CHAPTER 6

Discussion
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Pharmacovigilance is defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short-term adverse effects of medicines. Clinical trials safety and post-marketing pharmacovigilance (Popularly known as Post-marketing studies or Phase IV clinical trials) are critical throughout the product life cycle (Wanmali et al.). Early-detection efforts with respect to identification of risks associated with medicinal products are hindered due to lack of integration among diverse information sources, such as spontaneous reporting databases, prescription event monitoring databases, linked administrative databases and electronic medical records (Cognizant). The spontaneous reporting systems differ by country regarding accepted reporters (e.g., physicians, pharmacists, consumers) and the managing of the systems (national authorities, university based or independent institutions). A few standardized terminologies for coding adverse events and drugs are applied, which lend the opportunity to assemble and analyzed information from different sources to detect and act on new safety signals. The original signal detection method of case-by-case assessment of spontaneous reports of adverse drug reactions (ADR) is effective, but resource consuming, especially in large ADR databases with high volumes of incoming reports (Finney 387–93).

Pharmaceutical industries can no longer afford to take days or weeks to analyze data; they need to automate the data analysis process, with tools commonly used during post-market surveillance, such as data mining and signal detection (Cognizant). Particularly during the target discovery phase, researchers would greatly benefit from expanding beyond pure genome driven target discovery. Using signal detection technologies throughout the clinical trials process allows researchers to perform ad hoc and close-to-real-time data analysis, reducing time in the interchange between researchers, clinicians and statisticians. Signal detection in spontaneous reporting databases has proven to be a simple and cost effective tool for identifying suspected new adverse drug reactions (Cognizant). Some of the better known examples of safety signals detected include apart from phocomelia from thalidomide during pregnancy, vaginal clear cell cancer in girls of mothers using diethylstilbestrol during pregnancy, suicidal ideation and suicide induced by the anti-obesity drug rimonabant and the latest example; narcolepsy in relation to the pandemic vaccine Pandemrix (Finney 1-10).

Working Group VIII of the Council for International Organizations of Medical Sciences (CIOMS VIII) defined a drug safety signal as “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” (Shibata and Hauben 1-7). The WHO defines a safety signal as
reported information on a possible causal relationship between an adverse event and a drug, the
relationship being unknown or incompletely documented previously. When a signal is detected,
further investigation is warranted to determine whether an actual causal relationship exists
(Garlapati and Priyanka e126).

A typical signal detection program (here the term “program” refers to a set of planned activities
and business procedures to be followed, not computer or software program) consists of a flow
of sequential steps of signal detection, prioritization, and evaluation as well as its linkage to risk
management activities. Pharmacovigilance and drug safety departments at biopharmaceutical
companies may be organized differently, but many follow their adaptations of this framework
explicitly or implicitly. Information relevant and important to the safety monitoring of
medicinal products, coming from multiple sources, not just adverse event reports, is reviewed
and observations prioritized by the safety team responsible for a given product. Prioritized
safety observations are then subjected to further investigation or assessment and the team makes
recommendations based on assessment results. After the team assessment (signal evaluation),
recommendations are brought to a cross-functional safety committee, which makes decisions
on risk communication and other actions to be taken. The level of urgency for risk
communications and other actions is driven by clinical and public health impact of the new
information on patient safety (Shibata and Hauben 1-7).

Signal detection uses data imports from the safety database or other clinical, laboratory, or
epidemiological databases, as well as regulatory data sources. A compliant and suitable safety
database should be able to process data related to signal detection. Signals can be suggested by
alerts or trends in incoming data (Gagnon, Schueler and Fan). During the last five years,
automated signal detection methods have been developed to supplement qualitative clinical
methods. While these automated methods cannot replace expert clinical reviewers, they can
assist with the difficult task of screening huge numbers of drug-event combinations in databases
for potential signals. Through commonly used methods that are based on an underlying model
of statistical association, databases are scrutinized for a significant occurrence of
disproportionalities or dependencies between drug-event pairs (Cognizant). The 21 CFR Part
guidelines recommend the use of data mining tools to aid in signal detection. They also specify which analyses a company should undertake and suggest comparisons with external databases such as the U.S. Federal Drug Administration (FDA) AERS and World Health Organization (WHO) data. Quantitative analysis of spontaneous adverse drug reaction reports is increasingly used in drug safety research. The role of data mining in pharmacovigilance explains how signal detection algorithms work and address questions regarding their validation, comparative performance, limitations and potential for use and misuse in pharmacovigilance. Quantitative signal detection using spontaneous ADR reporting describes the core concepts behind the most common methods, the proportional reporting ratio (PRR), reporting odds ratio (ROR), information component (IC) and empirical Bayes geometric mean (EBGM) (ENCePP-Guideline). The WHO and the FDA are currently using automated detection algorithms based upon Bayesian analysis to achieve signal generation. However, to date, these methods have not been evaluated, and there is no gold standard for signal detection (Cognizant).

