CHAPTER 2

Review of Literature
2.1 Signal

The prime objective of this thesis is to identify potential signals by using various signal detection methods. WHO defines a signal 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 Medicines - a Guide to Detecting and Reporting Adverse Drug Reactions - Why Health Professionals Need to Take Action"). Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and quality of the information.

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 (Norén).

2.1.1 Signal Detection

2.1.1.1 Need of Signal Detection

The main objective of ADR signal detection is to generate, strengthen and refine hypotheses 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, every month the WHO database receives massive inflow of thousands of reports. This requires efficient computational methods to help clinical experts focus on the groups of reports most likely to represent important public health or patient safety issues (Shibata and Hauben 1-7).
Recent drug withdrawals and cases of adverse drug effects on patients have reduced the confidence among people in using certain drugs. The only way to instill confidence in patients is to make the promise of safety and adherence to quality standards in available medicines. And signal detection in PV is one of the best ways to detect and prevent adverse events.

Drug safety is an issue because no one is fully aware of what side effects a drug may have. So it is important to detect an adverse event with the assistance of signal detections. The practice of PV allows detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. It is carried out by pharmaceutical companies on their products and by government agencies on all medicinal products.

Having detected the potential signals, a validation of whether or not they are signals related to ADRs is made since they are cases when signals occur due to a disease and not from a Drug. Following this, a review of the drug is made to consider its potential risks and benefits, on the basis of which its marketing authorization is revoked or suspended.

This method of detection assesses the merits of individual drugs as it bank upon a several AEs rather a single AE. This method also helps detect signals for subsequent adverse events by ensuring drug safety. Signal detection in PV and effective adverse event reporting system help to deal with and avoid adverse events (Wilson, Thabane and Holbrook 127-34).

2.1.2 The Process of Signal Detection

The process of signal detection comprises several phases (Figure 3). 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). Based on these data, signal detection analyses are conducted (Wilson, Thabane and Holbrook 127-34; Poluzzi et al.; Orre et al. 473-93; Bate et al.). 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. Which are usually applied to a broad range of combinations of drug exposures and subsequent AEs, 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) The possible health risk with a DEC indicated by data mining should be closely monitored for further confirmatory studies. After the first data-mining step the Surveillance techniques have been applied to consolidate knowledge on these suspected DECs.

**Figure 2.1:** 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).

### 2.1.3 Data Mining Process and PV

We will define data mining as the application of statistical techniques, e.g. predictive modelling, clustering, link analysis, deviation detection and disproportionality measures to databases.

### 2.1.3.1 Identification of Objectives/Goals

Although there is no detailed hypothesis in Knowledge Discovery Database (KDD), and one should keep an open mind when exploring for possible ADEs, it is important to have an aim, as KDD is costly in terms of data collection and management (Hand and Yu 385-98).
2.1.3.2 Selection of Variables

A clearly defined aim makes it easier to determine the type of variables and data mining technique to be used. For example, assessing drug-related birth defects would require a different data set than drug–drug interactions. However, in order to maximize the chance of detecting a signal, the most inclusive collection of relevant variables should be used. The World Health Organization (WHO) Adverse Reaction Terminology and Medical Dictionary for Regulatory Activities (MedDRA) are examples of datasets used for PV, but their list of variables is limited to those determined by prior assessments of causation. In terms of variable availability, electronic medical records hold potential in being the repository of the widest possible medical terminology. For example, new medical conditions, such as Severe Acute Respiratory Syndrome, will be used within electronic medical records before they are incorporated into adverse reaction terminology dictionaries (MacKay).

2.1.3.3 Selection of data sources/databases

As data collection is expensive, data mining processes are often performed on existing databases, for the purposes of PV. The necessary size of the dataset required is difficult to determine but will depend on the data quality, the background frequency of the event and the strength of the association of the event with the drug. However, for even moderately rare events, large databases are required.

2.1.4 Data Logs Used for Data Mining

2.1.4.1 Spontaneous Reporting Databases

In Post Marketing Surveillance (PMS) the spontaneous reporting of a possible ADR by healthcare providers to governmental agencies or drug companies (i.e. to the UK Yellow Card Scheme) is an important procedure. However, inconsistent reporting with more frequent reporting for unusual reactions, reactions for new drugs and serious reactions limits the importance of Spontaneous reporting (Matsuda 3096). Furthermore, the accuracy of the data contained within the reports is uncertain. However, spontaneous reporting databases do contain large amounts of data, for example the Food and Drug Administration (FDA) spontaneous reporting database contains over 2 million reports over a period of 35 years. These databases can therefore be mined to obtained details of ADEs. For example, a retrospective data mining of the FDA spontaneous reporting database was shown to identify ADEs many years prior to collecting reports alone (Heister and Froehlich 299-304).
2.1.4.2 Prescription Event Monitoring Databases

Prescription event monitoring (PEM) is used to detect ADEs by collecting high-quality data from family doctors, on a selected group of patients exposed to a specific (new) drug, for a limited period of time (Orre, Bate and Lindquist 215-20). The role of database exploration is to detect ADE signals from a PEM database, which contains 1 million reports of events from 78 PEM studies. They point out that a limitation of PEM database mining is the lack of an adequate control group, as the database contains details of clusters of patients exposed to certain drugs. For example, tolterodine did not show evidence of hallucinations as an ADE because the control group contained patients prescribed other drugs known to cause hallucinations. When the data from these patients were removed, an ADE signal for tolterodine was discovered (Barar 240-41).

2.1.4.3 Linked Administrative Databases

Large linked health administrative databases, such as Medicaid in the USA and the Ontario provincial databases contain data on millions of subjects and may also be used as a source for data mining. The data are available at relatively small additional costs and are not subject to recall or interviewer bias. However, the completeness of details, such as diagnoses, is questionable in many circumstances, and they tend to apply to elderly or low-income populations only, so may not be representative of the whole population.

The Saskatchewan-linked administrative healthcare utilization database and the Tayside Medicines Monitoring (MEMO) are examples of linked medical health databases & both have been utilized to identify risks of benzodiazepine therapy (MacKay ; Matsuda 3096; Heister and Froehlich 299-304).

2.1.4.4 Electronic Medical Records

Electronic medical records (EMRs) contain a large number of data fields, including details such as the use of tobacco products, smoking and nonprescription drugs, symptoms and signs, laboratory data and social circumstances, on a smaller number of patients and may also be used for data mining. Because of the large number and detail of the variables, which can be combined to generate new diagnoses of adverse events, hypotheses, which are not restricted to existing diagnoses, can be explored. Although Honigman et al have investigated the use of EMR in detecting known ADEs, there have been no studies of data mining using EMR.
2.1.4.5 Other Databases

Clinical trials databases and specialist databases such as overdose or toxicology databases may also contain valuable information. Data mining has been used to explore cardiovascular clinical trial databases, the US Vaccine Adverse Event Reporting System and a large prescription database. Signals for liver-related ADEs have been reported from analysis of a biochemistry laboratory database at a higher rate than that reported by physicians. Poison information centres also record details of ADEs and may contribute to the pharmacovigilance process.

