness of the PV program and betterment of safety concerns.

Table 1.3: Responsibilities at different levels of PV program (Adithan 347)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Responsibilities</th>
<th>PPC</th>
<th>RPC</th>
<th>ZPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>To collect ADE notifications</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>2</td>
<td>To receive blank ADE forms and acknowledge receipt</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>3</td>
<td>To fill or get filled the ADE forms (fill all mandatory data)</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>4</td>
<td>To forward duly-filled ADE forms to next higher level centre</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>5</td>
<td>To maintain a log of all ADE notification forms received and forwarded</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>6</td>
<td>To identify, induce PPC / RPC (with concurrence of NPC), provide them with general technical support, coordinate and monitor their functioning</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>7</td>
<td>To identify and deploy a pharmacologist for management of PV tasks</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>8</td>
<td>To identify and deploy a data manager for data management under NPP</td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>9</td>
<td>To carry out (or review) causality analysis of all ADE forms or review such analysis by the RPC</td>
<td>Optional</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>10</td>
<td>To forward all duly-filled ADE forms (those generated at the same centre and those received from immediate lower-level centre) as per pre-determined time line</td>
<td>* Weekly (Monday)</td>
<td>* Every 15 days (alternate Monday)</td>
<td>* Only archiving</td>
</tr>
<tr>
<td>11</td>
<td>To report all serious adverse events within two week days, subsequent to receipt of its notification at the centre</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>12</td>
<td>To forward periodic report to next higher centre</td>
<td>Every 15 days (1st &amp; 15th of every month)</td>
<td>Monthly (1st of every month)</td>
<td>Monthly (1st of every month)</td>
</tr>
<tr>
<td>13</td>
<td>To liaison with health care professionals in order to inculcate / foster the culture of ADE notification / reporting</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>14</td>
<td>To organize and attend training programs / interactive meetings for all lower level centers</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

*Information of all serious ADE’s must be conveyed to the NPC within 2 working days by fax, email, telephone, courier as per stipulated guideline.
1.2.8.4 **Future Prospective of National Pharmacovigilance Program**

A periodic newsletter shall be published, may be quarterly, by the NPC, with the inputs and support from ZPCs. The publication may be printed or in an electronic format, and shall be widely circulated in the participating centers among doctors, nurses and pharmacists.

Professional bodies and non-government organizations [NGOs] shall be approached for collaboration. Other promotional strategies that may be considered include:

- Posters
- Annual celebration of Pharmacovigilance Day
- Leaflets for patients / doctors
- Integrating PV learning sessions into undergraduate curriculum
- Interface with Indian Medical Association, Indian Pharmaceutical Association and other professional societies
- Email /referral system
- Cross links on the websites
- PV-related articles in the newspapers/health journals

A dedicated PV web site may be created by the NPC. While a dedicated web site is under preparation, a PV link may be provided from the CDSCO web site. The AE reporting form shall be available on the web site for health care professional to down load or completion through a web based database.
1.2.8.5 Alternative Systems of Medicines Available in India

Since ancient times, it has been in the roots and culture of India that, more than one medicinal therapy system like Ayurvedic, Siddha, Unani, and Homeopathic systems were followed. It is very essential that a systematic, organized PV approach should be established.

The Unani system, also known as the Greco-Arab system of medicine, covers roughly a millennium, from around 500 BC to around 500 AD. The Greek God Apollo was the inventor of healing, “who chased away all ills” (Apollo). The physicians after noticing any unknown side effects (Muzarrat) used to note it down in their notebook (Bayaz) but still there was lack of ADR monitoring system (Rahman, Khan and Latif S17-S20).

The diagnosis and treatment in Unani medicine depends a lot upon examination of Temperament (Mijaz) and Pulse rate (Moain-e Nabdh) (Rahman 53-61). Thus, after determining a temperament of substitutes of a drug and, its usefulness in the disease condition of the patient is taken into consideration. This pattern may cause lesser side effects. The Jadwar (Delphinium Denudetam Wall) as a whole may exhibit a one temperament. But, it contains different forms of alkaloids and, the temperament of its active ingredient like (Delphinine and Methyllycaconitine) may not be the same. Thus, inactive ingredients may sometime change the temperament of body and may cause ADR (Singhal, Rahman and Adiva 22-24).

The ayurvedic medicine system was established in India since ancient time. The ”Charak Samhita” and ”Sushru Samhita” are available in Sanskrit stanzas and a lot about Ayurveda was also mentioned in four ”Vedas” of Indian culture (Dahanukar and Thatte Ayurveda Revisited ; Dahanukar and Thatte Ayurveda Unraveled). The consumption of Ayurvedic medicines is very popular in India now a days a current survey made in USA clearly indicates that 7,51,000 people have ever used ayurveda and 1,54,000 have used in the past 12 months (NCCIH). Associated with this increase use there is a growing safety concerns about ayurvedic medicines (Gogtay et al. 1005-19).