The information of safety of antineoplastic agents derives solely from clinical studies that have a number of limitations, such as the number of patients enrolled, selected case studies, follow-up of short duration; therefore, it is not possible to identify the complete profile of safety and possible side effects of the drugs under study (Tenti et al. 95-96). The critical issues that lead to having a low signal compared to drugs commonly used are related to the underestimation of the phenomenon typical of the therapeutic approach in oncology, the complexity of the therapeutic care paths and the process of management of oral therapies. In 2012, about number 70,150 reports of ADRs have been received and processed every month and subsequently made them available for signal detection and analysis of data by the European Medicines Agency (EMA). Out of these reports, 15% were associated with antineoplastic drugs since this reflects the low reporting of the total number of drugs used in clinical practice. In Italy, from 2004 to 2010 the incidence of reports of suspected ADRs to antineoplastic drugs included in RNF has progressively increased from 4.6% to 22.5% (EU-Guideline "First Annual Report on Eudravigilance for the European Parliament, the Council and the Commission"). In India, antineoplastic agents are the common drug class causing the ADRs, and were found to be total of 21.8% of the reported ADRs in a study. The crude incidence rates of cancer varied between 57.5 and 78.6 per 100,000 men; and between 57.7 and 89.7 per 10,000 women in urban registry areas (Palaniappan et al. 152-57).
Paclitaxel is an anticancer agent used for the treatment of breast and ovarian cancer. The major side-effects are bone marrow suppression, alopecia, polyneuropathy and cardiac toxicities.

The cardiac toxicities range from asymptomatic bradycardia, atrioventricular conduction blocks, atrial arrhythmias, left bundle branch block, ventricular tachycardia, congestive cardiac failure and fatal myocardial infarction (Londhey and Parikh). Hypersensitivity reactions include a wide array of symptoms from mild flushing and itching to lethal anaphylaxis. Hypersensitivity reactions (HSRs), though rare in response to anticancer agents, are caused by certain classes of agents including platinum agents (cisplatin, carboplatin, and oxaliplatin), taxanes (paclitaxel and docetaxel), procarbazine and asparaginase, and epipodophyllotoxins (teniposide and etoposide). It was previously reported that docetaxel was associated with flushing whereas carboplatin reported hypersensitivity reactions (rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension) in 2% of the patients (Kadoyama et al. 93). Cisplatin-induced adverse drug reactions such as ototoxicity, hypersensitivity reactions, and electrolyte disturbances are not preventable due to the poor predictability of the ADRs, poorly understood mechanisms and due to lack of reporting of these ADRs. As per recent study in India, 9.8 percentage of patients reported ototoxicity possibly due to cisplatin (Surendiran et al. 40).

Peripheral neuropathy is a well-known complication of vincristine treatment. The literature regarding exact incidences of peripheral neuropathy with vincristine is sparse. The frequency of vincristine-induced peripheral neuropathy is increasing partly because of the wider use of high-dose vincristine, longer survival for many patients with cancer who experience (Verstappen et al. 1076-77). Recently, it was also reported that cyclophosphamide also caused neutropenia during the course of the treatment (Brodsky et al.).

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) of the Marketed Health Products Directorate (MHPD) of Health Canada collects reports of suspected adverse events to health products (including pharmaceuticals, biologics, natural health products, and radiopharmaceuticals) marketed in Canada (Canada). The data received from line listing request to CADRMP indicates that in 30 years’ time duration of 01/01/1970 to 01/03/2010.

