

**REVIEW ARTICLE**ISSN:2394-2371
CODEN (USA):IJPTIL**A PROSPECTIVE REVIEW ON PHARMACOVIGILANCE PROGRAM****Dr. Vikram Kumar, Poornima Sharma***

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ABSTRACT

Pharmacovigilance, defined by the World Health Organization as ‘the science and series of activities relating to the detection, evaluation, understanding and avoidance of adverse effects or any other drug-related problem’ plays an important role in ensuring that patients be given safe drugs. The knowledge of a drug’s Adverse Drug Reactions (ADRs) can be augmented by various means such database studies, intensive monitoring, spontaneous reporting, and other new processes at dictatorial and a scientific level are being developed with the intention of escalation pharmacovigilance.

An increase in drug safety concerns in recent years with some high profile drug withdrawals have led to raising the bar by various stakeholders, more importantly by the regulatory authorities. The number of Adverse Drug Reactions (ADRs) reported, have also resulted in an increase in the volume of data handled. To understand pharmacovigilance a high level of expertise is required to rapidly detect drug risks as well as to defend the product against an inappropriate removal.

Proactive pharmacovigilance throughout the product life cycle is the way forward and the future direction for drug safety. It is a challenge to codify and standardize the act of signal detection and risk management in the context of clinical trials and post-marketing pharmacovigilance. While major advancements of the discipline of pharmacovigilance have taken place in the West, not much has been achieved in India. However, with more clinical trials and clinical research activity being conducted in India, there is an immense need to understand and implement pharmacovigilance. For this to happen in India, the mind set of people working in regulatory agency (DCGI Office) and the Indian Pharmaceutical companies need to change. This article describes and discusses the various strategies and proposals to build, maintain and implement a robust pharmacovigilance system for various stakeholders and eventually make it happen in India. The main objective of review is to unfold various aspects of pharmacovigilance including new methodological developments.

Keywords: - Pharmacovigilance, Adverse drug reactions, Adverse event.***Corresponding Author:****Poornima Sharma**Amity Institute of Biotechnology, Amity University
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Article Received on: 20-11-2015

Published on: 30-12-2015

INTRODUCTION

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.[1]

Pharmacovigilance is a very important and inseparable part of clinical research. Both 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. With a reasonably high number of recent high-profile drug withdrawals, both the pharmaceutical industry as well as various regulatory agencies across the globe have raised the bar. Early detection of signals from the post-marketing surveillance studies and clinical trials in early phases have now been adapted by major pharmaceutical companies in order to identify the risks associated with their medicinal product/s as early as possible. If any such risk is present then effectively managing the risks by applying robust risk management plans throughout the life cycle of the product is adopted. These risk management plans are also widely known as Risk Minimisation Programmes/Strategies. Thalidomide which is reintroduced for Multiple Myeloma and Leprosy reactions through S.T.E.P.S. programme (System for Thalidomide Education and Prescribing Safety) is a classical example. Signal detection and risk management/minimisation has added a new dimension to the field of pharmacovigilance

and has led it to be an evolving discipline; which requires ongoing refinement in order to increase its applicability and value to public health.

HISTORY OF PHARMACOVIGILANCE IN INDIA

It was not until 1986 that a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centres, each covering a population of 50 million, was proposed for India.[2] In 1997, India joined hands with the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. Three centres for ADR monitoring were identified, mainly based in teaching hospitals : A National Pharmacovigilance Centre located in the Department of Pharmacology, All India Institute of Medical Sciences(AIIMS), New Delhi and two WHO special centres in Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh Muslim University). These centres were to report ADRs to the drug regulatory authority of India. The major role of these centres was to monitor ADRs to medicines which are marketed in India. However, they hardly functioned as information about the need to report ADRs and about the functions of these monitoring centres were yet to reach the prescribers and there was lack of funding from the government. This attempt was unsuccessful

and hence, again from the 1st of January 2005, the WHO- sponsored and World Bank-funded National Pharmacovigilance Program for India was made operational.[3]

The National Pharmacovigilance Program established in January 2005, was to be overseen by the National Pharmacovigilance Advisory Committee based in the Central Drugs Standard Control Organization (CDSCO), New Delhi. Two zonal centres-the South-West zonal centre (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the North-East zonal centre (located in the Department of Pharmacology, AIIMS, New Delhi), were to collate information from all over the country and send it to the Committee as well as to the Uppsala Monitoring centre in Sweden. Three regional centres would report to the Mumbai centre and two to the New Delhi centre. Each regional centre in turn would have several peripheral centres reporting to it. Presently there are 24 peripheral centres.