There are several examples plotted here under which indicate the need of PV in India for herbal medicines. The St. John’s wort, is widely prescribed for various psychopathologic conditions involving depression and anxiety is reported to lower serum concentrations of cyclosporine (Fugh-Berman and Ernst 587-95), theophylline (Nebel et al. 33:502), Warfarin (Yue, Bergquist
and Gerdén 576-77; Hall et al. 525-35), oral contraceptives (Cheng 2546-46), digoxin (Johne et al. 338-45), indinavir (Scott and Elmer 339-47), and clopidogrel (Piscitelli et al. 547-48) by inducing CYP 450 (CYP 3A4, CYP 2C9, & CYP 1a2) (Fugh-Berman and Ernst 587-95; Lau et al. 382A-83A; Tatro; Roby et al. 451-57; Kerb et al. A186). Caution is warranted when using St. John’s wort with several medications like barbiturates, carbamazepine, dextromethorphan, fenfluramine, phenytoin, photosensitizing drugs reserpine and simvastatin during pregnancy and lactation for the risk of potential interactions (Cozza, Armstrong and Oesterheld).

Gingko biloba, the second most common herb involved in drug interactions are reported to have potent drug interactions with Fluoxetine, buspirone, insulin, Mono amino oxidase inhibitor and with drugs metabolized by Cytochrome P4503A4, P4503A5, P450 1A2 and P4502D6 enzymes. Hence, Gingko biloba should be used with caution during pregnancy and lactation (Dugoua et al. e277-e84). It is also reported to inhibit platelet aggregation activity resulting in spontaneous bleeding when used simultaneously with aspirin (Dugoua et al. e277-e84), acetamenophan (Rosenblatt and Mindel 1108-08), trazodone (Rowin and Lewis 1775-76), ibuprofen (Galluzzi et al. 679-80; Meisel, Johne and Roots 367), and warfarin (Matthews 1933-33; Biloba 1239-44; Almeida and Grimsley 940-41; Callaway and Grob 367-69).

Kavakava is having additive effects with CNS depressants and caution is advised with regards to use with benzodiazepines, barbiturates, alcohols, and antipsychotics (Dugoua et al. e277-e84). Patient with Parkinson’s disease are also discouraged from using kava products. Warfarin was found to interact with at least 19 types of different herbs with a total of 34 cases of interaction adding to the list of 18 interactions previously reported.

Some herbs involved in interactions with various drugs and cause drug-drug interaction. These interactions may result in possible adverse reactions to cause harm to the individuals life which was rarely been focused earlier.
### Table 1.4: List of herbs involved in drug-drug interaction

<table>
<thead>
<tr>
<th>Herb</th>
<th>Interaction with</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayahuasca</td>
<td>Fluoxetine</td>
<td>(Callaway and Grob 367-69)</td>
</tr>
<tr>
<td>Alfaalfa</td>
<td>Immunosuppressants</td>
<td>(Light and Light 1608-09)</td>
</tr>
<tr>
<td>Celery</td>
<td>Thyroxin</td>
<td>(Brisbane 6-7)</td>
</tr>
<tr>
<td>Chemomile</td>
<td>Enalapril</td>
<td>(Segal and Pilote 1281-82)</td>
</tr>
<tr>
<td>Fennel</td>
<td>Enalapril</td>
<td>(Dicpinigaitis 169S-73S)</td>
</tr>
<tr>
<td>Garlic</td>
<td>Saquinavir</td>
<td>(Piscitelli et al. 234-38)</td>
</tr>
<tr>
<td>Ginger</td>
<td>NSAID's</td>
<td>(Srivastava and Mustafa 25-28)</td>
</tr>
<tr>
<td>Licorice</td>
<td>Laxative</td>
<td>(Brinker ; Ishiguchi et al. 59-62)</td>
</tr>
<tr>
<td>Prickly pear</td>
<td>Oral hypoglycemic</td>
<td>(Meckes-Lozyoa and Roman-Ramos 116-18)</td>
</tr>
<tr>
<td>Shankhpushpi</td>
<td>Phenytoin</td>
<td>(Dandekar et al. 285-88)</td>
</tr>
<tr>
<td>Soya bean</td>
<td>Warfarin</td>
<td>(Cambria-Kiely 1893-96)</td>
</tr>
</tbody>
</table>

**NSAID**: Non-Steroidal Anti-Inflammatory Drugs

These above mentioned cases urges regulatory authorities to establish a new approach of PV to deal with Ayurvedic, Unani, and Homeopathic medicine systems available in India. With this thesis, a new idea is generated about therapeutic class specific signal detection of any drug. With the help of this method we can predict whether that targeted AE is associated with all drugs commonly which fall within same therapeutic class or it is prominent with specific to one drug.