Canada has a well-developed pharmacovigilance system & an effective spontaneous reporting system of adverse drug reactions. A significant population of Canada is also of Indian and Asian origin. In addition, in most cases drug adverse reactions show same pattern of incidence and prevalence worldwide. Also, ADR information from Canadian database is easily available for mining. In India, we don’t have yet any robust PV system; the size of the entire national data
base is still small (just over hundred thousand cases for all ADRs) and assessments of adverse events through mining is not yet possible for all ADRs. Canadian data base was easily accessible & this data-base had more one hundred thousand of adverse events were reported due to anti-cancer drugs alone.

The reason behind selection of anticancer drugs, during my professional career, I have worked practically on many phase II & phase III clinical trials of various types of cancer (e.g., Non-small cell lung cancer, Prostate cancer & Bladder cancer) wherein the interventions were paclitaxel, docetaxel, cisplatin, and cyclophosphamide. Discussions with oncologist & cancer patients and their reported and unreported adverse events during clinical trials made me believe that there are still significant adverse reactions which can be invented as signals by data mining. Thus, I decided to do research work in pharmacovigilance of anticancer drugs.

In this study, quantitative signal detection methods were applied for significant signal detection of following drug-ADR pairs like; Paclitaxel- Tachycardia; Docetaxel- Flushing; Cisplatin- Ototoxicity; Cyclophosphamide- Neutropenia; Vincristine- Neuropathy; and Carboplatin- Pruritus.

As per regulatory criteria, statistic value of PRR should be ≥ 2, the PRR calculated by chi square statistics ($\chi^2$) should be ≥ 4 and ROR ≥ 1 to indicate significant signal (EU-Guideline "Eudravigilance Expert Working Group (Ev-Ewg)"). Further, the lower bound limit of 95% confidence interval of PRR should be ≥ 1 and number of individual adverse drug reporting case should be ≥ 3 for SD to be declared significant (EU-Guideline "Eudravigilance Expert Working Group (Ev-Ewg)"). As per PV guidelines for BCPNN method: if IC $- 2SD \leq 0$, then no signal; if $0 < IC − 2SD \leq 1.5$, then weak signal; if $1.5 < IC − 2SD \leq 3.0$, then middle signal; if $IC − 2SD > 3.0$, then strong signal (Zhou et al. 79-85). Thus, the therapeutic class specific signal of tachycardia associated with paclitaxel was found potent enough to cause significant signal.

The Paclitaxel is widely used an anti-cancer drug which had reported tachycardia as a major side effect (EU-Guideline "First Annual Report on Eudravigilance for the European Parliament, the Council and the Commission"). Therefore, the signal has been calculated for tachycardia associated with paclitaxel therapy (drug-ADR). The PRR was detected by placing all the values from 2X2 contingency table into equations. The PRR was found to be 4.2367 which is greater
than 2 and the ROR was found to be 4.4125 which indicates significant signal for tachycardia associated with paclitaxel. The Chi-square statistic test was also applied to the PRR. The PRR determined by chi-square was found to be 77.2788, which is a significant signal as mentioned above. As per statistical analysis by SAS version 9.3 software, the Chi square value was observed 77.27 that was higher than 4 (Chi square should be ≥ 4 as per regulatory guideline for Signal (EU-Guideline "Eudravigilance Expert Working Group (Ev-Ewg)")) which was further supported by P value <.0001 who showed significant signal of tachycardia associated with paclitaxel. Here the 95% confidence interval was found to be 1.10 for lower bound limit and 1.79 for upper bound limit which also fulfills the criteria to indicate significant signal. The Observed to expected ratio was found to be 3.8629. Then value of expected ‘a’ was calculated to get the final answer of PRR by Du Mouchel, which was found to be 4.3928. Further, the value of IC is 1.974 and the value of IC-2SD is observed 0.646 signifies weak signal of tachycardia associated with Paclitaxel. However, the potential strong signal probability should be further confirmed with the help of larger database. When stratifying whole data on the basis of gender we could predict that female were more prone to tachycardia associated with Paclitaxel as high as 68.17% as compared to 30.80% of male. Also, when stratified on the basis of age group it clearly indicated that prevalence of tachycardia associated with Paclitaxel was high in age group of; 19-60 years with 56.75%; while 28.37% in 60-108 years and just 10.73% in 0-18 years age group. The maximum tachycardia event associated with paclitaxel was reported in the duration of 1996 to 2000 years.