INTERNATIONAL COLLABORATIONS:

To record and report adverse effects of drugs in different country patients is the main principal basis for the WHO International Drug Monitoring Program, through which over 90 member countries had send their reports to the Uppsala Monitoring Centre where they are

processed, evaluated and entered into the WHO International Database [4].

The **Uppsala Monitoring Centre** (the UMC), located in Uppsala, Sweden, is the field name for the World Health Organization Collaborating Centre for International Drug Monitoring. The UMC works by collecting, assessing and communicating information from member countries national pharmacovigilance programs in regards to the benefits, harm, effectiveness and risks of drugs.

EUROPE:

The national competent authorities (NCAs) coordinate and conduct the European Medicines Agency (EMA). The pharmacovigilance database of human and animals consisting of all suspected serious adverse reactions are maintained and developed by the EMA in the European Community and the system is called [EudraVigilance](#).

JAPAN:

Pharmaceuticals and Medical Devices Agency (PMDA) and Ministry of Health, Labour and Welfare (MHLW) regulate the pharmacovigilance in Japan.

UNITED STATES:

Three primary branches of pharmacovigilance in the U.S. include the FDA, the pharmaceutical manufacturers, and the academic/non-profit organizations.

SERBIAN:

To achieve the optimum number of 2000 spontaneous reports/year, regular contact with healthcare professionals, and finally Good Pharmacovigilance Practice is the final goal of the Serbian Pharmacovigilance System [5].

ADVERSE DRUG REACTIONS (ADRS)

An adverse drug reactions (ADRs) can be defined as an unintended and noxious responses to a health product which causes at the doses usually used or tested for the diagnosis, prevention or treatment of a disease or the alteration of an organic function.[6-8]

Though, it is difficult to recognize the causative agent related with the adverse drug reactions (ADRs) encountered because the medicinal preparations generally contain more than ingredients.[9] All drugs are capable of producing adverse drug reactions (ADRs) and whenever a drug is given a risk is taken.[10]

The magnitude of risk has to be considered along with magnitude of expected therapeutic benefit in deciding whether to use or not to use a particular drug in a given patient. The adverse drug reactions (ADRs) may develop promptly or only after prolonged medication or even after stoppage of drug. Adverse drug reactions (ADRs) are not rare; an incidence of 10- 25% has been documented in different clinical settings and are more common with the multiple drug therapy. Adverse drug reactions

(ADRs) have been classified in to two ways;

A. Predictable (Type-A) Reactions [9,11]

These are based on pharmacological properties of drug like augmented but quantitatively normal response to the drug which include side effects, toxic effects and consequences of drug withdrawal.

B. Unpredictable (Type-B) Reactions

These are based on peculiarities of patient and not on drug's known actions; include allergy and idiosyncrasy. They are less common, often non dose related, generally more serious and require withdrawal of drug.

**Adverse Drug Reactions (ADRs) Reporting/
Adverse Event (AE) Reporting**

Adverse Drug Reactions (ADRs) Reporting/
Adverse Event (AE) Reporting is the most commonly associated with Pharmacovigilance (PV) and consumes a considerable amount of resources of government agencies or drug regulatory authorities or drug safety departments in pharmaceutical organizations.[12] Adverse Event (AE) reporting includes the receipt, triage, data maintaining, evaluation, distribution, reporting of AE data.[13-15] The foundation of AE reports may include solicited reports from patient support programs, reports from clinical or post-marketing studies, spontaneous reports from healthcare professionals or patients or other intermediaries, reports from literature

sources, reporting is a regulatory requirement in most countries, reports from the media including social media and websites and reports reported to drug regulatory authorities themselves.[16] For pharmaceutical companies AE reporting also provides data that play an important in assessing the risk-benefit profile of a given drug. The following are several elements of Adverse Event (AE) Reporting: [17,18]

- An identifiable patient.
- An identifiable reporter.
- A suspect drug.
- An adverse event.

NEED OF PHARMACOVIGILANCE

The forceful marketing of new drug products by pharmaceutical companies and the consequential rapid disclosure over a short period of time of large numbers of patients to them necessitate the formation of a system for global assessment of drug safety concerns. These actions need an effective and efficient pharmacovigilance system that has been realized more than ever to make sure safe use of drugs. There are several rationales for increasing requirement of pharmacovigilance system. The bases of need are as follows: [15,17,19,20]

1. Untrustworthiness of pre-clinical safety information.

- Well-controlled environment.