2.1.5 Methods Used for Data Mining

2.1.5.1 Predictive Modeling

Predictive modeling is a technique used to develop a model to relate a dependent variable with a set of independent variables in a manner similar to multiple regression analysis. The predictive modeling, namely classified into; categorical dependent variables, and value prediction, for continuous dependent variables. Classification is appropriate if the goal is to predict group membership of new records based on their characteristics (independent variables). Using classification, the most influential variable is identified and used to split the data into groups. This is then repeated with the next most influential variable until the data are fully characterized. For example, it may be possible to determine a classification criterion or rule that discriminates between different groups of patients with and without side-effects based on age, sex or socio-economic class. Value prediction uses classification and regression to predict the future outcome of a patient based on, for example, their demographic or socio-economic characteristics. However, we need to use caution as, in any data analysis of continuous outcomes, the results of value prediction can be influenced by the presence of outliers in the data.

2.1.5.2 Clustering or Database Segmentation

Clustering uses an algorithm that segregates a database by evaluating the dissimilarity between records. Pairs of records are compared by the values of the individual fields within them, and clustering into groups provides fast and effective ordering in large datasets. Segmentation could be used to group patients with similar symptoms or diagnoses to determine whether there is a drug association. Thus, clustering is a technique of choice if the goal is to reduce a large sample of records to a smaller set of specific homogeneous subgroups (clusters) without losing much information about the whole sample. Because of the heterogeneity between clusters, this analysis can also be helpful in hypothesis development about the nature of the variation between
subgroups. For example, if a database contained details of different cardiac pathologies (e.g. valvular heart disease) and medication (e.g. fenfluramine-phentermine), clustering analysis may have segregated patients according to heart disease and identified fenfluramine-phentermine as one of the main factors in this group. We could then explore the hypothesis of an association or causal link between cardiac valvular disease and fenfluramine-phentermine (Connolly et al. 581-88; Surapaneni et al. 581).

2.1.5.3 Link Analysis

Link analysis refers to methods that identify associations or links between records or sets of data (Canada; Hutter 399-406; Bate et al. 99; Orre et al.). It assesses associations by using an ‘if $x$ then $y$’ type rule, by assessing patterns of behavior or by identifying similar time sequences of events. In pharmacovigilance, link analysis could be used to identify associated factors such as the effect of renal impairment on the safety profile of diuretics.

2.1.5.4 Deviation Detection

Deviation detection looks for outliers or values that deviate from the norm and can be seen either graphically or statistically. Visualization techniques are used to determine patterns hidden in data, e.g. scatter plots or histograms, multidimensional graphs for multivariate data, and time series plots. Statistical methods are then employed to measure significance of deviations once they have been detected. This process could be used to identify patients with idiosyncratic reactions or unusual symptoms, which could be related to medication and may constitute an ADE signal. Regression analysis and stratification can be used to assess the influence of age, sex and comorbidity on ADE signal generation.

2.1.5.5 Measures of Disproportionality - Data Mining Algorithms (DMA)

Signal detection can be performed by two methods:

1. Case-by-case basis (traditional approach)

2. Through automated procedures to support the clinical evaluation of spontaneous reports, also called “data mining approach”.

In general terms, data mining can be considered as the process of extracting information from a large database (Bate et al. S163). Thus, data mining is referred to as the computer-assisted procedures, starting from processing of dataset by data “cleaning” and culminating into the
application of statistical techniques, often known as Data Mining Algorithms (DMAs). DMAs are currently and routinely used by pharmacovigilance experts for quantitative signal detection. The purposes of quantitative signal detection are many-fold and may vary depending on the local habit of Pharmacovigilance experts.

For instance, DMAs can be used as-
- An aid to the traditional case-by-case assessment;
- Screening tool to periodically generate a list of signals requiring in depth investigation (i.e., to prioritize signals) to detect complex data dependencies, which are difficult to be manually detected (e.g., drug-drug interactions or drug-related syndromes) (Bate et al. S163).

2.1.5.6 Use of Data Mining Algorithms (DMAs)

Although DMAs are relatively new as compared to clinical trials and epidemiological studies, the first published attempt to assess the extent of reporting in drug safety through disproportionality, was made by Bruno Stricker. In 1997, the study by Moore et al, introduced the concept of “case/non-case method” when performing pharmacovigilance analyses. They postulated that this term was a more effective representation than case-control: controls are not actual controls since they are all exposed to at least one drug, and have at least one event (there are no untreated ‘healthy’ controls).

The accuracy of data mining techniques has been already tested retrospectively to determine if already known safety issues would have been detected ‘earlier’. However, it is generally difficult to determine when a known safety concern was first detected. Moreover, the surrogate endpoint that has been used (e.g., the date of implementation of new labeling) is unlikely to truly represent the time of first detection of a new safety signal, thus affecting the results in favor of DMAs. Overall, DMAs often provided a high level of accuracy in terms of timely prediction of risk and, therefore their use have been encouraged as an early source of information on drug safety, particularly new drugs, thus guiding the proper planning of subsequent observational studies (Poluzzi et al.).

Although the rationale and the methodology of the various approaches differ, all DMAs query databases for disproportionality and express the extent to which the reported ADR is associated with the suspected drug compared with all other drugs (or a subgroup of drugs) in the database.
The reporting of ADRs related to other drugs in the database is used as a proxy for the background occurrence of ADRs. In other words, they assess whether statistically significant differences in the reporting exist among drugs (the so-called “unexpectedness”) and provide an answer to the question: “does the number of observed cases exceed the number of expected cases”.

Though these approaches are known as “quantitative” signal detection methodologies, no risk quantification can be assessed. Moreover, the presence of a statistically significant result does not necessarily imply an actual causal relationship between the ADR and the drug, nor does the absence of a statistically significant result necessarily disprove the possible relationship. As a matter of fact, the term “signal of disproportionate reporting” has been suggested by Hauben & Aronson to emphasize the uncertainty in causality assessment.

![Data mining algorithms](image)

**Figure 2.2:** Data mining algorithms

### 2.1.6 Classification Data Mining Algorithms (DMA)

DMAs can be classified into two broad categories (Harpaz et al. 1010-21):

a. Frequentist approach (Classical Approach)

b. Bayesian approach
Among the former, the Reporting Odds Ratio (ROR) is applied by the Netherlands Pharmacovigilance Centre Lareb, whereas the Proportional Reporting Ratio (PRR) was first used by Evans et al. Frequentist or classical methods are particularly appealing and therefore widely used due to the fact that they are relatively easy to understand, interpret and compute as they are based on the same principles of calculation using the 2x2 table.