The aim of this thesis is to improve the safest use of medication and to educate the health professionals about this newer concept of Therapeutic class specific signal detection.

### 1.3 Signal Detection

Key component of, and main reason for Pharmacovigilance is the act of looking for and/or identifying new adverse events (AEs) or signals i.e. Signal detection.

#### 1.3.1 Signal

According to the World Health Organization (WHO), a safety signal is defined as, “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously” (WHO "Safety of
A more recent definition was given by the Council for International Organizations of Medical Sciences (CIOMS): “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, that is judged to be of sufficient likelihood to justify verificatory action (CIOMS "Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals").

Signal detection (SD) is a very important tool of PV system. Safety signal detection plays a crucial role in monitoring and maintaining a drug safety profile – the rapid identification of potential unwanted side effects to protect patient safety is a key component in the current clinical safety and pharmacovigilance.

This is a statistical tool to prioritise possible signals and decide the next step that should be taken. This takes into consideration the strength of evidence as well as the seriousness of the ADR.

Here, the terminology that is used, addresses the inclusion of other sources of information besides ADR reporting, reinforces the notion that a possible safety risk is only suggested, and takes into account the needed verification of the potential association between drug exposure and clinical event. Both definitions interpret the term “signal” as a “signal of disproportionate reporting” as proposed by Hauben and Reich, not a signal or “alert” as known from a clinical context, where an underlying causality is strongly suspected and has undergone clinical review (Hauben et al. 967-70).

1.3.2 Signal Detection Process

The process of signal detection ideally begins at the product’s introduction to the market. Nevertheless, in practice, it is carried out at various stages of a product’s life cycle, such as when a safety concern is already suspected, or when monitoring for very serious safety risks of special interest.
The process of signal detection comprises several phases. The basis and one of the most crucial parts is the collection and preparation of the data to be analyzed. Different types of data with a variety of available information can be used, ranging from spontaneous reports of ADRs to detailed information from Electronic Medical Records (EMRs) (Suling and Pigeot 607-40). Based on these data, signal detection analyses are conducted. We can coarsely distinguish between two different strategies to detect safety hazards:

1. Data-mining techniques that strive to uncover so far unknown and unsuspected associations. These methods are usually applied to a broad range of combinations of drug exposures and subsequent adverse events, often without limiting the search to pre-defined drug classes or specific medical conditions. They can be regarded as a broad search over the whole spectrum of drug-event combinations (DECs) in the underlying dataset.

2. If the data-mining search has indicated a possible health risk with a certain DEC, it may be advised to closely monitor this DEC over time to decide whether it should be considered further in confirmatory studies. Surveillance techniques have been developed to consolidate knowledge on these already suspected DECs and are often applied after the first data-mining step.

After the detection of potential signals in the data-mining process, they have to be adjudicated thoroughly to identify all DECs that
(a) are already known and well documented;
(b) occur very seldom or
(c) are highly implausible from a medical perspective and thus can be regarded as artificial false-positive signals.

This triage process is crucial in the entire signal detection process as, on one hand, it can drastically reduce the workload in the following steps, but on the other hand, it can also lead to the dismissal of correctly identified safety signals. Subsequently, each remaining potential signal has to be classified regarding its safety risk. This can either lead to immediate action like confirmatory studies that can result in halt of marketing or even withdrawal of the drug, or given a non-negligible but not critical risk—the decision to closely monitor the DEC via surveillance analysis techniques, or to discard the potential signal as non-hazardous.
There are two main methods for identifying safety issues: Qualitative Methods whereby experts manually review individual case reports, and Quantitative Methods or data mining involving the use of computerised algorithms to discover hidden patterns of associations or unexpected occurrences (i.e. ‘signals’) in large databases (Suling and Pigeot 607-40).

1.3.3 Data Mining
Actual data analysis does not only limit with knowledge discovery process but also includes: data collection, cleaning and preparation; reduction and projection; data analysis and interpretation, and finally dissemination, incorporating into existing structure and action based on discovered knowledge.

The main objective of ADR signal detection is to generate, strengthen and refine hypothesis related to suspected drug toxicity. Hypothesis testing is not possible on account of the inherently non-systematic nature of data collection and the lack of proper comparison groups. In-depth clinical evaluation and scrutiny of reports remain at the core of the ADR signal detection process. However, the WHO database receives thousands of reports every month and this massive inflow of reports require efficient computational methods to help clinical experts focus on the groups of reports most likely to represent important public health or patient safety issues (Poluzzi et al.).