- Appropriate and precise sample size.
 - Pressure from various systems to decrease time to authorization.
2. Altering pharmaceutical marketing policies. Aggressive marketing
 - Launch the drug in many countries at a time
 3. Varying physician's, patient's and other health professional's preferences
 - Increasing use of newer drugs
 - Increasing use of drugs to get better quality of life Shift of manage to self-administered treatment.
 4. Easy convenience
 - Growing conversion of prescription drugs to over the counter drugs
 - Easy access to drug information on the Internet.

According to International Conference on Harmonization Efficacy Guidelines 2 (ICHE2E) guidelines pharmacovigilance techniques can be categorized as:

Passive surveillance

- Spontaneous reporting system (SRS).
- Case series.

Stimulated reporting

I. Active surveillance

- (1) Sentinel sites
- (2) Drug event monitoring

- (3) Registries

II. Comparatives observational studies

- (1) Cross sectional study
- (2) Case control study
- (3) Cohort study

III. Targeted clinical investigations

- (1) Descriptive studies
- (2) Natural history of disease
- (3) Drug utilization study

Pharmacovigilance techniques can be also classified as hypothesis generation techniques and hypothesis testing techniques as follows:

I. Hypothesis generating techniques

- (1) Spontaneous ADR reporting
- (2) Prescription event monitoring

II. Hypothesis testing techniques

- (1) Case control study
- (2) Cohort studies
- (3) Randomized controlled trials

Most frequently used methods for monitoring of drug safety are as follows:

Spontaneous reporting systems (SRSs)

Spontaneous reporting systems involve the recording and reporting clinical observations of a suspected Adverse Drug Reactions (ADRs) with a marketed drug. It is also known as spontaneous or voluntary reporting. There are slight differences in this reporting system among the various countries but the ideology are the same. Safety of medicines is frequently monitored through spontaneous reporting

systems (SRSs). Moreover the standardized forms are used for reporting of alleged adverse drug reactions to the regulatory system by physicians, pharmacists, nurses and consumers as well. [10,12]

Prescription-event monitoring (PEM)

Prescription-event monitoring (PEM) is an observational cohort and non-interventional form of pharmacovigilance. Prescription-event monitoring (PEM) studies are cohort studies in which exposure is collected from a centralized service and outcomes from simple questionnaires finished by general practitioners. Moreover the follow-up forms are used for selected Adverse Events (AE). Prescription-event monitoring (PEM) captures all Adverse Events (AE) and the alleged drug reactions (ADRs). Prescription-event monitoring (PEM) cohorts potentially are different in deference to the distribution of number of Adverse Events (AE) per person depending on the character of the drug under study. [10,12,18,21]

LINKING PHARMACOVIGILANCE WITH PUBLIC HEALTH PROGRAMMES USING MEDICINES:

An important arm of patient carries Pharmacovigilance. Treatment or prevention of disease by use of medicines is the main aim of the Pharmacovigilance. Unfortunately some medicine will sometimes harm patient. For avoiding or minimizing harm associate with

medicines, good pharmacovigilance will identify the hazard aspects in the short period of time. Public Health Programmers (PHP) are intended to develop the health of target inhabitants by use of medicines, education, environmental modifications, nutrition involvement, behavioral changes and preventive actions such as immunization, hypertension and assessment for breast cancer are the important components of a PHP [21].

The systematized efforts of the public to care for and encourage people's health are known as Public health. Through mutual or community actions can be increase the health of all the people, this can be mainly done by the combination of sciences and skills.

In developing countries, agencies and health workers with a skill and proficiency conducts PHPs. In developed countries, patients have direct contacts with PHPs instead of usually contact with a physician. In developing countries PHPs, without proper instruction and training can lead to higher risks of adverse events, ADRs or medication error. These problems could be related to various syndromes, population characteristics, drugs, health-care providers or the health-care system. Sometimes use of the substandard products for the formulation of medicines creates many tragic results. By mistake death of more than 500 people, mostly children occurred when

diethylene glycol (DEG) when incorporated in pharmaceutical preparations. Federal Food, Medicine & Cosmetic Act passed by United State Congress in 1938, because of the DEG poisoning 105 people died in 1937. Acute renal failure was caused by DEG because it is a highly toxic organic solvent when ingested. Death of many people occurred because it was used as a diluent for sulfonamides.

Before launching new medicines in the market, it should be tested for toxicity. Number of children death occurred in 1998 due to the contaminated-DEG cough syrup in India but still toxicity due to DEG continues to appear [22].

The risks of adverse reactions, their diagnosis and reporting should be to know by the public health team and the PHP Manager. Serious and/or unexpected adverse reactions have been confidently deal by PHP Manager and should contribute to any subsequent decision-making process.

Due to some reason, pharmacovigilance is not mentioned as a part of public health which is as follows:

- Misunderstanding of the meaning o Intentions of the discipline;
- Deficiency of services for receipt,

- Administration and exploration of reports o Absence of a commentary culture.

