Pharmacovigilance

Of late, every few months we hear of a product being withdrawn due to unexpected adverse events, often life threatening. In such a situation, pharmacovigilance should be regarded as a public health function that monitors the safety of medicines while taking action to reduce their risks and increase benefits .

Pharmacovigilance is the study of adverse reactions to marketed drugs, their assessment, understanding and actions to minimize risk to patients

Need for pharmacovigilance

- During the premarketing stage however close one tries to mimic the human pharmacokinetics in animals it is not a foolproof method. Pharmacokinetics can vary with species, so even in dogs, rats, mice or monkeys which are considered close to humans, one may not be able to obtain the same exposure without causing toxicities. Hence often animal models may be deficient and insufficiently predictive of human safety .

- The information collected during the pre-marketing phase of a drug is inevitably incomplete with regard to possible adverse reactions simply by virtue of the limited number of patients it has been tried on. e.g if the total sample size from all premarketing studies is 10,000, we will be able to identify only those adverse effects whose incidence is 1:10,000. If a gender bias existed it would be still less

- Further, in clinical trials, due to a list of exclusion criteria , selected patients are included and the conditions and duration of use differ from those in clinical practice

- Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available.

- Pharmacovigilance helps us keep track of all adverse events of a drug as it is used by the larger population, and preventive actions for population safety can be taken in a timely manner

International actions towards ideal pharmacovigilance

The Thalidomide disaster in early 60s drew public attention to long term adverse effects of drugs and the need for constant monitoring. Gradually every country had its

own set of rules regarding safety monitoring and regulatory actions there from. But it was also required to coordinate this effort between countries.

Various world bodies help coordinate these activities between countries, companies, investigators, health care providers, patients, regulatory bodies and other stakeholders. They provide guidelines so as to have a common platform for sharing information amongst stakeholders. Each regulatory authority like the FDA, EMEA or DCG(I) have their own guidelines. Some international bodies are

- WHO – Since 1978, the WHO international drug monitoring programme has been carried out at Uppsala monitoring centre in Sweden. This center provides data, references, consultation and training resources to various regulatory bodies, health professionals, researchers and also the pharmaceutical industry all over the world. The centre also maintains WHOART, a dictionary meant to serve as a basis for rational coding of adverse reaction terms

- CIOMS – Council for International Organizations of Medical Sciences is an international, nongovernmental, not-for-profit organization established jointly by WHO and UNESCO in 1949.Apart from guidelines on Ethics and conduct of clinical research, it also publishes guidelines on ADR reporting. In fact the CIOMS form is the template commonly used as such or with minor modifications for ADR reporting around the world. It forms an important link between the industry & regulatory authorities for the purpose of exchange of ADR information

- ICH – International Conference on Harmonization also provides guidelines on ADR reporting in E2D.

With so much international focus on drug safety one comes across a long list of drugs that have been withdrawn over the past several years. Some examples are

Drug	**Year of launch**	**Year of Withdrawal**	**Reason**
Phenylbutazone	1940s	1970s	Bone marrow suppression
Thalidomide	1956	1962	Phocomelia
Terodiline HCl	1965	1991	Torsade de pointes
Practolol	1970	1975	Blindness
Nomifensine	1976	1986	Haemolytic anaemia
Benoxaprofen	1982	1982	Renal & liver failure, Bone marrow depression
Terfenadine	1985	1997	Torsade de pointes
Temafloxacin	1992	1992	Haemolytic anaemia
Cisapride	1993	2000	Torsade de pointes
Cerivastatin	1997	2001	Rhabdomyolysis, death
Bromfenac	1997	1998	Hepatotoxicity

From the table it appears that international efforts are bearing fruit and we are detecting fatal flaws early. But is this really true?

For every Benoxaprofen or Temafloxacin we have a Terfenadine or a Cisapride. The reason for this dichotomy lies in the aetiology of adverse reactions.