Bayesian methods such as Multi-item Gamma Poisson Shrinker (MGPS) and Bayesian Confidence Propagation Neural network (BCPN) are based on Bayes’ law to estimate the probability (posterior probability) that the suspected event occurs given the use of suspect drug.

2.1.6.1 Frequentist Methods

The Proportional Reporting Ratio (PRR)

The PRR is defined as the ratio between the frequency with which a specific adverse event occurs for the drug of interest (relative to all adverse events reported for the drug) and the frequency with which the same adverse event occurs for all drugs in the comparison group (relative to all adverse events for drugs in the comparison group).

The calculation 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 database as follows-

<table>
<thead>
<tr>
<th></th>
<th>Targeted Event Y</th>
<th>All other events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Targeted Drug X</strong></td>
<td>A</td>
<td>B</td>
<td>A+B</td>
</tr>
<tr>
<td><strong>All other drugs</strong></td>
<td>C</td>
<td>D</td>
<td>C+D</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>A+C</td>
<td>B+D</td>
<td>A+B+C+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
In this table the elements counted were ICSRs available in database. Thus, a given ICSR may contribute to only one of the cells of the table, even if the individual case refers to multiple medicinal products or multiple adverse events. The approach of performing the computations of the PRR on the individual case counts instead of number of ADRs has been chosen to keep the independence between the variable used to compute the PRR so that, the variance of the PRR will not be underestimated.

General criteria to calculate the PRR are 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)-

\[
PRR = \frac{A}{C} \div \frac{A + B}{C + D}
\]

For Example-
- Proportion of individual cases of nausea involving a medicinal product ‘Trade Name’ = 5% (e.g. 5 reports of nausea amongst a total of 100 reports reported with medicinal product ‘Trade Name’).
- Proportion of reports of nausea involving all the other medicinal products in a database (but medicinal product ‘Trade Name’) = 5% (e.g. 5000 reports of nausea amongst 100,000 reports reported with all other medicinal products). Therefore, the PRR is equal to 1 (0.05/0.05).
The 95% Confidence Interval of the PRR

The 95% confidence interval of the PRR is calculated on the basis of the standard deviation of the natural logarithm of the PRR using the following formula (EU-Guideline "Eudravigilance Expert Working Group (Ev-Ewg)")-

\[
s = \frac{1}{A+1/C} - \frac{1}{A+B} - \frac{1}{C+D}
\]

The 95% confidence interval for ln(PRR) is then estimated as ln(PRR)+1.96s and, taking the exponential, the following result is obtained-

95% confidence interval for PRR = (PRR / exp(1.96s), PRR x exp(1.96s))

Significance

a. The PRR measures a reporting relationship between a medicinal product P and an adverse event R on the basis of a relative increase of the proportion of individual cases related to an adverse event. This does not necessarily imply a causal relationship between the administered medicinal product P and the occurrence of the adverse event R. Such statistical disproportionality may reflect one or more number of biases and artefacts inherent in pharmacovigilance data as well as "statistical noise”. Consequently, there is a scientific consensus that SDRs identified with quantitative methods should always be medically assessed.

b. The initial decision on whether a drug-event combination should be further investigated is based on thresholds applied to the estimates of the PRR and other statistics (e.g. the estimated lower bound of the confidence interval). There is no ‘gold standard’ on the thresholds that should be adopted for SDRs.

c. The thresholds commonly used to detect SDRs are a trade-off between two options: either generating too many ‘false positive signals’ if the threshold is too low or missing ‘potential signals’ if this threshold is too high.

d. The PRR involves the comparison of a reporting relationship for a specific medicinal product P with all other medicinal products in a database. Therefore, the value of the PRR and consequently the SDRs identified with this method depend on the data in the database on which the PRR is computed.
Therefore the PRR interpretation should take the following elements into account:
- The type of medicinal products included in the database
- The medical terminology (ies) applied
- The coding practices
- The date of the creation of the database
- The source of ICSRs (i.e. all unsolicited reports)

These elements influence the value of the PRR and may induce masking effects. Alternatively they may exaggerate the importance of a medicinal product-adverse event statistical association.

The Reporting Odds Ratio (ROR)
The odds ratio is used to quantify how strongly the presence or absence of an adverse effect A is associated with the presence or absence of adverse effect B in a given population. If each individual in a population either does or does not have an adverse effect “A”, (e.g. "high blood pressure"), and also either does or does not have an adverse effect “B” (e.g. “moderate alcohol consumption”) where both adverse effects are appropriately defined, then a ratio can be formed which quantitatively describes the association between the presence/absence of "A" (high blood pressure) and the presence/absence of "B" (moderate alcohol consumption) for individuals in the population. This ratio is the odds ratio (OR) and can be computed following these steps-

1) For a given individual that has "B" compute the odds that the same individual has "A"
2) For a given individual that does not have "B" compute the odds that the same individual has "A"
3) Divide the odds from step 1 by the odds from step 2 to obtain the odds ratio (OR).

The term "individual" here does not have to refer to a human being, as a statistical population can measure any set of entities, whether living or inanimate.

If the OR is greater than 1, then having “A” is considered to be “associated” with having “B” in the sense that the having of “B” raises (relative to not-having “B”) the odds of having “A”. Note that this is not enough to establish that B is a contributing cause of “A”: it could be that
the association is due to a third property, “C”, which is a contributing cause of both “A” and “B”.

The OR is a measure of effect size, describing the strength of association or non-independence between two binary data values. It is used as a descriptive statistic, and plays an important role in logistic regression (Dandekar et al. 285-88).

**Calculation of Odds Ratio**

Imagine there is rare disease, afflicting, say, only one in many thousands of adults in a country. We suspect that being exposed to something say, having had a particular sort of injury in childhood, makes it more likely to develop that disease in adulthood. The most informative thing to compute would be the risk ratio, RR. To do this in the ideal case, for all the adults in the population we would need to know whether they (a) had the exposure to the injury as children and (b) whether they developed the disease as adults. From this we would extract the following information: the total number of people exposed to the childhood injury, $N_E$ out of which $D_E$ developed the disease and $H_E$ stayed healthy; and the total number of people not exposed, $N_{NE}$ out of which $D_{NE}$ developed the disease and $H_{NE}$ stayed healthy. Since $N_E = D_E + H_E$ and similarly for the “NE” numbers, we only have four independent numbers, which we can organize in a table-

**Table 2.2:** 2x2 Contingency table for the computation of odds ratio

<table>
<thead>
<tr>
<th>DISEASED</th>
<th>HEALTHY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>$D_E$</td>
</tr>
<tr>
<td>Not exposed</td>
<td>$D_{NE}$</td>
</tr>
</tbody>
</table>

To avoid possible confusion, we emphasize that all these numbers refer to the entire population, and not to some sample of it.