To develop a complete understanding of the importance of pharmacovigilance, this document will help in encouragement of programme manager.

The aims of pharmacovigilance in PHPs are same as those of the national pharmacovigilance centre. These are:

- Health professionals should be knowledgeable for safe use of medicines;
- Evaluation of the hazards and efficiency of remedies used
- Educating and advising patients.

The control and treatment of tuberculosis, malaria, HIV/AIDS, schistosomiasis and immunization programmes provide by the Phamecovigilance. It is also essential in providing the necessary infrastructure for vital drugs programmes.

PHARMACOGENOMICS- A COMPONENT OF PHARMACOVIGILANCE:

For the treatment of different type of disorders, different classes of medication are available. A major issue in clinical world is that why particular person with particular disease respond to a particular drug or tolerate a drug well and other patient does not respond or can not tolerate the same drug. Due to difference in

genetic pattern, patient may respond differently to medication and develop different adverse effects [23].

Difference in drug response and drug tolerability can be understood by use of Pharmcogenomics and Pharmacogenetics. Many types of assumed ADRs are complex and involve or depend upon several factors which cause disease for examples it include the metabolic syndrome, suicidality, hepatic dysfunction and cardiac abnormalities. Pharmcogenomics and Pharmacogenetics are clinically substantial and are frequently associated with drug therapies, but they cannot be easily or completely recognized to a drug exposure. Individual who are susceptible to ADRs and has a potential to reduce the personal and population costs of drug related morbidity can be helped by Pharmacogenetics. The most common example of enzyme deficiency is glucose -6-phosphate dehydrogenase (G6PD) deficiency, with many of discrepancies. It is associated with acute haemolysis on exposure to oxidizing drugs such as primaquine, sulfonamides and sulfones. For G6PD deficiency phenotypic tests are recommended before using drugs such as primaquine, but it is not known how often this is carried out.

Although promising, the eventual impact of pharmacogenomics profiling for identification

of ADR susceptibility among individuals would depend upon incidence of drug toxicity, prevalence of variants severity of consequence and also the availability of rapid, reliable and cost effective assays. Several researchers have proposed the integration of genomic information with the pharmacovigilance database, which can not only enhance signal detection but also aid in determining whether genotypic examination should be performed prior to initiation of drug therapy. However, several key operational, regulatory, ethical and legal issues need to be addressed before the potential role of pharmacogenomics in ADR detection and prevention can be realized.

LINKING OF PHARMACO ENVIRONMENTOLOGY WITH PHARMACOVIGILANCE:

When drug administered orally in human or animal through the gastrointestinal tract drug may either be fully or poorly absorbed and along with through the feces unabsorbed drug will pass into the surroundings. When route of administration is parenteral or oral the drug may be metabolized to some amount and expelled into the surrounding areas (including through respired air) as main drug or its metabolites, or as a mixture of both. So if once they are inserted into the environment, they enter food chains and concentrate as they move to other life cycles^[9]. Insertion of elements or

remedies into the environment through anyway and at any attentiveness disturbing the balance of environmental science is called as Ecopharmacology (Ecosystem + pharmacology). If these drugs enter through living organisms via elimination subsequent to pharmacotherapy, it should be a specific field of pharmacology and not of environmental studies. This domain may be referred as Pharmacoenvironmentology [24].

Before proposing a new drug to market, it must be evaluated for the risk assessment and concentrations in the environment by FDA. The drug is assumed to cause acceptable risks when the risk valuation determines that the concentration will be less than billion. FDA has never turned down a proposed new drug based on estimated environmental concentrations, and no actual testing is conducted after a drug is marketed to see if the environmental concentration was estimated correctly. At given therapeutic doses of particular drugs, it is possible to find the adverse effects on environment. Same as clinical trials, we can also estimate drugs on environs is accomplished elaborately. Pharmacovigilance concerns to the undertakings adverse effects of medication at therapeutic doses on human and animal. At the therapeutic concentrations of given drugs, the frame work of Pharmacoenvironmentology may be an

enlargement of Pharmacovigilance which is allocating with the possessions related to the surrounding areas and ecosystem. Pharmacologists having this particular expertise (pharmacoenvironmentologist) may be is a compulsory component of the team assessing different aspects of drug safety. We need to monitor the effects of drugs not only as a good medical practice, but also to safe guard our environment.