Adverse reactions could be classified Type A or type B. The type A reactions are accentuations of the pharmacological effects and hence expected while the Type B reactions are the ones that are not very common, idiosyncratic in nature and may not have a dose response relationship. These are often identified a long time after the launch of the drug

Another way of classifying adverse reactions is the A to F classification

- Type A – Augmented - excess desired effect as in case of Anti diabetics, known side effect like asthma with , beta blockers
- Type B – Bizarre anaphylaxis - idiosyncratic
- Type C – Chronic - long term exposure
- Type D – Delayed – carcinogenesis breast Ca in relation to OCs
- Type E – Post termination of therapy - antidepressants
- Type F – Failure of effect – contraceptives, vaccines

It is obvious that Types B,C,D and to some extent E are the ones that may take years to be identified in numbers sufficient for the regulators to take strong action. Efforts have created an awareness and we are ever vigilant about ADRs, but the identification has to take its own course in time.

Regulations for safety reporting

Regulators across the world have laid down specific and stringent guidelines for reporting. They specify the nature of events to be reported, the contents of the report and the timelines that have to be adhered to. Submissions can be submission of death cases, Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Events (SUSARs) and in the form of spontaneous reports, annual reports, Periodic Safety Update Reports(PSURs) etc.

Regulators could undertake surprise audits of the pharmacovigilance departments of pharma companies. Generally the following events act as a trigger for such inspections

- Non-submission of data
- Submission of data after the deadline agreed in the letter of undertaking from the company, without previous agreement from the Competent Authority

- Failure to implement a specific obligation
- Failure to implement a follow-up measure
- Poor quality of a report requested as a follow-up measure
- Poor quality of a report requested as a specific obligation
- Failure to implement an urgent provisional measure
- Info from another authority of the above above.

Regulatory action

If any irregularity is observed during the audit or inspection, the regulatory action is decided on a case to case basis but generally considering public impact of the action. It could be one or more of the list below

- Awareness Education & assistance to comply
- Inspection
- 'Name & shame', 483s in US
- Warning
- Urgent safety restriction
- Variation, Suspension or Revocation of the Marketing Authorisation
- Prosecution

Basic steps in Pharmacovigilance Case Processing

Pharmacovigilance comprises of

- Safety data management
- Signal detection for any new altered safety issue
- Signal evaluation and making decisions with regard to safety issues
- Actions, including regulatory, to protect public health
- Informing all concerned parties or stakeholders

Safety Data Management

A Serious Adverse Event for a molecule could be generated during the preregistration or postmarketing phase. They could occur during clinical trials or be reported spontaneously by a patient, caregiver, relation, doctor, nurse or pharmacist. Another regulatory body or a licencee company could also be the informant. It could be received on phone, mail, fax, journals, newspapers or the latest social media.

Unexpected adverse events could arise anytime in the life of a product. These could put the user to serious risk and could curtail the life of the product. As part of the risk management plan, safety data is gathered throughout the life of a product. Consequently, every company that markets even a handful of products across many countries, gathers thousands of reports per year. The only way to manage this load is using latest software and automation.

The steps in safety data management are

- Data collection and verification
- Coding of adverse reaction descriptions
- Coding of drugs
- Case causality assessment
- Timely reporting to authorities

Data Collection and verification:

Acknowledgement : A valid case needs to have four elements; an adverse event, a reporter, a patient and a drug. Every report needs to be acknowledged, more so the valid reports. Acknowledgement establishes a contact with the reporter for more information whenever required . It builds company image with the stakeholder and also protects from litigation. A consentious reporter may continue to send the same report repeatedly till it is acknowledged, hence this simple action avoids duplication.

Duplicate search: Due to, greater awareness , stringent regulations and multiple reporting sources, duplicate reports is a common phenomenon. Every safety management software has a facility to identify and delete duplicates. . Certain characteristics of a case (sex, age or date of birth, dates of drug exposure, clinical trial code, country, etc.) may be used to identify duplicate reporting. This action is of significance for further processing of the case. The duplicate could actually be follow up information that could alter the seriousness and hence reporting timeline of the case. Missed out duplicates could send misleading information to signal detection systems.