The risk of developing the disease given exposure is-

$$D_E/N_E \text{ (where } N_E = D_E + H_E)$$
and of developing the disease given non-exposure is $D_E/N_E$. The risk ratio, $RR$, is just the ratio of the two-

$$RR = \frac{D_E N_E}{D_{NE}/N_{NE}}$$

This can be rewritten as-

$$RR = \frac{D_E N_E}{D_{NE}/N_E} = \frac{D_E D_{NE}}{N_E/N_{NE}}$$

In contrast, the odds of developing the disease given exposure is $D_E/H_E$ and of developing the disease given non-exposure is $D_{NE}/H_{NE}$. The odds ratio, $OR$, is the ratio of the two-

$$OR = \frac{D_E / H_E}{D_{NE}/H_{NE}},$$

This can be rewritten as

$$OR = \frac{D_E H_{NE}}{D_{NE} H_E} = \frac{D_E / D_{NE}}{H_E / H_{NE}}$$

We can understand this with the help of a simple example: Suppose that in a sample of 100 men, 90 drank wine in the previous week, while in a sample of 100 women only 20 drank wine in the same period. The odds of a man drinking wine are 90 to 10, or 9:1, while the odds of a woman drinking wine are only 20 to 80, or 1:4 = 0.25:1. The odds ratio is thus 9/0.25, or 36, showing that men are much more likely to drink wine than women. The detailed calculation is-

$$\frac{0.9/0.1}{0.2/0.8} = \frac{0.9 \times 0.8}{0.1 \times 0.2} = \frac{0.72}{0.02} = 36$$
**Merits of the Frequentist Methods**
- Analysis is quick and inexpensive
- Gives valuable information on ADR and drug safety
- Helps in validation of a pharmacological hypothesis about the mechanism of occurrence of ADRs.
- Can also be used to generate automatic signals from large postmarketing or pharmacovigilance databases.

**Disadvantages of the Frequentist Methods**
- The results are not always satisfactory.
- The case- non case analysis necessitates a double analysis, first a pharmacological and second medical.
- In order to obtain valid results, it is necessary test before analysis, each ADR report is validated.

**2.1.6.2 Bayesian Confidence Propagation Neural Network [BCPNN]**
The BCPNN method assists in the early detection of adverse drug reactions (ADRs) but also further analysis of signals. The method uses Bayesian statistical principles to quantify apparent dependencies in the data set. This quantifies the degree to which a specific drug-ADR combination is different from a background (in this case the WHO database). The measure of disproportionality used, is referred to as the Information Component (IC) because of its origins in Information Theory. A confidence interval is calculated for the IC of each combination. A neural network approach allows all drug-ADR combinations in the database to be analyzed in an automated manner.

The BCPNN is used for the work reported in this thesis for IC analysis (consideration of weights between specific pairs of variables and pattern recognition. The BCPNN has also been used in so called Mutual information analysis where summed weights between variables are used for detecting and coding for dependency between input variables, and in cross-validation used to test the predictiveness of the output based on the input data. (Bate et al personal communication). Although implemented differently the BCPNN has been used in other guises for other tasks. Initial testing of the BCPNN on the WHO database began in 1995, as a cooperation between a neural network research group headed by Anders Lansner from the Royal Institute of Technology in Stockholm (KTH) and the UMC. The first reference in the
literature to the potential use of the method on WHO data was in 1996 in a chapter on International Drug Monitoring by Edwards (ICH) in the 13th Edition of Meylers Side Effects of Drugs, the method was implemented in routine signal detection in 1998 (Bishop; Holst; Holst and Lansner 257-67; Orre and Lansner 128-36; Lansner and Holst 115-28; Holst and A.; Lansner and Ekeberg 77-87; Edwards; Koski and Orre).

**IC Analysis in General**

IC analysis is a method that uses Bayesian statistical principles to quantify apparent dependencies in a data set relative to the generality of the data set. The measure of disproportionality used in the BCPNN, is referred to as the Information Component (IC) because of its derivation from measures used in Information Theory (discussed in the next section). A confidence interval is calculated for the IC of each combination.

**Choice of Measure of Disproportionality**

The logarithmic measure of disproportionality (IC) is defined as-

\[ IC = \log_2 \frac{p(x,y)}{p(x)p(y)} \]

Where- \( p(x) = \) Probability of a specific drug ‘x’ being listed on a case report; \( p(y) = \) Probability of a specific ADR ‘y’ being listed on a case report; \( p(x,y) = \) Probability that a specific drug-ADR combination ‘x’ and ‘y’, is listed on a case report.

This equation can also be written as:

\[ IC = \log_2 \frac{p(y|x)}{p(y)} \]

where: \( p(y|x) = \) Conditional Probability of ‘y’ given ‘x’, i.e. the probability of a specific ADR ‘y’ being listed on a case report given the information that a specific drug ‘x’ is listed as suspected on that case report. When the information present on y is positively associated with x, then \( p(y|x) \) is greater than \( p(x) \).
Multi-Item Gamma Poission Shrinker Method

It is a screening algorithm and computer system developed by Food and Drug Administration which is used to detect signals by identifying combinations of drugs and adverse events in spontaneous reports. The MGPS algorithm is believed to detect unusually frequent item sets-pairs and multiple item interactions.

The techniques discussed so far assess the risk of 2-way DECs, \textit{i.e.}, one drug and one ADR. Another serious concern is due to potential interactions between several drugs taken simultaneously in relation to the occurrence of an ADR. For the sake of simplicity, let us assume that we are interested in a specific ADR, denoted as A, and in two drugs D1, D2, where neither exposure to D1 nor D2 alone results in an elevated risk for A. If the joint exposure to both drugs poses a safety risk, this risk would not be detected in two-way analyses. A famous example is the interaction of cerivastatin and gemfibrozil, leading to an elevated risk of rhabdomyolysis and resulting in the withdrawal of cerivastatin from the worldwide market in 2001 (Lau, Leachman and Lufschanowski 142).

DuMouchel and Pregibon introduced the Multi-item Gamma-Poisson Shrinker (MGPS) as an extension of the GPS algorithm in 2001 to deal with multi-item sets of a size \( n > 2 \) (e.g., \( n = 3 \); drug-drug-event interactions). The basic idea is to assess how much of the observed frequency of the joint occurrence of the multi-item-set can be explained by the occurrence of all \( 0.5n(n-1) \) possible two-way interactions in the set of (n-1) drugs under inspection and the event A of interest. Given the above set of two drugs (D1,D2) and one ADR A, the number \( N_{AD1D2} \) of reports on A after simultaneous exposure to D1 and D2 is considered to be “interesting” if the number of reports involving the two-way interactions (\textit{i.e.}, \( D1 \times D2, D1 \times A \) and \( D2 \times A \)) does not explain the observed count of the triplet.