BUILDING A NETWORK OF PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGISTS:

Pharmacovigilance and pharmacoepidemiology is relatively new fields in India, it is absolutely essential for a group of experts to come together to formulate guidelines for the set-up and implementation of relevant processes within pharmacovigilance. A core group will need to be formed which will have representatives from Indian pharmaceutical companies and personnel's from the regulatory authority. Epidemiologists, pharmacists and other people can also contribute to the development of the system [25].

LINKING PHARMACOVIGILANCE WITH ACADEMICS:

Good pharmacovigilance programmes needed for every country. In many developed countries pharmacovigilance is being taught in theory, but they should move toward the practical area.

Pharmacovigilance should ideally be taught to small groups of medical students, interns, postgraduates etc. Teaching of PV should be problem-based, activity-based and linked to the rational use of medicines. Students should be trained during their internship and residency and problem-based learning serve as hesitant blocks for the success of the concept. Pharmacovigilance can be taught at the under graduate course. Awareness of pharmacovigilance among doctors in their specialties and extending their support in teaching the subject should be created by Pharmacologists [26].

The clinicians and other healthcare workers should participate in spontaneous ADR reporting, during post-marketing observation from drug use in public. The knowledge and training of the clinicians will generate the quality of reports. Teaching pharmacovigilance to medical students makes them realize that all medicines can cause ADRs and their responsibility to participate in the national pharmacovigilance system.

A major source for pharmacovigilance to get information about drug is spontaneous reporting. Pharmacovigilance must be linked to component on the rational use of medicines (RUM). Pharmacovigilance course for pharmacologists and other healthcare personnel has been suggested by Uppsala Monitoring

Centre (UMC) and the international collaborating centre for ADR.

The UMC's training programme is a good starting point for a thorough knowledge of pharmacovigilance to postgraduate (PG) students and pharmacology. They should be active members of pharmacovigilance programmes in their medical colleges or teaching hospitals.

PG students should also be made aware of the need and importance of reporting ADRs and the reporting procedure.

Doctors (general practitioners and specialists) are important in reporting ADRs to the pharmacovigilance programme. Educated doctors in the community will increase the effectiveness of the reporting programme. Pharmacologists have an important role in creating awareness among doctors working in the community. Training programmes for doctors should be problem-based, activity-based and carried out in small groups. In Wales, a distance-learning programme in pharmacovigilance, linked to educational credits, was found to significantly improve the rate and quality of ADR reporting by general practitioners and pharmacists.

OBJECTIVES OF PVI:

The program has three broad objectives :

- The short-term objective is to foster a reporting culture,

- The intermediate objective is to involve a large number of healthcare professionals in the systems for information provision (reporting) and in information dissemination and
- The long-term objective is for the program to be a benchmark for global drug monitoring.

THE ENORMITY OF THE PROBLEM OF ADRS

A number of studies conducted throughout the world have demonstrated that ADRs significantly decrease the quality of life, increase hospitalizations, prolong hospital stay and increase mortality. A landmark study by Lazarou in 1998 described ADRs to be the 4th-6th leading cause of death in the US and ADRs are estimated to cause 3-7% of all hospital admissions[27]. More than half of these ADRs are not recognized by the physicians on admission and ADRs may be responsible for death of 15 of 1000 patients admitted[28]. To worsen the situation further, the financial cost of ADRs to the healthcare system is also huge. With more new medicines being approved for marketing more quickly without long-term safety studies by the regulatory authorities and switching of prescription-only medicines (POM) to over-the-counter (OTC) to be used more widely by patients for self-medication, the general public is at risk of exposing itself to ADRs. The scenario will

further be more ugly in our country where poverty, illiteracy, corruption and practicing by quacks is very rampant.

In past, India's regulatory agencies and drug companies based their safety assessments on experiences derived from long-term drug use in the Western markets and there was no real urgency for the government to establish a strong pharmacovigilance system of its own. In past few decades, however, the lag between when a drug is placed on the market and its subsequent availability in India has decreased considerably so that the much needed long-term safety data is no longer available. In addition, India-based drug companies have increased their capacity to develop and launch new drugs through their own R&D units and this has heightened the importance of developing adequate internal pharmacovigilance standards to detect adverse drug events.[29]

However, what needs to be more important along with the funding is a focussed vision and effective strategy for developing the pharmacovigilance systems, especially in the DCGI Office, which is lacking. Traditionally, pharmacovigilance was never done in India in Pharmaceutical companies, be it Indian or MNCs, so there is an immense shortage of knowledgeable people who will be able to advice the DCGI on this matter, as

pharmacovigilance is a very complex subject, intertwined with regulations and complex systems. The need is therefore to engage a completely independent adviser who has an extensive and practical knowledge on pharmacovigilance, who can act as a Pharmacovigilance Advisor to the Government of India to effectively implement the systems and policies on pharmacoovigilance. This will help the DCGI to spearhead the activities and implementation of pharmacovigilance.