Triage: Collins dictionary defines triage as

- (Medicine) the principle or practice of sorting casualties in battle or disaster or other patients into categories of priority for treatment
- (Government, Politics & Diplomacy) the principle or practice of allocating limited resources, as of food or foreign aid, on a basis of expediency rather than according to moral principles or the needs of the recipients

Triage in safety means prioritizing the case for reporting to authorities. An oversimplification of triage would be to report deaths and life threatening unexpected reports in 7 days and other adverse reactions in 15 days as there are also other occasions where expedited reporting is required.

Data Entry: A seemingly repetitive and inconsequential step in the process but something that forms the basis of good reporting. The quality of data entry affects the further processing of the case. Details of the four pillars of a valid case have to be reported meticulously. Patient information has to follow the HIPPA code for confidentiality. Reporter information has to clear and detailed enough to be able to contact the person if necessary. Drug identifiers like name, formulation and dose have to be captured correctly. Event report has to be detailed enough for the evaluator to decide on the cause of the adverse event. This would include chronological description of the event or events, nature, localisation, severity, characteristics of the event, results of investigations and tests, start date, course and outcome, concomitant medications and other risk factors .

Case narrative: Provides summary of events to readers who do not have access to original data sets. During the course of safety data management, it is seen and used by various groups like case reviewers to decide seriousness, upgrade etc , affiliate companies to triage for their countries, , during preparation of PSURs and other summary reports and also by regulatory authorities. One should ensure completeness, chronology and sufficient detail in a narrative so that the reader is able to come to a conclusion.

Coding of adverse reactions: This step ensures that everyone is talking the same language and the data can be shared internationally, Most commonly used system is the MedDRA(Medical Dictionary for Regulatory Activities). Use of MedDRA has lead to a global standardization across regulatory agencies, across companies & across countries. This step usually needs oversight by a medically qualified person.

Coding for drugs: Both the suspect drug and concomitant medication have to be coded. The principle is again to be talking the same language across countries, companies and regulatory bodies. Most common dictionary is the WHO Drug Dictionary enhanced. This is provided as a product by the Upsala Monitoring centre of the WHO. Entries are updated 4 times a year. The majority of entries refer to prescription-only products, but some over-the-counter (OTC) preparations are included. The dictionary also covers biotech and blood products, diagnostic substances and contrast media. For chemical and therapeutic groupings the WHO drug record number system and ATC classifications are considered.

Causality assessment: Non spontaneous case reports usually indicate whether an adverse drug reaction is suspected due to the administered drug. In these circumstances and even otherwise, a causality assessment is required to be conducted. Various approaches have been developed for the structured determination of the likelihood of a causal relationship between drug exposure and adverse events. These systems are largely based on following considerations:

- the chronology or association in time (or place) between drug administration and event
- current knowledge of nature and frequency of adverse reactions due to the suspect molecule; or the pharmacology
- medical or pharmacological plausibility based on signs and symptoms, laboratory tests, pathological findings, mechanism of action
- likelihood or exclusion of other causes for the same adverse events; often the disease condition or concomitant medication.

Timely reporting to authorities: this is the end goal for which all the above has to be done in a timely manner. The reporting could be by sending data back to the sponsor or by a click of a button based on the software used. The latter will provide an extra couple of days for case processing

Safety data management is the most basic step in pharmacovigilance. This is often outsourced so that internal company resources can focus on the domain related, mentally stimulating activities like signal detection, regulatory responses, information to stakeholders

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Signal Detection

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. Usually more than a single report is required to detect a potential signal, depending upon the seriousness of the event and the quality of the information”

CIOMS VI defines it as, “A report or reports of an event with an unknown causal relationship to treatment, that is recognised as worthy of further exploration and continued surveillance”

Sources of signals: Signals can be generated through various sources. Given below is a list of possible sources of signals

- Clinical Studies- Any clinical study with the product, whether company sponsored or otherwise, both pre and post marketing, is a rich pool of information for astute observers. Discussion with investigators often leads to identification of suspect situations which need to be explored further
- Post marketing information from prescribers, consumers, other regulatory bodies, ECs, IRBs
- Single cases, or case series in aggregate review, PSURs
- Medical Literature, internet, newspapers other media
- WHO database or other regulatory databases