1.3.4 Signal Detection through Drug-ADR Association
The signal detection process in routine use on the WHO database consists of a combination of automated knowledge discovery methods, triage algorithms and clinical review. The knowledge discovery methods highlight drug – ADR pairs with unexpectedly large numbers of reports relative to the average reporting rates in the database. A triage algorithm uses a combination of quantitative and qualitative information to focus attention on the most urgent issues for follow-up. Reports related to drug–ADR pairs singled out by the triage algorithm are forwarded to a panel of international experts for clinical review. In the context of the clinical review, pattern discovery methods may often be useful to profile larger groups of reports and suggest alternative explanations to observed excessive reporting rates. Hypothesis of suspected ADRs first highlighted in automated knowledge discovery that remain after clinical review are routinely communicated to the drug safety community, and some have been published in the mainstream medical literature. However, the risk of distortion from undiscovered data quality
problems and the difficulty of obtaining complete, detailed information on reported ADR incidents mean that signals of suspected ADRs (Poluzzi et al.).

**Figure 1.3:** Schematic overview of the signal detection process

(DEC = drug-event-combination, PRR = proportional reporting rate, ROR = reporting odds ratio, MGPS = Multi-item Gamma-Poisson Shrinker, BCPNN = Bayesian confidence propagation neural network, LD = longitudinal data, ICTPD = information component temporal pattern discovery, SPRT = sequential probability ratio test, SCCS = self-controlled case series)

### 1.3.5 Disproportionality

Disproportionality is not an inferential exercise. The frequency or relative frequency of a particular drug-event pair is of direct interest in a database. ‘Signals of Disproportionate Reporting’ are specific measure to implement the disproportionality of reporting drug-event pair.
1.3.6 Quantitative and Statistical Methods for Signal Detection
Various quantitative & statistical methods are implemented for signal detection process by going through a systematic literature review.

1.3.6.1 The Proportional Reporting Ratio (PRR)
The assumption is made in this method about a particular medicinal product X and its disproportional frequency or relative frequency of Y associated with it and with other medicinal products. The relative increase in adverse event Y associated with medicinal product X is reflected in 2X2 contingency table based on the total number of ICSR’s collected from a suitable database as follows-

Table 1.5: 2X2 Contingency table for the computation of PRR

<table>
<thead>
<tr>
<th>Targeted Drug X</th>
<th>All other events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted Event Y</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>All other drugs</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Total</td>
<td>A+C</td>
<td>B+D</td>
</tr>
</tbody>
</table>

Where,
A= Targeted adverse event Y caused by particular drug X
B= All other adverse events caused by drug X except Y
C= Targeted adverse event Y caused by all other drugs except X in database
D= All other adverse events caused by all other drugs except drug X in database

General criteria to calculate the PRR were as follows-
- The value A indicates the number of individual cases with the suspected medicinal product X involving an adverse event E.
- The value B indicates the number of individual cases related to the suspected medicinal product X involving any other adverse events but not A.
- The value C indicates the number of individual cases involving adverse event A in relation to all other medicinal products but not X in the Class specific database.
- The value D indicates the number of individual cases involving all other adverse events but in relation to all other medicinal products other than X.
The PRR is computed as follows (Norén),

\[
P_{\text{RR}} = \frac{A}{(A + B)} \cdot \frac{C}{(C + D)}
\]

### 1.3.6.2 The Reporting Odds Ratio (ROR)

All the procedure followed to compute a signal by this ROR method is same as like PRR method. The contingency table which was prepared for PRR is followed in the same manner in case of ROR here.

The ROR is computed as follows (Norén),

\[
R_{\text{OR}} = \frac{A/B}{C/D}
\]

### 1.3.6.3 The Chi-Square (X²) Statistic

The Chi-square statistic tests the independence of categorical variables. Chi-square is used as an alternative measure of heterogeneity in the contingency table built with the medicinal product X and the adverse event Y (Norén).