India is a vast country and there is a surfeit of drug brands-more than 6,000 licensed drug manufacturers and over 60,000 branded formulations. India is the fourth largest producer of pharmaceuticals in the world and quite recently is also emerging as a clinical trials and health tourism hub. Many new drugs are being introduced in the country, so there is an immense need to improve the pharmacovigilance system so as to protect not only the Indian population from potential harm that may be caused by some of the new drugs but also the people from other countries coming to India for treatment purpose recently and those in other countries likely to receive medicines developed and manufactured in India. However, there are many issues and problems that have, over a long period of time, prevented building a robust pharmacovigilance system in India, which are described below :

- Pharmacovigilance systems are not well funded and organized for a vast country like India to serve patients and the public. The Drug Controller General of India (DCGI) Office which handles the pharmacovigilance system is embedded within the Ministry of Health and Family Welfare. Yet there is very little sharing of information on ADRs between the regulatory authority and health professionals. There is also an extreme shortage of qualified trained people to handle pharmacovigilance within the DCGI. The National Pharmacovigilance Program is at present running with the funding obtained from the World Bank, but there is no funding at all from the budget of the Health Ministry. However, what needs to be more important along with the funding is a focussed vision and effective strategy for developing the pharmacovigilance systems, especially in the DCGI Office, the will and strong commitment for which is lacking.
- The information obtained to date in the zonal centres from various peripheral centres is often poor and not well-analyzed. There is insufficient research on ADRs in India, so the exact incidence of specific ADRs is unknown. There are various local teaching hospitals in India that carry out some work on pharmacovigilance as part of postgraduate theses, but this is hardly shared with the regulatory authorities or other peer groups within the country. Nor do these hospitals inform the pharmaceutical manufacturer regarding the particular product and the ADRs. The reporting forms used by various people engaged in some pharmacovigilance work hugely differ from the reporting form used by the National Pharmacovigilance Program, which in turn becomes extremely difficult to transfer data to the national database, even if this has been shared by the various parties.
- Understanding by healthcare professionals (both in rural areas and urban cities and hospitals) and knowledge and motivation for pharmacovigilance itself is almost negligible. There is hardly any encouragement from the department of health to provide more training and create more awareness amongst them for better reporting.
- In India, there are several consumers' groups who encourage patients to report any adverse reactions encountered by them, although there is no information for patients to report ADRs directly to the

regulatory authority. Direct reports from the patients, who are the ones that actually experience ADRs, are not accepted by the monitoring centres and by regulatory authorities, as is the case in US. To add to this is the total lack of any awareness about ADRs in the general population.

- There is further lack of confidence or trust by healthcare professionals on reporting the ADRs either to the NPP or Pharmaceutical manufacturers and vested personal interest in reporting/publishing such ADRs only as interesting case reports.

With more and more clinical trials and other clinical research activities being conducted in India, there is an immense need to understand the importance of pharmacovigilance and how it impacts the life cycle of the product. Given this situation at present, the DCGI should act quickly to improve pharmacovigilance so as to integrate Good Pharmacovigilance Practice into the processes and procedures to help ensure regulatory compliance and enhance clinical trial safety and postmarketing surveillance.

Proactive pharmacovigilance : The way forward in India

A properly working pharmacovigilance system is essential if medicines are to be used safely. It will benefit all parties including healthcare professionals, regulatory authorities,

pharmaceutical companies and the consumers. It helps pharmaceutical companies to monitor their medicines for risk and to devise and implement effective risk management plans to save their drugs in difficult circumstances.

Having considered the problems and challenges facing the development of a robust pharmacovigilance system for India, we would like to make the following proposals :

Strategies and Proposals

- **Building and maintaining a Robust pharmacovigilance system**

So far, considerable work has been put in place by the dedicated staff at the DCGI to develop a robust pharmacovigilance system. But experience till date clearly points that this is not enough as more needs to be done to meet the challenges of ensuring that all data is captured and analyzed for rapid detection of signals and for putting effective measures in place to overcome the risks. The DCGI could go a step ahead to invite experienced private firms to help, train and set up the pharmacovigilance system to combat the problems of inexperience and shortage of trained personnel.

- **Making pharmacovigilance reporting mandatory and introducing pharmacovigilance inspections**

The Government of India's Health Ministry needs to pass a law and make Pharmacovigilance reporting mandatory. This should be valid not only for the multinational companies (MNCs) operating within India and the Indian Pharmaceutical Companies but also for various medical colleges and health care professionals in the country. A department for Pharmacovigilance Inspections should be incorporated within the DCGI with the view of starting inspections in all pharmaceutical companies operating in India. All pharmaceutical companies should be instructed to maintain and submit to the DCGI the Summary of Pharmacovigilance System document operating within the company, which would serve as the base for future pharmacovigilance inspections.