The Docetaxel is also most widely an anti-cancer drug. Many studies have reported flushing as adverse event during docetaxel treatment. Therefore, the signal was calculated for flushing associated with docetaxel (drug-ADR). The PRR was found to be 4.13 which greater than 2 and the ROR was found to be 4.38 which indicates it as a significant signal. The PRR determined by chi-square was found to be 205.09, which is a significant signal as mentioned above. As per statistical analysis by SAS version 9.3 software, the Chi square value was observed 205.09 that was higher than 4 (Chi square should be ≥ 4 as per regulatory guideline for Signal (EU-Guideline "Eudravigilance Expert Working Group (Ev-Ewg)")) which was further supported by P value <.0001 who showed significant signal of flushing associated with docetaxel. Here the 95% confidence interval was found to be 1.21 lower bound limit and 1.62 upper bound limit which fulfills criteria as mentioned above. The Observed to expected ratio was found to be 3.67. Then value of expected ‘a’ was calculated to get the final answer of PRR by Du Mouchel, which was found to be 3.67. Further, the value of IC is 1.8853 and the value of IC-2SD is observed 1.72 signifies middle signal of flushing associated with Docetaxel. When stratifying whole data
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on the basis of gender we could predict that female were more prone to flushing associated with Docetaxel as high as 75.55% as compared to 21.52% of male. Also, when stratified on the basis of age group it clearly indicated that flushing associated with Docetaxel prevalence was high in age group of: 19-60 years with 62.08%; while 24.16% in 60-108 years and just 3.51% in 0-18 years age group. The maximum flushing event associated with Docetaxel was reported in the duration of 2001 to 2005 years.

The cisplatin which is also widely prescribed anti-cancer drug. Cisplatin associated adverse drug reactions such as ototoxicity, hypersensitivity reactions, and electrolyte disturbances are not preventable due to the poor predictability of the adverse drug reactions. As per previous certain reports, it is concluded that ototoxicity associated with cisplatin is due to genetic variants of Thiopurine S-methyltransferase (TPMT) and catechol O-methyltransferase (COMT). Therefore, the signal was calculated for cisplatin- ototoxicity (drug-ADR). The PRR was found to be 53.44 and the ROR was found to be 55.03 which indicate it as a highly-significant Signal. The PRR determined by chi-square was found to be 544.70 which is a significant signal as mentioned above. As per statistical analysis by SAS version 9.3 software, the Chi square value was observed 544.70 that was higher than 4 (Chi square should be ≥ 4 as per regulatory guideline for Signal (EU-Guideline "Eudravigilance Expert Working Group (Ev-Ewg)")) which was further supported by P value <.0001 who showed significant signal of Ototoxicity associated with Cisplatin. Here, the 95% Confidence interval was found to be 3.67 lower bound limit and 4.57 upper bound limit which also fulfills above mentioned criteria. The Observed to expected ratio was found to be 20.91. Then value of expected ‘a’ was calculated to get the final answer of PRR by Du Mouchel, which was found to be 20.79. Further, the value of IC is 4.4031 and the value of IC-2SD is observed 2.91 signifies middle signal (close to strong signal) of ototoxicity associated with Cisplatin. When stratifying whole data on the basis of gender we could predict that male were more prone to ototoxicity associated with Cisplatin as high as 51.11% as compared to 33.33% of female. Also, when stratified on the basis of age group it clearly indicated that ototoxicity associated with Cisplatin prevalence was high in age group of: 0-18 years with 53.33%; while 20.00% in 19-60 years and 15.56% in 61-108 years age group. The maximum ototoxicity event associated with cisplatin was reported in the duration of 2006 to 2010 years.