### 1.3.6.4 Du Mouchel Method

The method is based on 2X2 contingency table values. The ratio of values of A and expected A are taken into consideration for calculation (Suling and Pigeot 607-40).

\[
P_{\text{RR}} = \frac{A}{(A + B)} \cdot \frac{C}{(A + C)} / N
\]

\[
E(a) = \frac{(A + B)(A + C)}{N}
\]

\[
P_{\text{RR}} = \frac{A}{E(a)}
\]

### 1.3.7 Bayesian Methods in Pharmacovigilance

#### 1.3.7.1 Spontaneous Report Databases

Pharmaceutical companies, health authorities and drug monitoring centre on the use of SRS databases for global drug safety screening. These databases comprise case reports of suspected adverse drug reactions and/or adverse events (i.e. any medical event coincident with drug therapy). The precise details of each SRS differ in terms of size and scope, statutory reporting mandates, surveillance selectivity or intensity, and organizational structure. Prominent SRSs include the Adverse Event Reporting System (AERs) of the United States Food and Drug
Introduction

Administration (FDA), the Yellow Card Scheme of the Medicines and Healthcare Products Regulatory Agency (MHRA), and the international pharmacovigilance program of the World Health Organization (the WHO Uppsala Monitoring Centre). The regulators created these systems to provide early warnings of possible safety problems that would be difficult to detect during clinical drug development because of the power limitations, constricted range of demographics, and exclusion of patients with extensive co-morbid illnesses and co-medications, and limited duration of follow-up, characteristic of clinical trials. At the outset, drug safety professionals review individual reports and can instigate extensive follow-up, especially for serious events. Since SRS databases only contain reports of adverse effects, they fail to provide a denominator, i.e., the number of individuals consuming a particular drug.

1.3.7.2 Disproportionality Methods

Disproportionality analysis methods for drug safety surveillance comprise the most widely used class of analytic methods for signal detection in SRSs. These methods include the Du Mouchel's Bayesian multi-item Gamma-Poisson shrinker (MGPS), the Bayesian confidence propagation neural network (BCPNN), proportional reporting ratios (PRR), and reporting odds ratios (ROR). The methods search SRS databases for potential signals, focusing on low-dimensional projections of the data, specifically 2-dimensional contingency tables.

The basic task of a disproportionality method then is to rank order these tables in order of “interestingness.” Different disproportionality methods focus on different statistical measures of association as their measure of interestingness. MGPS focuses on the “reporting ratio” (RR) (Suling and Pigeot 607-40).

Table 1.6: Common measures of association for 2X2 tables in SRS analysis

<table>
<thead>
<tr>
<th>Measure of Association</th>
<th>Probabilistic Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting Ratio (RR)</td>
<td>( \frac{Pr(\text{AE}</td>
</tr>
<tr>
<td>Proportional Reporting Ratio (PRR)</td>
<td>( \frac{Pr(\text{AE}</td>
</tr>
<tr>
<td>Reporting Odds Ratio (ROR)</td>
<td>( \frac{Pr(\text{AE}</td>
</tr>
<tr>
<td>Information Component (IC)</td>
<td>( \log_2 \frac{Pr(\text{AE}</td>
</tr>
</tbody>
</table>
1.3.7.3 Bayesian Logistic Regression

Disproportionality analyses typically stratify by age, sex, and year of report but otherwise provide no protection against confounding. One particular kind of confounding risk has come to be known as the “innocent bystander” effect in the drug safety literature. Regularized or Bayesian logistic regression addresses these concerns.

Concretely, the main interest is in conditional probability models of the form

\[ p(y_i = +1/\beta; x_i) = \psi(\beta^\top x_i) \]

where \( y_i \) represents the presence or absence of a particular adverse effect in the \( i \)th report, \( x_i \) is a binary vector of drug indicators, and \( \psi \) is the logistic link function.

Here experiment with two choices of prior distribution for the regression coefficient vector \( \beta \) is carried out. Perhaps the simplest Bayesian approach to the logistic regression model is to impose a univariate Gaussian prior with mean 0 and variance \( \Sigma > 0 \) on each parameter \( \beta_j \).

Finding the maximum a posteriori (MAP) estimate of \( \beta \) with this prior is equivalent to ridge regression for the logistic model (Santaner and Duffy; Le Cessie and Van Houwelingen 191-201). Alternatively, a sparseness inducing hierarchical prior distribution for \( \beta \) gives each \( \beta_j \) a Gaussian prior with mean 0 and variance \( \Sigma_j \) and then an exponential prior on the \( \Sigma_j \)'s:

\[ p(\Sigma_j / \gamma) = \gamma_j / 2 \exp(-\gamma_j / 2 \Sigma_j) \]

with \( \gamma > 0 \). Integrating out \( \Sigma_j \) then gives a (nonhierarchical) double exponential or Laplace prior distribution. MAP estimation in this context corresponds to the well-known lasso. Computing the full posterior distribution for \( \beta \) is computationally demanding and even efficiently calculating the posterior mode requires some care (Bate).

1.3.7.4 Longitudinal Observational Databases

Newer data sources have emerged that have overcome some of the limitations of SRSs but present methodological and logistical challenges of their own. Longitudinal observational databases (LODs) provide time-stamped patient-level medical information. Typical examples include medical claims databases and electronic health record systems. The scale of some of these databases presents interesting computational challenges.