- **High-level discussions with various stakeholders**

A high-level discussion with various stakeholders, i.e., Ministry of Health, Indian Council of Medical Research(ICMR), Medical Council of India (MCI), Pharmacy Council, Nursing Council, Dental Council, Pharmaceutical Companies and their associations like Organization of Pharmaceutical Producers of India (OPPI), Consumer Associations,

non-governmental organizations (NGOs) working in this field and Patient Groups should be initiated in order to make them aware of how the DCGI is planning to improve and develop a robust system in pharmacovigilance and to understand and resolve their quires and problems.

- **Strengthen the DCGI office with trained scientific and medical assessors for pharmacovigilance**

Intensive training should be given in all aspects of pharmacovigilance to officials working within the pharmacovigilance department of the DCGI and the peripheral, regional and zonal centres. This should be an ongoing activity with training scheduled twice a year.

- **Creating a single country-specific adverse event reporting form to be used by all**

A single countrywide specific adverse event reporting form needs to be designed, which should not only be used by the National Pharmacovigilance Centres, but also by all registered hospitals (both private and government), teaching hospitals, Drug Information Centres and pharmacies throughout the country. It should also be made available to all primary healthcare centres (PHCs) in rural areas and all

practicing general practitioners and physicians. This can be done by incorporating approximately ten forms in say the monthly index of medical specialities (MIMS), which can be distributed to all healthcare professionals. Also, DCGI needs to make healthcare professionals aware of the website from which the form can be downloaded or filled up electronically (CDSCO website) and sent to the concerned official.

- **Creating a clinical trial and postmarketing database for SAEs / SUSARs and ADRs for signal detection and access to all relevant data from various stakeholders**

Create a central database for all protocols and clinical trials run within India along with clinical study reports and results (both for preclinical toxicology studies and clinical trials) across various therapeutic areas with specific registration numbers. Registration numbers should be given at the time of starting the trial and should cover both drug and nondrug therapies and be therapeutically aligned. It is worth noting that DCGI has recently started online registry of clinical trials in India, however these trials are neither classified into various therapeutic areas nor are the results or reports accessible.

Full data should be made available to the DCGI and also publicly from the date of first registration of the trial. This data should comply with consolidated standards of reporting trials (CONSORT) guidelines including overall benefit-risk profile of the product.

Current standards of safety reporting as outlined in schedule Y and information about all AEs and ADRs per study arm should be systematically included as well as detailed description of cases with previously unknown AEs / ADRs and the reasons for study withdrawals.

For drugs already in the market, type and frequency of all adverse events (serious and non-serious) should be submitted in periodic safety update reports (PSURs) and also added to the summary of product characteristics (SPCs).

- **List all new drugs / indications by maintaining a standard database for every pharmaceutical company.**

A list should be maintained by the regulatory authorities and pharmaceutical companies for all new drugs/indications in the database. All new issues need to be put under heightened surveillance. Pharmaceutical companies in these circumstances should have meetings set up with the DCGI to outline their risk

management plan (RMP) for the safety issues in question and describe how they would put effective strategies in place to mitigate them.

- **Education and training of medical students, pharmacists and nurses in the area of pharmacovigilance.**

There are several courses conducted by various organizations focusing in clinical research, but to date there is no course relevant to pharmacovigilance in the country. The various stakeholders including the MCI should incorporate a pharmacovigilance syllabus within the pharmacology and medicine curricula so that proper theoretical and practical training can be imparted to physicians. This will not only train young minds but also change the mindset for future reporting of ADRs when these doctors go into practice. Similarly, nurses and pharmacists should also be trained in pharmacovigilance so that they are able to recognize ADRs and develop a culture of reporting ADRs in the future.

For those healthcare professionals in rural areas where the need to recognize ADRs is more important, continuous medical education (CMEs) programs need to be conducted annually by the relevant professional councils. Newsletters developed by the DCGI in conjunction with

the relevant councils should be distributed and mailed to doctors, nurses and pharmacists posted to the primary healthcare centers (PHCs).

An awareness program and a training schedule (both by distance education and face-to-face learning) covering all aspects of pharmacovigilance have now been designed by many CRO's and universities including Maharashtra University of Health Sciences (MUHS) Nashik. These are meant for the R&D-based pharmaceutical companies, particularly those involved in new drug research, the medical professionals, the pharmacists and chemist-druggist traders and the patients, to be alert in detecting ADRs and reporting them to the Indian regulatory agencies, which in turn will investigate and take timely corrective action.