The cyclophosphamide is an anti-cancer drug which is associated with the neutropenia as a major side effect. Therefore, the signal was calculated for neutropenia associated with
cyclophosphamide (drug-ADR). The PRR was found to be 4.73 and the ROR was found to be 4.97 which we could indicate it as a significant signal. The PRR determined by chi-square was found to be 236.02, which is a significant signal as mentioned above. As per statistical analysis by SAS version 9.3 software, the Chi square value was observed 253.50 that was higher than 4 (Chi square should be ≥ 4 as per regulatory guideline for Signal (EU-Guideline "Eudravigilance Expert Working Group (Ev-Ewg)") which was further supported by P value <.0001 who showed significant signal of Neutropenia associated with Cyclophosphamide. Here the 95% Confidence interval was found to be 1.34 lower bound limit and 1.76 upper bound limit which also fulfills the above mentioned criteria. The Observed to expected ratio was found to be 3.93. Then value of expected ‘a’ was calculated to get the final answer of PRR by Du Mouchel, which was found to be 3.93. Further, the value of IC is 1.9811 and the value of IC-2SD is observed 1.68 signifies middle signal of neutropenia associated with Cyclophosphamide. When stratifying whole data on the basis of gender we could predict that female were more prone to neutropenia associated with Cyclophosphamide as high as 60.28% as compared to 35.53% of male. Also, when stratified on the basis of age group it clearly indicated that neutropenia associated with Cyclophosphamide prevalence was high in age group of; 19-60 years with 51.90%; while 30.14% in 60-108 years and 7.19% in 0-18 years age group. The maximum neutropenia event associated with cyclophosphamide was reported in the duration of 2001 to 2005 years.

The vincristine is a popular anti-cancer drug which is associated with the neuropathy side effect. Therefore, the signal calculated for peripheral neuropathy associated with vincristine (drug-ADR). The PRR was found to be 25.10 and the ROR was found to be 26.63 which we could indicate it as a highly-significant signal. The PRR determined by chi-square was found to be 623.36 which is a highly-significant signal as mentioned above. As per statistical analysis by SAS version 9.3 software, the Chi square value was observed 639.63 that was higher than 4 (Chi square should be ≥ 4 as per regulatory guideline for Signal (EU-Guideline "Eudravigilance Expert Working Group (Ev-Ewg)") which was further supported by P value <.0001 who showed significant signal of peripheral neuropathy associated with Vincristine. Here the 95% Confidence interval was found to be 2.85 lower bound limit and 3.58 upper bound limit which also fulfills the above mentioned criteria. The Observed to expected ratio was found to be 16.43. The value of expected ‘a’ was calculated to get the final answer of PRR by Du Mouchel, which was found to be 16.43. Further, the value of IC is 4.0544 and the value of IC-2SD is observed 3.58 signifies strong signal of peripheral neuropathy associated with Vincristine. When stratifying whole data on the basis of gender we could predict that female were more prone to
neuropathy associated with Vincristine as high as 57.50% as compared to 34.17% of male. Also, when stratified on the basis of age group it clearly indicated that neuropathy associated with Vincristine prevalence was high in age group of; 19-60 years with 41.67%; while 28.33% in 60-108 years and 11.67% in 0-18 years age group. The maximum neuropathy event associated with vincristine was reported in the duration of 1976 to 1980 years.

The carboplatin is also an anti-cancer drug which is associated with the pruritus adverse effect. Therefore, the signal calculated for pruritus associated with carboplatin (drug-ADR). The PRR was found to be 7.04 and the ROR was found to be 7.60 which we could indicate it as a highly-significant signal. The PRR determined by chi-square was found to be 458.43, which is a highly-significant signal as mentioned above. As per statistical analysis by SAS version 9.3 software, the Chi square value was observed 486.62 that was higher than 4 (Chi square should be $\geq 4$ as per regulatory guideline for Signal (EU-Guideline "Eudravigilance Expert Working Group (Ev-Ewg"))) which was further supported by P value <.0001 who showed significant signal of pruritis associated with carboplatin. Here, the 95% confidence interval was found to be 1.75 lower bound limit and 2.14 upper bound limit, which do not fulfills the above, mentioned criteria. The Observed to expected ratio was found to be 5.58. The value of expected ‘a’ was calculated to get the final answer of PRR by Du Mouchel, which was found to be 5.57. Further, the value of IC is 2.4851 and the value of IC-2SD is observed 2.1995 signifies middle signal of pruritus associated with Carboplatin. When stratifying whole data on the basis of gender we could predict that female were more prone to pruritus associated with Carboplatin as high as 75.55% as compared to 23.66% of male. Also, when stratified on the basis of age group it clearly indicated that pruritus associated with Carboplatin prevalence was high in age group of; 19-60 years with 59.44%; while 27.44% in 60-108 years and 6.96% in 0-18 years age group. The maximum pruritus event associated with Carboplatin was reported in the duration of 1996 to 2000 years.