A log-linear analysis can be conducted to determine if any of the observed frequencies of the two-way combinations depends on the third item. From this analysis one obtains an estimate \( e_{AD1F} \) of the frequency of reports on the joint occurrence of D1, D2 and A if all associations were strictly pairwise and independent from the third item. DuMouchel and Pregibon define the EXCESS2 value as number of excess reports on D1, D2 and A over what might be expected if all associations were only pairwise-
EXCESS2= (EBGM_{AD1D2} \cdot E_{AD1D2}) - eAll2F

Thus, high EXCESS2 values of an examined triplet might indicate that a safety risk is given under combined exposure to D1 and D2 (Suling and Pigeot 607-40).

**Table 2.3: Summary of major DMAs used for signal detection**

<table>
<thead>
<tr>
<th>DMA</th>
<th>Computation</th>
<th>Published threshold criteria</th>
<th>Advantage</th>
<th>Limitations</th>
<th>Regulatory Agencies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bayesian methods</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-item Gamma Poisson</td>
<td>$\frac{a(a+b+c+d)}{(a+c)(a+b)}$</td>
<td>EBGM_{a} &gt; 2 N&gt;0</td>
<td>Always applicable; More specific as compared to frequentist method*</td>
<td>Relatively non-transparent for people non-familiar with Bayesian statistics; Lower sensitivity</td>
<td>FDA (AERS)</td>
</tr>
<tr>
<td>Shrinker (MGPS) [36]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayesian Confidence</td>
<td>$\log_2 \frac{a(a+b+c+d)}{(a+c)(a+b)}$</td>
<td>IC-2 SD&gt;0</td>
<td>Always applicable; More specific as compared to frequentist method*</td>
<td>Relatively non-transparent for people non-familiar with Bayesian statistics; Lower sensitivity</td>
<td>UMC (WHO-Vigibase)</td>
</tr>
<tr>
<td>Propagation Neural</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>network (BCPN) [37]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Frequentist methods</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportional Reporting</td>
<td>$\frac{a}{a+b}$</td>
<td>PRR_{a}2, \chi^2\text{d.f.}, N=3</td>
<td>Easily applicable; Easily interpretable; More sensitive as compared to Bayesian method*</td>
<td>Cannot be calculated for all drug-event combinations; Lower specificity</td>
<td>EMA (Eudravigilance)</td>
</tr>
<tr>
<td>Ratio (PRR) [35]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Italian Regulatory Agency</td>
</tr>
<tr>
<td>Reporting Odds Ratio</td>
<td>$\frac{c}{d}$</td>
<td>95% CI &gt; 1, N=2</td>
<td>Easily applicable; Easily interpretable; More sensitive as compared to Bayesian method*; Different adjustment for covariates in logistic regression analysis</td>
<td>Odds ratio not calculated if denominator is zero (specific ADRs); Lower specificity</td>
<td>Lareb (Netherlands)</td>
</tr>
<tr>
<td>(ROB) [46]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* when commonly cited thresholds are used.

\(\chi^2\)-chi-squared; N= number of cases; IC= Information Component; CI= Confidence Interval; SD= Standard Deviation; EBGM= Empirical Bayesian Geometric Mean; \(a^{th}\) percentile of the posterior distribution, i.e., there is a 95% probability that the "true" relative reporting ratio exceeds the EBGMs.
2.1.7 Legal Basis of Pharmacovigilance

2.1.7.1 Introduction

Before we talk about the new EU pharmacovigilance legislation, it is important to define what we mean by Europe. Here is a map of the EU:

- EU = European Union
- EEA = European Economic Area (EU + Norway, Iceland and Liechtenstein)
- EFTA = European Free Trade Association (EU + Norway, Iceland, Liechtenstein and Switzerland)
- Norway, Iceland and Lichtenstein have agreed to follow the new EU PV legislation.

The new legislation represents the biggest change to EU pharmacovigilance requirements since the formation of the European Medicines Agency (EMA) and will have a significant impact for regulators and industry. The legislation was initially enacted on December 31st, 2010 and comprises the following acts:

- **Directive 2010/84/EU** amending, as regards PV, Directive 2001/83/EC. Member States were required to implement the Directive by 21st July 2012.


The legislation is underpinned by an EC Implementing Measures Regulation and a series of modules on Good Pharmacovigilance Practice (GVP). These modules specify the detailed requirements that all companies who have received marketing authorization for their products in Europe must follow.

An important reason for companies to take note of the new EU PV laws is the fact that financial penalties to MAHs in Europe were introduced in 2007. For infringements associated with non-compliance for centrally authorized products, penalties can be imposed of up to 5% of total EU annual turnover per annum. Those aspects of non-compliance that are subject to penalties include the following-
• Maintaining up to date product information
• Providing data requested by an agency
• Maintaining a comprehensive pharmacovigilance system
• Submitting a PSMF at agency request
• Having a risk management system
• ICSR recording and reporting
• PSUR submission
• Conducting a Post Authorization Safety Study (PASS)
• Notifying the agency of public communications, such as Dear Doctor letters
• Collating and assessing pharmacovigilance data
• Having an EEA QPPV

Detailed aspects of the new EU PV legislation are to be found in the GVP Modules.

Table 2.4: GVP modules released

<table>
<thead>
<tr>
<th>Module number</th>
<th>Module title</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pharmacovigilance Systems and Quality Systems</td>
</tr>
<tr>
<td>II</td>
<td>Pharmacovigilance System Master File</td>
</tr>
<tr>
<td>III</td>
<td>Pharmacovigilance Inspections</td>
</tr>
<tr>
<td>IV</td>
<td>Pharmacovigilance System Audits</td>
</tr>
<tr>
<td>V</td>
<td>Risk Management Systems</td>
</tr>
<tr>
<td>VI</td>
<td>Management and Reporting of Adverse Reactions</td>
</tr>
<tr>
<td>VII</td>
<td>Periodic Safety Update Reports</td>
</tr>
<tr>
<td>VIII</td>
<td>Post-Authorisation Safety Studies</td>
</tr>
<tr>
<td>IX</td>
<td>Signal Management</td>
</tr>
<tr>
<td>X</td>
<td>Additional Monitoring</td>
</tr>
<tr>
<td>XV</td>
<td>Safety communication</td>
</tr>
</tbody>
</table>

With the application of the new pharmacovigilance legislation in July 2012, Volume 9A will be superseded by the guidance on Good Pharmacovigilance Practices (GVP). However, GVP will indicate where there is a transition period for the implementation of the new requirements and/or where the GVP modules are not yet available. Thus, Volume 9A remains the reference as applicable until the transition period ends or until that specific GVP modules are published as final.
The ultimate arbiter of benefit-risk assessment in the EU is now the PV Risk Assessment Committee. Membership of the PRAC consists of a Chair and vice chair, elected by serving PRAC members. Dr June Raine from the MHRA was recently elected as the chair. The diagram below explains the role of the new Pharmacovigilance Risk Assessment Committee (PRAC):

**Figure 2.3 - Role of pharmacovigilance risk assessment committee (PRAC)**

We will now discuss in more detail some of the important aspects of the key GVP modules (EMA).