Confirming the signal: Having gathered data from various sources it is almost impossible to manually screen all the data. Complex statistical modeling, apart from routine statistical methods are required to confirm that the signal exists. e.g. Latest techniques like Empirical Bayesian Neural network, Proportional Reporting Ratio(PRR) and MGPS (Multi-Item Gamma Poison Shrinker), using exclusive software, have been developed

This is called data mining where spontaneous reports are systematically screened for interesting associations. Another method is disproportionality analysis again towards the same goal of detecting “higher than expected” drug-event frequencies without having actual exposure data

Signal evaluation: Various associations and possible signals are prioritised based on frequency, seriousness, impact on or risk to patient. In today’s litiginous society, companies also have to guard their reputation and protect against liabilities. Having prioritised the signals they need to be further evaluated to ascertain their cetainity, frequency, seriousness

Further evaluation could include

- Sub group analysis of existing data
- Advanced data-mining
- Pharmacoepidemiologic studies to corroborate findings
- The signal could be evaluated as part of a new safety study
- Flag the adverse event and monitor it in all ongoing studies
- Design an exclusive preclinical study in an animal model to study the signal

- Use of latest pharmacogenetic techniques including biomarker research to obtain quicker and specific answers

Possible outcomes after signal evaluation : Depending upon the strength of the signal, possible outcomes could range from no action at all to withdrawal of the drug from the market, with many intermediate actions in between. These are generally decided after a discussion with the regulatory authorities. Since every authority refers the matter to its own set of experts and also due to conditions typical to that population, the action may not be the same in all countries. The classic example is that of the antiamoebic Iodochlorohydroxyquin which is banned in major countries but is allowed to be marketed in India. Summary of possible actions is,

- No action if signal is of no consequence.
- If there is a level of uncertainity, there could be increased monitoring for that adverse event
- Change product information
  - Addition of new event
  - Modification of current wording
  - Addition of a frequency descriptor
- Restriction of use
- Withdrawal from the market or aborting development plans if not yet marketed
- Passing on Information of the change in prescribing information to all stakeholders like ECs, IRBs, doctors, regulatory authorities, licencee partners, consumers

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Dr. Vishwas Sovani, November 2012

Impact of new EU regulations

New pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) was adopted by the European Parliament and European Council in December 2010.This was accompanied by the implementing regulation # 520/2012, a legally binding act, published by the European Commission in 19 June 2012 that provides details on the operational aspects for the new legislation.

To help implementation, a new set of guidelines (Good PV Practice) for the conduct of pharmacovigilance in the EU is under development. These guidelines are organised into 16 modules, of which about 10 have been published

Together this has brought in a dramatic change in the handling of pharmacovigilance data and in the way Pharmacovigilance will be looked at in future. Although volumes can be written about each change implemented, here is a brief summary

Aims of the new legislation

Major aims of these new regulations are (2)

• To make roles and responsibilities clear, between the authorities, sponsors, licensees etc

• To minimise duplication of effort, as in dual reporting of the same AE by sponsor and licensee

• To free up resources by rationalising and simplifying adverse drug reaction (ADR) reporting and periodic safety update report (PSUR) reporting

• To establish a clear legal framework for post authorisation monitoring indicating when such a demand could be made and how it is expected to be fulfilled by the sponsor

Impact of the changes

Pharmacovigilance has changed from a passive discipline to a proactive one. Earlier sponsors used to report AEs in time and feel contented. The authorities, WHO Upsala center or other bodies, analysed available data and raised concerns to which sponsors responded by providing past data, creating additional data and agreeing to make changes in the package insert, product withdrawal being the last resort. Only on rare occasions did we find sponsors proactively discussing the product with authorities.

All this is about to change. PV plan including risk management plan will now be a part of every new drug applications. The sponsor will evaluate all data available till submission, evaluate the possible risks, point out gaps in data and provide a plan to manage the same. Risk management system will be part of every new application.

Post-authorisation safety and efficacy studies could be a condition for authorization if the available data so indicates. Earlier sponsors were not very enthusiastic about fulfilling these obligations, hence focused studies needed to evaluate certain risks did not happen in time.