Hence, for all medicines there is a trade-off between the benefits and the potential for harm. To minimize the harm; it is necessary that medicines of good quality, safety and efficacy are used rationally, and that the expectations and concerns of the patient are taken into account when therapeutic decisions are made. To achieve this is to serve public health, and to foster a sense of trust in patients in the medicines they use that would extend to confidence in the health service in general. The discipline of PV has developed considerably since the 1972 WHO technical report, and it remains a dynamic clinical and scientific discipline. It has been essential
to meet the challenges of the increasing range and potency of medicines (including vaccines), which carry with them an inevitable and sometimes unpredictable potential for harm. The risk of harm, however, is less when medicines are used by an informed health profession and by patients who themselves understand and share responsibility for their drugs. When adverse effects and toxicity appear – particularly when previously unknown in association with the medicine – it is essential that they should be analyzed and communicated effectively to an audience that has the knowledge to interpret the information (WHO "The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products").

The future trends in PV like globally established link for operation of PV for exchange of knowledge and also the web based information for easy accessibility of data. The uniform regulatory guidelines and implementation of guidelines throughout the world is necessary. The updated information on periodic bases needs to be circulated for every medicinal product existing in the market and last but not least ongoing process of safety monitoring is expected.

Oncovigilance has been expanding in recent years, as companies are required to monitor drug safety post launch. It’s increasingly important worldwide, especially to avoid reoccurrences of serious, costly problems damaging to the industry. Oncovigilance is designed to provide crucial data on how drugs work in medical practice/cancer treatment, from the palliative to curative therapy. This information can aid drug development and marketing if harnessed properly, being a boon rather than a hindrance.

It is important to recognize the distinction between an "adverse event (AE)" and an "adverse drug reaction" (ADR). While an adverse event is any undesirable medical occurrence that develops after the administration of a drug, regardless of the suspected relationship between the drug product and the event, to classify an event as an adverse drug reaction, a causal relationship must be established.

Some of the practical challenges of establishing an Oncovigilance system for anticancer treatment in India related to the detection of adverse events and the determination of the severity and relationship of events to a specific product.
Health workers at the point of data collection are required to detect adverse events, which are often difficult to distinguish from common symptoms of Cancer. Once an adverse event has been detected, the maximum severity of the event should be established. Standardized guidelines have been provided by the World Health Organisation and other organizations but the grading may be subjective.

This study concludes that Tachycardia, Flushing, Ototoxicity, Neutropenia, Peripheral Neuropathy and Pruritis associated with Paclitaxel, Docetaxel, Cisplatin, Cyclophosphamide, Vincristine & Carboplatin respectively are significant signals.

The therapeutic class specific signal has been detected for tachycardia associated with paclitaxel, flushing associated with docetaxel, ototoxicity associated with cisplatin, neutropenia associated with cyclophosphamide, peripheral neuropathy associated with Vincristine and pruritis associated with carboplatin. Hence, it is recommended that treating physician should anticipate and counsel the patient adequately prior to starting of above therapy to minimize side effects. Further, treating physician should also prescribe prophylactic medications along with listed anticancer drugs for cancer treatment to minimize respective adverse effects.

The frequency of tachycardia-associated with paclitaxel, flushing-associated with docetaxel, neutropenia associated with cyclophosphamide, peripheral neuropathy associated with vincristine and pruritis associated with carboplatin were more common in females as compared to males whereas ototoxicity-associated with cisplatin were more common in males as compared to females.

The frequency of tachycardia-associated with paclitaxel, flushing-associated with docetaxel, neutropenia associated with cyclophosphamide, peripheral neuropathy associated with vincristine and pruritis associated with carboplatin more prominent with adults (19-60 years age) as compared to geriatrics and pediatrics except ototoxicity-associated with cisplatin which was more prevalent in pediatric population (0-18 years).
The whole thesis could be fruitful to the people who want to perform actual signal detection in pharmacovigilance study. Thesis itself was a self-explanatory in every aspect so, as to produce actual signal detection from available database.

There are some outputs, which arouse from this thesis work that we can detect a signal from a stratified group according to age, sex or other factors if possible like we have done it in this thesis for particular therapeutic class.