1.3.7.5 Statistical Methods for Signal Detection in LODs

Methods currently under investigation fall into four broad categories-
**Introduction**

**Cohort Methods**

The epidemiology literature describes various cohort-based methods and associated matching algorithms. Such approaches have been widely used in drug safety although infrequently with databases on the scale of current LODs. Both cohorts and comparators can be defined in various ways and current research focuses on basic design questions.

**Case-Based Methods**

Case-control methods are also widely used in drug safety, although again, applying them to LOD-sized databases presents new challenges. Matching is the central challenge in designing case control studies and propensity-based methods have the potential to work on large-scale data. The self-controlled case series approach offers many advantages, and scaling up appears feasible. A key challenge to address in the drug safety context is confounding by time-varying covariates such as disease airs.

**Surveillance Approaches**

All of the above methods estimate an effect size relating a drug (or group of drugs) to a medical outcome. As such these can be used in a surveillance context - the effect size is recomputed as new data arrive and a surveillance algorithm triggers an alarm when certain temporal patterns emerge. Standard surveillance techniques include SPRT, CUSUM, and hidden Markov models.

**The Self-Controlled Case Series Method**

Farrington (1995) proposed the self-controlled case series (SCCS) method in order to estimate the relative incidence of adverse events to assess vaccine safety. The major features of SCCS are that; (1) it automatically controls for fixed individual baseline covariates, and (2) only cases (individuals with at least one event) need to be included in the analysis. With SCCS, each individual serves as their own control.

SCCS is one of several self-controlled methods that the epidemiology literature describes, many of which are variants on the case-crossover method. However unlike the case-crossover method, which requires the choice of a comparator time period to serve as a control, SCCS makes use of all available temporal information without the need for selection.
Epidemiological applications of SCCS tend to focus on situations with small sample sizes and few exposure variables of interest. In contrast, the problem of drug safety surveillance in LODs must contend with millions of individuals and millions of potential drug exposures. The size of the problem presents a major computational challenge ensuring the availability of an efficient optimization procedure is essential for a feasible implementation.

1.3.7.6 Extensions to the Bayesian Self-Controlled Case Series Method (SCCS Model)

Hierarchical Model: Drugs
Drugs form drug classes. For example, Vioxx is a Cox-2 inhibitor. Cox-2 inhibitors in turn are non-steroidal anti-inflammatory. A natural extension assumes regression coefficients for drugs from within a single class arise exchangeably from a common prior distribution. This hierarchy could extend to multiple levels.

Hierarchical Model: AEs
AEs also form AE classes. For example, an MI is a cardiovascular thrombotic (CVT) event, a class that includes, for example, ischemic stroke and unstable angina. In turn, CVT events belong to a broader class of cardiovascular events. This extension assumes that the regression coefficients for a particular drug but for different AEs within a class arise from a common prior distribution. Again this hierarchy could extend to multiple levels.

Relaxing the Independence Assumptions: Events
Farrington and Hocine (2010) explore one particular approach to allowing for event dependence although other approaches are possible.

Relaxing the Independence Assumptions: Exposures
As discussed above, the SCCS model assumes that events are conditionally independent of subsequent exposures. Farrington et al. (2009) present a relaxation of this assumption based on an estimating equations approach (Farrington, Whitaker and Hocine 3-16).

1.3.8 Discussion: Frequentist Methods versus Bayesian Methods

1.3.8.1 Frequentist
Frequentist inference is one of a number of possible techniques of formulating generally applicable schemes for making statistical inference: drawing conclusions from sample data by
the emphasis on the frequency or proportion of the data. An alternative name is Frequentist statistics. This is the inference framework in which the well-established methodologies of statistical hypothesis testing and confidence intervals are based.

Frequentist inference has been associated with the frequentist interpretation of probability, specifically that any given experiment can be considered as one of an infinite sequence of possible repetitions of the same experiment, each capable of producing statistically independent results. In this view, the frequentist inference approach to drawing conclusions from data is effectively to require that the correct conclusion should be drawn with a given (high) probability, among this notional set of repetitions. However, exactly the same procedures can be developed under a subtly different formulation. This is one where a pre-experiment point of view is taken. It can be argued that the design of an experiment should include, before undertaking the experiment, decisions about exactly what steps will be taken to reach a conclusion from the data yet to be obtained. These steps can be specified by the scientist so that there is a high probability of reaching a correct decision where, in this case, the probability relates to a yet to occur set of random events and hence does not rely on the frequency interpretation of probability. This formulation has been discussed by Neyman, among others (Neyman 333-80).