### 2.1.7.2 Quality System - Module 1

There are new requirements for Quality Systems. MAHs are now required to have a quality system in place which covers their pharmacovigilance activities, and documentation of the system will be necessary. Pharmacovigilance should be governed and managed in such a way that quality principles are routinely applied, particularly for:

- Resource management
- Staff training
- Procedural documentation
- Quality control
- Monitoring
• Improvement
• Audits

Audits of the PV system (including the quality system) will have to be conducted on a regular basis, ideally once every two years, and resources should be available to address this. The new legislation re-enforces the cooperation and harmonization of inspection activities in the EU: the new Regulation contains the legal basis for the conduct of pre-authorisation inspections, and there is also a clear requirement for an adequate pharmacovigilance system as a condition of marketing authorisation. Marketing authorisation applicants should be aware that the pharmacovigilance system master file may be requested for review during the application process, and an inspection may be conducted to establish the adequacy of the (proposed) pharmacovigilance system before authorization.

2.1.7.3 PV System Master File - Module II
Summary information only concerning the EU qualified person for pharmacovigilance (QPPV) and the location of a pharmacovigilance system master file will be contained in marketing authorisations. Full descriptive information about the pharmacovigilance system will have to be contained in a pharmacovigilance system master file, which should be made available to the National Competent Authorities upon request. The pharmacovigilance system master file will encompass the pharmacovigilance system and may therefore relate to one or more products, and changes to its content will not be automatically notifiable to the Competent Authorities. This differs from the current Detailed Description of the Pharmacovigilance system (DDPS), which will be phased out over the period from July 2012 to 2015.

The content of the PSMF is as follows-

• Product lists
• QPPV details
• Organizational descriptions
• Sources of safety data
• Databases
• Third parties
• Processes
• Compliance data
2.1.7.4 ADR Reporting - Module VI

The major change for the reporting of suspected ADRs will be the centralized reporting to the Eudravigilance database at the EMA. However, this will only come into effect six months after the Eudravigilance functionality has been updated, audited, and approved. This is likely to be sometime in 2015 and until then, transitional measures will apply. Another major change is the inclusion of reports from patients as valid, reportable ADRs. The definition of ADR has been extended to include all reports where harm has occurred to a patient or any reaction that is “noxious and unintended”. Reports of ADRs that are as a result of error, misuse, abuse, and off-label use should also be reported.

Table 2.5: ADR reporting during the transition period

<table>
<thead>
<tr>
<th>Marketing authorisation procedure</th>
<th>Origin</th>
<th>Adverse reaction type</th>
<th>Destination</th>
<th>Time frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centralised</td>
<td>EU</td>
<td>All serious</td>
<td>Member State where suspected adverse reaction occurred</td>
<td>15 days</td>
</tr>
<tr>
<td>Mutual recognition, decentralised or subject to referral</td>
<td>All non-serious</td>
<td>Member State where suspected adverse reaction occurred, if required (See Table 2)</td>
<td>90 days</td>
<td></td>
</tr>
<tr>
<td>Purely national</td>
<td>Non-EU</td>
<td>All serious</td>
<td>EudraVigilance database</td>
<td>15 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Member States where suspected medicinal product is authorised, if required (See Table 2)</td>
<td></td>
</tr>
</tbody>
</table>
2.1.7.5 ADR Reporting During the Transition Period

MHRA requires that all valid, serious ADR reports are expedited to the MHRA within 15 days. This includes reports from any source such as patients and consumers, the literature, media and digital media, and in the context of Post Authorization Studies.

Regarding non-serious reports, the Directive says these should now be reported within 90 days. However, MHRA will not require non-serious reports to be routinely submitted to them. Non-serious reports, or line listings may be requested during the assessment of a signal, but MAHs should not submit these routinely to MHRA. For reports originating outside the European Economic Area, during the transition period, MHRA will require that valid, serious, non-EEA reports are expedited to them.

2.1.7.6 ADR Reporting - Final Arrangements

MAHs shall submit all serious ICSRs that occur within or outside the EU (including those received from competent authorities outside the EU) to the EudraVigilance database only, and MAHs shall submit all non-serious ICSRs that occur in the EU to the EudraVigilance database only.
2.1.7.7 Literature Reports

Until further notice MAHs should continue to report cases they have identified from the literature. As these cases are the primary cause of duplicate reporting MAHs are asked to monitor the MHRA website for the weekly list of articles received and only report cases not listed. It is intended that at some point in the future the EMA will provide a service for literature reporting for certain products, however this is likely to be a year or two away.

2.1.7.8 About the Internet

MAHs have a responsibility to review sites under their control for valid cases and report them accordingly. There is no requirement to trawl Internet sites not under the MAH’s control. This requirement also refers to blogs, chatrooms and social media pages.

2.1.7.9 ICSR Format

Detailed requirements for format and content are provided in the EC Implementing Measures. Essentially the E2B (R2) standard is the current format and this will be accepted for some time. MAHs and medicines regulators will be required to implement the new ICSR E2B (R3), which will come into effect in 2015.

2.1.7.10 Special Requirement for Biological Products

ICSRs for biological and biosimilar products should include the batch number and product name. MAHs should conduct follow up for this information if it is not present in the initial report.

2.1.7.11 Additional Monitoring

Products to be subject to ‘additional monitoring’ activities are all medicinal products with a new active substance and biological medicinal products, including biosimilars. This may also apply to specific products that require post-authorization safety studies or have conditions or restrictions with regard to safe and effective use (as specified in the risk management plan). For example: products for pediatric use, those necessitating significant change in the marketing authorization (e.g. new manufacturing process for a ‘biotech’ product). Affected products will be identified by an inverted black equilateral triangle & standard explanatory sentence in the SPC & PIL, usually for 5 years from authorisation. The EMA will maintain a publicly available list of specified products.
2.1.7.12 Periodic Safety Update Report (Periodic Benefit-Risk Evaluation Report)

A new version of the PSUR focusing on Benefit-Risk assessment has reached step 4 in the ICH process and been adopted by the EU. The format and content of the new PSUR is specified in ICH E2C(R2) and also known as the PBRER (Periodic Benefit-Risk Evaluation Report).