- **Collaborating with pharmacovigilance organizations in enhancing drug safety.**

With advancements in information technology, there has been the emergence of new opportunities for national [30] and international [8] collaborations that can enhance postmarketing surveillance programs and increase drug safety. The Uppsala Monitoring Centre,(UMC) of WHO, is an example for an international collaboration to establish a harmonized postmarketing

surveillance database.[31] The system is based on the exchange of adverse reaction information among national drug monitoring centres in 80 countries.

The information is transferred, stored and retrieved in a timely and secure way through the internet. The UMC database collectively contains over four million records with a large number of data fields.

The development of large population-based administrative databases has addressed several of the limitations that were associated with other types of data sources previously used in pharmacovigilance systems. These include problems with small sample size, wide variations in sample data and possible misclassification of outcomes. A similar database can be built for the DCGI with the help of experienced private firms from the safety data received from clinical trials and postmarketing surveillance.

- **Building a network of pharmacovigilance and pharmacoepidemiologists in India**

Pharmacovigilance and pharmacoepidemiology being relatively new fields in India, it is absolutely essential for a group of experts to come together to formulate guidelines for the set-up and implementation of relevant processes within pharmacovigilance. A core group

will need to be formed which will have representatives from MNCs, Indian pharmaceutical companies and personnel from the regulatory authority (e.g. DCGI). Epidemiologists, pharmacists and other like-minded people can also contribute to the development of the system.

- **Interaction with the IT sector in building a robust pharmacovigilance system for India**

India boasts of a highly developed IT sector. Since pharmacovigilance and pharmacoepidemiology deal with large numbers of ADRs, it would be wise for pharmacovigilance experts to collaborate with software professionals to develop and build a robust systems. Software programs developed can be used for collection and analyses of data sets, determining trends of drug usage in various disease areas, compliance, medication errors and drug interactions leading to ADRs. In specific areas where knowledge is inadequate, i.e., pregnancy, paediatric population, patients with liver and renal dysfunction and the elderly, pharmacokinetic software programs can help in optimizing drug dosages in individuals in various diseased conditions. This will be useful not only in rational drug therapy but would also be an important asset in therapeutics.

A step in this direction has already been taken by the DCGI, however the private interest of the IT firms are making things quite difficult for the DCGI office.

CONCLUSION

Pharmacovigilance is a complex process and robust systems are essential to undertake the activity. The foundation for building a robust pharmacovigilance system has already been done to some extent by the DCGI staff. However, the system needs to be refined with the help of pharmacovigilance experts in collaboration with information technology. With more and more clinical research now being conducted in India, it will be worthwhile for the DCGI to invest in a robust pharmacovigilance system, which will enable assessors and decision makers to analyze safety data and take regulatory decisions without the need to depend on other countries. DCGI should take some tough decisions and make commitments to make pharmacovigilance mandatory and start the culture of pharmacovigilance inspections.

Pharmaceutical companies will need to show both regulators and consumers that they are doing everything possible to assure drug safety, while finding more effective approaches to manage drug safety data. This will require the ability to pull and analyze data from adverse

event reporting systems in conjunction with other internal company data or external data sources to respond to any ad hoc safety queries or issues from the regulators. In order to do so, an integrated approach to AE data systems and pharmacovigilance along with appropriate business processes need to be developed and put in place. The companies need to be reassured that by reporting AEs and continuously monitoring for signals and developing risk management plans for products, they can actually still keep marketing their product.

Reporting of ADRs after marketing should be actively encouraged and should involve all those concerned including doctors, pharmacists, nurses, patients and pharmaceutical companies. To enhance and facilitate this, a culture of learning about pharmacovigilance should start early in the professional training of healthcare students. This will help healthcare professionals to understand the subject and also create awareness by giving adequate information to patients at the start of any treatment about the potential benefits and risks of the therapy.

India is now considered to be a hub for clinical research. The DCGI has shown its commitment to ensure safe use of drugs by establishing the National Pharmacovigilance Program. More and more clinical trials are now being

conducted in India and business process outsourcing (BPOs) based in India are now also undertaking pharmacovigilance projects from MNCs. Healthcare professionals, consumer groups, NGOs and hospitals should appreciate that there is now a system in place to collect and analyze adverse event data.

They should start reporting adverse events actively and participate in the National Pharmacovigilance Program to help ensure that people in India receive safe drugs. With the help of all stakeholders, let us pledge to make this happen in India and build a world-class pharmacovigilance system. We can surely make this happen if we work together!

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