Similarly, Bayesian inference has often been thought of as almost equivalent to the Bayesian interpretation of probability and thus that the essential difference between frequentist inference and Bayesian inference is the same as the difference between the two interpretations of what a "probability" means. However, where appropriate, Bayesian inference is used by those employing a frequentist interpretation of probabilities. There are two major differences in the Frequentist and Bayesian approaches to inference that are not included in the above consideration of the interpretation of probability:

In a frequentist approach to inference, unknown parameters are often, but not always, treated as having fixed but unknown values that are not capable of being treated as random variates in any sense, and hence there is no way that probabilities can be associated with them.

In contrast, a Bayesian approach to inference does allow probabilities to be associated with unknown parameters, where these probabilities can sometimes have a frequency probability
interpretation as well as a Bayesian one. The Bayesian approach allows these probabilities to have an interpretation as representing the scientist's belief that given values of the parameter are true.

While "probabilities" are involved in both approaches to inference, the probabilities are associated with different types of things. The result of a Bayesian approach can be a probability distribution for what is known about the parameters given the results of the experiment or study. The result of a frequentist approach is either a "true or false" conclusion from a significance test or a conclusion in the form that a given sample-derived confidence interval covers the true value: either of these conclusions has a given probability of being correct, where this probability has either a frequency probability interpretation or a pre-experiment interpretation.

Poor choice of the complement set of drugs and ADRs will bias the results. These estimators heavily rely on the data and as a result the distributions of these estimators can be skewed highly. The calculation of the estimators at a specific cell is subject to the ‘complement’ set which may contain extremely large observations influencing their value. Small expected frequencies may tend to produce false positives (Type 1 error).

1.3.8.2 Bayesian

The distribution of the Relative Reporting Ratio will be pulled towards the chosen prior with a minimal data requirement. Over time, the updating of the parameters will cause the posterior to move towards the ‘true’ distribution.

In other words, in the short term, the results of signal detection algorithms will be dependent on the appropriateness of the prior distribution. Bayesian methods lower impact of random fluctuations of the relative reporting ratio (shrinkage). This may cause false negatives (Type 2 error).

Advantages to Bayesian Approach

In addition to explicitly stating how external information is used in defining the prior, Bayesian approaches provide a natural method of combining new data with this previous knowledge defined from external information. The Bayesian approach, in addition has no problem with repeated trials which can make calculation of appropriate confidence intervals more difficult.
from a frequentist perspective, as the concept of updating probability is a fundamental principle of Bayesian statistics. Ongoing monitoring for adverse drug reactions leads to a constant need to update posterior probabilities as data accumulates, for which the Bayesian approach is very suitable. In comparison to the interpretation of p values in classical statistical analysis, Bayesian precision estimates are easy to comprehend as the probability that a parameter lies within a certain set of values. The use of a prior distribution gives flexibility, as different prior assumptions can be made, and there is a formal method for incorporating external evidence into the analysis. Bayesian methods handle missing data intuitively. Estimations can be made despite zero counters, and in general less data results in more reliance on the prior and thus more uncertainty in the estimate.

**Limitations of Bayesian Approach**

While the concepts and philosophy of Bayesian statistical methods are simple, the mathematical formulae can be complex, and hard or impossible to solve exactly. However the advent of sampling methods such as Markov Chain Monte Carlo (MCMC) methods for empirically estimating the distributions of interest has facilitated implementation of Bayesian approaches, and consequently led to increased use of Bayesian approaches. Implementation can still be computationally demanding, but this varies from application to application and varies with the technique. Bayesian methods are often seen as ‘something different’, which can make the approaches harder to understand, and perhaps increase the chance of their inappropriate use.

**Applications of Bayesian Approach**

Other applications where Bayesian approaches are used are: in clinical trial analysis and causality assessment. Bayesian approaches can be used in supervised pattern recognition, classification tasks, and cluster analysis. Bayesian approaches are often used in neural networks. In clinical trials a sceptical prior is used to provide a handicap that trial data must overcome to provide convincing evidence of benefit. Thus in the light of positive results, the approach shows conservatism. Other applications include the testing of new drugs, astrophysics, and Bayesian inference has also been used in lawsuits and public policy decision making (Cambria-Kiely 1893-96).