Single assessment of PSUR is practiced within Europe by setting up the harmonized frequency and date of submission. This information is included in a list published by the Agency. The reporting periodicity varies from 6 months to 28 years, depending on the product, and some products no longer require PSURs for EU reporting.

The new features of the PBRER are-

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

2.1.7.13 Signal Management - GVP Module IX

Steps in the signal management process are defined in the new GVP module IX as follows-

- Signal detection
- Signal validation
- Signal analysis and prioritization
- Signal assessment
- Recommendation for action
- Exchange of information

Signal validation considerations include an assessment of the clinical plausibility of the signal, the seriousness and severity of the reaction; possibility of drug-drug interaction; reactions in special populations; the novelty of the reaction; and whether the signal has been previously recognized a safety concern.
Market Authorization Holders now have the following responsibilities for signal management-

- **Monitor** the safety of its products, via monthly EudraVigilance monitoring
- **Validate** any EudraVigilance signal
- **Notify** any emerging safety issue to the competent authorities
- **Notify** CA if findings impact the benefit-risk balance or public health
- **Maintain** signal detection activity audit trail

2.1.7.13 Risk Management Systems - Module V

The main risk management items in the new EU PV legislation are as follows-

- A risk management plan (RMP) will be required for all new applications
- The RMP should be proportionate to the risks
- There is a key role for the PRAC in relation to the RMP
- A post-authorization safety study (PASS) may be a condition of marketing authorization
- A post-authorization efficacy study (PAES) may be a condition of marketing authorization
- A summary of the RMP will be made public
- There is a requirement to monitor the effectiveness of risk minimization
- There is a new definition of a RMP

A risk management system is now defined as a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those interventions. A risk management plan is a detailed description of the risk management system.

2.2 Cancer

Cancers are a large family of diseases involving abnormal cell growth with the potential to invade other body parts forming the subset of neoplasms. A neoplasm or tumor is a group of cells that have undergone unregulated growth, and will often form a mass or lump, but may be distributed diffusely. The progression from normal cell to cancer cell involves multiple steps known as malignant progression.

About 14.1 million new cancer patients reported globally in 2012 leading to about 8.2 million deaths worldwide (WHO "World Cancer Report 2014"). The most common types of cancer in
males are lung cancer, prostate cancer, colorectal cancer, and stomach cancer, and in females, the most common types are breast cancer, colorectal cancer, lung cancer, and cervical cancer.

2.2.1 Signs and Symptoms
Symptoms of cancer vary according to the location of the tumor. Thus the symptoms can be in terms of:

Local Symptoms such as, tumor and or ulceration.
Systemic Symptoms such as, unintentional weight loss, fever, being excessively tired, leukemia,
Metastasis Symptoms Cancer can be spread from its original site causing enlarged lymph nodes, enlarged liver or spleen, pain or fracture of affected bones, and neurological symptoms.

![Pathophysiology of cancer](image)

**Figure 2.4:** Pathophysiology of cancer
2.2.2 Causes
90–95% of Cancer cases are due to environmental factors while remaining 5–10% are due to inherited genetics. Environmental factors include lifestyle, economic and behavioral factors, and not merely pollution. The most common environmental factors that contribute to cancer death include tobacco (25–30%), diet and obesity (30–35%), infections (15–20%), radiation (both ionizing and non-ionizing, up to 10%), stress, lack of physical activity, and environmental pollutants (Anand et al. 2097-116).

2.2.3 Pathophysiology
Cancer is a disease of tissue over-growth. The genes which regulate cell growth and differentiation must be altered to develop the cancerous cell.

The affected genes are divided into two broad categories; a) Oncogenes are genes which promote cell growth and reproduction, b) Tumor suppressor genes are genes which inhibit cell division and survival.

Changes in many genes are required to transform a normal cell into a cancer cell. Genetic changes can occur at different levels and by different mechanisms. The gain or loss of an entire chromosome can occur through errors in mitosis. More common are mutations, which are changes in the nucleotide sequence of genomic DNA.

2.2.4 Diagnosis
The earlier cancer is diagnosed and treated, the better the chance of its being cured. Cancer diagnosis begins with a thorough physical exam and a complete medical history. Laboratory studies of blood, urine, and stool can detect abnormalities that may indicate cancer. When a tumor is suspected, imaging tests such as X-rays, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and fiber-optic endoscopy examinations help doctors determine the cancer's location and size. To confirm the diagnosis of most cancers, a biopsy needs to be performed in which a tissue sample is removed from the suspected tumor and studied under a microscope to check for cancer cells.
2.2.5 Management of Cancer

Cancer can be managed by a variety of treatments which includes surgery, chemotherapy, radiation therapy, hormonal therapy, targeted therapy and palliative care. Choice of treatments depends upon the type, location, and grade of the cancer.

**Chemotherapy** is the treatment of cancer which includes large variety of different anticancer drugs, which are divided into broad categories such as alkylating agents and antimetabolites. Conventional chemotherapeutic agents act by killing cells that divide rapidly. The effectiveness of chemotherapy is often limited by toxicity to other tissues in the body.

**Radiation therapy** utilizes ionizing radiation to either cure or improve the symptoms of cancer. It works by damaging the DNA of cancerous tissue leading to cellular death. To spare normal tissues shaped radiation beams are aimed from several angles of exposure to intersect at the tumor.

**Surgery** is the conventional method of treatment of most isolated solid cancers. It is typically an important part of making the definitive diagnosis and staging the tumor as biopsies are usually required.

Chemotherapeutics are very frequently used anti-cancer drugs in recent clinical practice alone or in combination with above discussed therapies.

2.2.6 Chemotherapeutics

Chemotherapy may use one drug at a time (single-agent chemotherapy) or several drugs at once (polychemotherapy). The combination of chemotherapy and radiotherapy is chemoradiotherapy. Chemotherapy using drugs that convert to cytotoxic activity only upon light exposure is called photochemotherapy. Chemotherapeutic agents are classified as follows;

2.2.6.1 Alkylating Agents

These agents interfere with DNA replication to prevent cancer cells from reproducing. Alkylating agents can produce major toxicities affecting the hematopoietic system and the gastrointestinal and reproductive systems. The following cytotoxic drugs are examples of
alkylating agents: busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, mechlorethamine hydrochloride, melphalan, procarbazine, thiotepa, and uracil mustard.

2.2.6.2 Nitrosoureas
These agents interfere with enzymes needed for DNA repair. The nitrosoureas are able to cross the blood-brain barrier, so they are used to treat brain tumors as well as non-Hodgkin’s lymphoma, multiple myeloma, and malignant melanoma. Major toxicities occur in the hematopoietic and gastrointestinal systems. Carmustine, lumustine, and streptozocin are examples of nitrosoureas.