Such studies, when asked for, will be mandatory. The marketing authorization will be conditional, based on completing these studies expeditiously. There is a provision of withdrawal of authorization for non compliance

PSURs to PBRERs

In keeping with the thought to reduce duplication, as far as EU is concerned, there will be a single assessment for the same active substance or a combination of active substances. So, various formulations and combinations of a molecule will be evaluated in one PSUR (Periodic Safety Update Report). For old established products and those with low risk, even the once in a few years reporting is not necessary. However if a safety concern arises, reporting will be required. Reporting will now be electronic, directly to the European Medical Agency (EMA) since a EU repository(Eudravigilance database) has been established(3)

The PSUR will now be called PBRER(Periodic Benefit Risk evaluation Report). The EMA is clearly asking the Marketing Authorization Holder(MAH) to shoulder the responsibility of evaluating the benefit risk of the product. This will be based on all available data, new and old, at every scheduled submission. EU directive of December 2010 states “As a result of the submission of all suspected adverse reaction data directly to the Eudravigilance database, it is appropriate to amend the scope of periodic safety update reports so that they present an analysis of the risk-benefit balance of a medicinal product rather than a detailed listing of individual case reports already submitted to the Eudravigilance database”(4)

The PBRER retains most of the basic elements of the PSUR .Compared to the PSUR, the PBRER has more information on:

- Clinical trials and observational studies
- Signals that are new, ongoing, or closed
- Risk evaluation and effectiveness of risk minimization
- Benefit evaluation
- Benefit-risk analysis for approved indications

The PBRER is a more comprehensive document The construction is modular so that sections can be used as is for other regulatory submissions e.g. risk management plan.

PV System Master File (PVSMF)

PVSMF is a detailed description of the pharmacovigilance system used by the MAH with respect to one or more authorised medicinal products. It need not be submitted along with marketing application but should be ready for review by authorities anytime . Over time, it will help do away with DDPS(Detailed Description Of Pharmacovigilance System). The file could exist electronically on various servers in the company but the company should be able to provide a soft or a hard copy of the PMF within 7 days if requested.

Elements of PVSMF

This file will be a one stop shop for all information related to pharmacovigilance in the company. Where is the QPPV(Qualified Person for Pharmacovigilance) located, the site(s) where the pharmacovigilance functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, PSUR production, signal detection and analysis, risk management plan management and regulatory status of various products. It will also cover computer systems, outsourcing agreements, quality systems and change logs (5)

Role of QPPV

The role of QPPV has now become much more important. Earlier he/she was only the responsible person for pharmacovigilance, but now he/she will be the custodian of the total pharmacovigilance process. He will oversee and manage the system, ensure compliance with requirements, operate a risk management system for each medicinal product , monitor the outcome of risk minimisation measures and monitor pharmacovigilance data to determine whether there are changes to the benefit-risk balance of medicinal products. If there is a change in the balance, ensure that appropriate action is taken.

Individual Case Safety Reports (ICSRs)

These are the basic elements in PV. Changes due to new regulations have been summarized in GVP module VI. Here are a few points in short.

The definition of adverse reaction has been modified to include response to normal dose as well as misuse and abuse, medication error, overdose and occupational exposure.

The MAH has to report all serious and non serious adverse reactions within the stipulated timelines. It is important to note here that relatedness is no longer relevant

The case is to be submitted electronically on Eudra Vigilance database, where it will be visible to various stakeholders. This will make the process transparent by making data available to all concerned parties, and also eliminate duplication.

An internationally standardised reporting format across regulators, with agreed terminologies, formats and standards is being generated to make data sharing and analysis easy.

Administrative guidance

Each member state will have its own pharmacovigilance system to be able to review the risk status of authorized products in the state. At the EMA level a Pharmacovigilance Risk Assessment Committee (PRAC) has been formed. Each state will nominate members to this committee. At the state level if any safety issue of concern is noticed the state will submit it to the EMA so as to have a union wide assessment of the issue through the PRAC. This committee will guide on all issues regarding pharmacovigilance.

In case of signals where urgent action is deemed necessary the PRAC may hold public hearings involving the MAH, and subject experts.

Even when the Committee for Medicinal Products for Human Use (CHMP) or the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) have to decide on any issue, they will take the views of the PRAC into consideration.(4)

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