**Benefits of Using Bayesian Statistics When Data Mining**

A Bayesian network is a high-level representation of a probability distribution over a set of variables that are used for building a model of the problem domain. The benefit of the Bayesian
network representation lies in the way such a structure can be used as a compact representation for many naturally occurring and complex problem domains.

a) External information based on for example the goals of the data mining project can be incorporated into the statistical model.

b) The use of a conservative prior allows a dampening at low counter values, stopping inappropriate fluctuations at low counter values and thus stopping unwanted spurious associations or patterns.

c) Flexibility of choice of prior, so an alternative attitude to external information can be taken.

d) Formal approach for looking at how results differ with different priors, including sensitivity testing of results.

e) Repeated testing is fundamental to the approach, rather than an additional issue to be considered in the analysis. Method can readily handle missing data, can make calculations when no data, and simply have more uncertainty (wider credibility intervals) around precision estimate.

g) Credibility intervals easier to interpret than conventional confidence intervals.

h) A probability distribution with the addition of data leads to a new probability distribution, thus emphasizing the immediacy of any conclusion, as magnitude and certainty of the change is obvious.

i) Tractable to calculate estimate of parameter even without data (this is the prior distribution), some classical estimates have problems before data is collected.

j) Other methods have an implicit Bayesian perspective Irwig wrote of meta-analysis: that it “should be an ongoing process: as each new trial result becomes available, it should be added to the meta-analysis available up to that time”. This applies to data mining or quantitative signal detection which should be an ongoing process as more data is added and our knowledge accumulates. In addition, fuzzy logic is in some ways similar to Bayesian statistics in that it formalizes concepts of uncertainty rather than seeing events as occurring or not occurring and has been implemented in several medical applications.

k) Bayesian approaches are often used for neural network learning (Bate).

At last, using Bayesian statistics one can evaluate patients' reactions to a drug beginning early in a clinical trial and modifies the trial in accord with those findings, these kind of trials are called Adaptive clinical trials. The adaptation process continues throughout the trial. Modifications may include dosage, sample size, drug undergoing trial, patient selection criteria
and "cocktail" mix. In some cases, trials have become an ongoing process that regularly adds and drops therapies and patient groups as more information is gained. The aim is to more quickly identify drugs that have a therapeutic effect and to zero in on patient populations for whom the drug is appropriate (Wang). A key modification is to adjust dosing levels. Traditionally, non-adverse patient reactions are not considered until a trial is completed (Huber).

In the 2007–2009 period, the Department of Biostatistics at the M. D. Anderson Cancer Center was running 89 Bayesian adaptive trials, According to FDA guidelines, an adaptive Bayesian clinical trial can involve:

- Interim looks to stop or to adjust patient accrual
- Interim looks to assess stopping the trial early either for success, futility or harm
- Reversing the hypothesis of non-inferiority to superiority or vice-versa
- Dropping arms or doses or adjusting doses
- Modification of the randomization rate to increase the probability that a patient is allocated to the most appropriate arm

An adaptive trial design enabled two experimental breast cancer drugs to deliver promising results after just six months of testing, far shorter usual. Researchers assessed the results while the trial was in process and found that cancer had been eradicated in more than half of one group of patients. The trial, known as I-Spy 2, tested 12 experimental drugs (Wang).

I-SPY 2 is an adaptive clinical trial of multiple Phase 2 treatment regimens combined with standard chemotherapy. I-SPY 2 linked 19 academic cancer centers, two community centers, the FDA, the NCI, pharmaceutical and biotech companies, patient advocates and philanthropic partners. The trial is sponsored by the Biomarker Consortium of the Foundation for the NIH (FNIH), and is co-managed by the FNIH and Quantum Leap Healthcare Collaborative. I-SPY 2 was designed to explore the hypothesis that different combinations of cancer therapies have varying degrees of success for different patients. Conventional clinical trials that evaluate post-surgical tumor response require a separate trial with long intervals and large populations to test each combination.
Instead, I-SPY 2 is organized as a continuous process. It efficiently evaluates multiple therapy regimes by relying on the predictors developed in I-SPY 1 that help quickly determine whether patients with a particular genetic signature will respond to a given treatment regime. The trial is adaptive in that the investigators learn as they go, and do not continue treatments that appear to be ineffective. All patients are categorized based on tissue and imaging markers collected early and iteratively (a patient's markers may change over time) throughout the trial, so that early insights can guide treatments for later patients. Treatments that show positive effects for a patient group can be ushered to confirmatory clinical trials, while those that do not can be rapidly sidelined. Importantly, confirmatory trials can serve as a pathway for FDA Accelerated Approval. I-SPY 2 can simultaneously evaluate candidates developed by multiple companies, escalating or eliminating drugs based on immediate results. Using a single standard arm for comparison for all candidates in the trial saves significant costs over individual Phase 3 trials. All data are shared across the industry (Wang).

Such experiences with Bayesian statistics are significant enough to conclude that systemic utilization of this method especially in anti-cancer drugs can safeguard the patients from side effects & enhance their chances of survival.