2.2.6.3 Antimetabolites
These agents interfere with DNA and RNA growth. Antimetabolites are used to treat chronic leukemias as well as tumors of the breast, ovary, and the gastrointestinal tract. Most antimetabolites are cell cycle specific and act in the S phase of the cell cycle. Major toxicities occur in the hematopoietic and gastrointestinal systems. Antimetabolites include drugs such as 5-fluorouracil, 6-mercaptopurine, capecitabine, cytosine arabinoside, floxuridine, fludarabine, gemcitabine, methotrexate, and thioguanine.

2.2.6.4 Antitumor Antibiotics
These agents interfere with DNA by stopping enzymes needed for cell division or by altering the membranes that surround cells. Major toxicities affect the hematopoietic, gastrointestinal, reproductive, and cardiovascular systems. Antitumor antibiotics include dactinomycin, daunorubicin, doxorubicin, idarubicin, mitomycin-C, and Mitoxantrone.

2.2.6.5 Plant Alkaloids
These agents inhibit or stop mitosis or inhibit enzymes that prevent cells from making proteins needed for cell growth. Most plant alkaloids are cell cycle specific, acting in the M phase. Major toxicities occur in the hematopoietic, integumentary, neurologic, and reproductive systems. Frequently used plant alkaloids include vinblastine, vincristine, vindesine, and vinorelbine.
2.2.6.6 Taxanes

Such as paclitaxel and docetaxel, affect cell structures called microtubules that play an important role in cell functions. Thus, Taxanes have a unique way of preventing the growth of cancer cells. They stop the microtubules from breaking down and cancer cells become so clogged with microtubules that they cannot grow and divide. Paclitaxel is used for advanced ovarian cancer and as an initial treatment for ovarian cancer in combination with cisplatin.

2.2.7 Role of PV in Anti-Cancer Drugs

Oncology treatment types vary hugely, and newer molecularly targeted drugs are posing novel safety challenges. Pharmacovigilance departments and medical monitors draw on a number of resources to assess the benefit risk and build the safety profile of new drugs.

Many phase 3 studies have shown the superiority of systemic chemotherapy over best supportive care in patients with locally advanced and metastatic lung cancer (Sher, Dy and Adjei 355-67). Platinum based compounds have been widely accepted as the standard of care. Agents such as paclitaxel, gemcitabine, and vinorelbine have been incorporated into platinum based doublets and have proven to be effective. Platinum based regimens are associated with significant increase in hematological toxicity, nephrotoxicity, and nausea and vomiting, but no such increases were noted in neurotoxicity, febrile neutropenia rate or toxic death rate (Molina et al. 584-94).

Pharmacologists and pharmacists play an important role in initiating and conducting PV Programmes. Pharmacists can sensitize clinicians by highlighting the importance of PV and by helping to apply its principles in daily practice. PV is important to ensure the safe use of medicines.

These facts and figures about cancer and treatment related toxicities necessitate the requirement of monitoring, assessment, and reporting of ADRs associated with anticancer drugs. Periodic reporting of ADRs to higher centres like Uppsala MONITORING CENTRE will help in dissemination of information to the physician, pharmacists and patients for better treatment options.
A prospective study was conducted at the Peter MacCullum Cancer Centre from 28 February to 2 June 2000 for the assessment of incidence, predictability, preventability and severity of adverse drug reactions (ADRs) in hospitalised oncology patients. One hundred and sixty-seven patients associated with 171 admissions were interviewed. Four hundred and fifty-four ADRs were identified in 127 (74.3%) separate admissions. Eighty-eight percent of ADRs were predictable. Of these, 1.6% was classified as definitely preventable and 46.1% probably preventable. The ten most common ADRs were constipation, nausea +/- vomiting, fatigue, alopecia, drowsiness, myelosuppression, skin reactions, anorexia, mucositis, and diarrhea (Lau, Stewart and Dooley 626-33).

A prospective study involving 600 in-patients in a period of six months concluded that 18 patients (3%) developed ADR. A significant number (77.78%) of patients developed ADR between 3rd and 10th days of administering drugs. As the number of drugs increased, the incidence of ADR also increased. Majority of ADR (72.22%) occurred due to chemotherapeutic agents. 66.67% of ADR involved the gastrointestinal tract (Gor and Desai 37).

A retrospective, observational study evaluated hypersensitivity reactions (HSR’s) which captured them through Electronic Medical Record (EMR) system for weekly paclitaxel infusions. In a period of 18 months study, they identified 51 HSRs in 36 patients. The administration of paclitaxel is complicated by HSRs including bronchospasm, dyspnea, hypotension/hypertension, shortness of breath, chest pain/tightness, flushing, wheezing, anxiety, and urticaria, which has earned black box warning by the Food and Drug Administration, the drug approval and regulation body in the USA (Lal et al. 1311-15).

Gefitinib, a potent drug used in the treatment of non-small cell lung cancer (NSCLC), has been reported with frequent, but mild adverse drug reactions. Reported complications include acne-like skin rash, diarrhoea, nausea, vomiting and asthenia. But this case report describes a patient who had been given gefitinib and developed a severe alveolar haemorrhage (Ieki, Saitoh and Shibuya 179-81). Gefitinib also has been reported with adverse drug reactions which are frequently observed in the skin, gastrointestinal tract, and liver. However, acute lung injury has been reported to occur in up to 11% of the patients. The present report described of a patient with NSCLC who developed bilateral subdural haemorrhage (SDH) as a possible ADR after gefitinib therapy (Kim et al. 121-23).
5-Fluorouracil (5-FU) is a frequently administered chemotherapeutic agent in various malignant neoplasms. Its adverse effects involves bone marrow, skin, mucous membranes, gastrointestinal, and CNS, which are well known, whereas cardio toxicity is an important, relevant but underestimated problem (Singh, Sagar and Ramanan 35). More than half of all the pharmaceutical agents have serious ADRs identified after they have received FDA approval for marketing.

In one study, they found that 25 serious ADRs associated with 22 oncology drugs were identified from 2000 to 2002 by pharmaceutical suppliers (or) investigator associated with this study. 25 serious ADRs were identified with the drugs approved before 1995, six with the drugs approved via standard approval after 1995, and seven with drugs approved via accelerated approval. The most common toxicities were severe infusion reactions (13%) and interstitial pneumonitis (13%) (Ladewski et al. 3859-66).

Continuous monitoring and carefully considered safety strategies help mitigate safety risks and support real time responses to emerging safety issues. Real-time monitoring of potential and identified events is required in early phase oncology. "Good communication is required between pre-clinical, medical and PV groups to identify potential safety issues..."

Thus this thesis aims to provide a tool for establishing impending safety concerns and safeguarding patient’s health by communicating the risk involved and ensuring the safety of the drug.