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Pharmacovigilance: An Overview

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ABSTRACT

Pharmacovigilance is defined as the pharmacological science that is relating to the detection, assessment, understanding, prevention of adverse effects, particularly the long term &short term adverse effects of medicines. The Pharmacovigilance is the important and integral part of clinical research. This article describes and discusses the aims, objectives, role, need for the Pharmacovigilance, different Pharmacovigilance programme, various Pharmacovigilance methods, Pharmacovigilance reporting and functioning.

Keywords: Pharmacovigilance, adverse effects, clinical research

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INTRODUCTION

Pharmacovigilance is an important and integral part of clinical research [1]. Both the clinical trials safety & the post marketing pharmacovigilance are critical throughout the product lifecycle. Pharmacovigilance is "defined as the pharmacological science relating to the detection, assessments, understanding &the prevention of adverse effects, particularly the long term & short term adverse effects of the medicines. The Pharmacovigilance is still in its infancy inIndia & there exists very limited knowledge about the discipline. While major advancements of discipline of the Pharmacovigilance have taken place in the western countries but not much has been achieved in India. There is more need to understand the importance of the Pharmacovigilance & how it impacts the lifecycle of the products. This will enable integration of the good pharmacovigilance practice in the process and procedures to help ensure the regulatory compliance and enhance the clinical trials safety & post marketing surveillance. The Pharmacovigilance is not new to India and has been going on from 1998 [2]. It is widely accepted that the drug has to go through various phases of clinical trial to establish its safety & the efficacy before it is marketed commercially. However, the clinical trials offers the various limitations like strict criteria of inclusion & exclusion make it to be used in a very selective group of the patients & special population groups like children, pregnant woman, and old age population are not studied during the trials & the other factors causing drug reactions such as the genetic factors, environmental factor & the drug-drug interactions may not have been studied during the clinical trials [3]**.** Hence, the need of pharmacovigilance has been demanded, which include the detection, assessments & prevention of adverse drug reactions in humans[4-5]**.** Moreover, its concerns have been widened to include the traditional & the complementary medicines, the herbal drug products, blood products & the biological, medical devices & the vaccines. In addition, the Pharmacovigilance possess various roles like identification, quantification & the documentation of drug-related problems, which are responsible for the drug related injuries[6-7]**.** Further, national pharmacovigilance programmes have been introduced which occupies a prime role in increasing the public awareness about the drug safety[8-9]. This review article discusses about the need & objectives of the pharmacovigilance in day-to-day lives. Additionally, the various adherents & followers of the pharmacovigilance have been argued in the present review.

Aims of Pharmacovigilance

a. Improve patient care and safety in relation to the use of medicines & all medical and Para-medical interventions [10].

b. The Research efficacy of drug & by monitoring the adverse effects of drugs right from the lab to the pharmacy & then on for many years.

c. The Pharmacovigilance keeps track of any drastic effects of drugs.

d. Improve public health and safety in relation to the use of medicines.

e. Contribute to the assessment of the benefit, harm, effectiveness & the risk of medicines, encouraging their safe, rational & more effective (including cost-effective) use.

f. Promote understanding, education and clinical training in Pharmacovigilance and its effective communication to the public. The processes involved in the clinical development of medicines. Once put into the market, a medicine leaves the secure and protected scientific environment of clinical trials & is legally set free for consumption by the general population. At this point, most of the medicines will only have been tested for short term safety and efficacy on a limited number of carefully selected individuals. In some cases as few as 500 subjects & rarely more than 5000 will have received the product prior to its release. For good reason, it is essential that new & medically still evolving treatments are monitored for their effectiveness &the safety under real-life conditions post release. The More information is generally needed about the use in specific population groups, pregnant women, notably children and the elderly &about the efficacy & the safety of chronic use, especially in combination with other medicines[11].The Experience has shown that many adverse effects, interactions (i.e. with foods or other medicines) & the risk factors come to light only during the years after the release of a medicine.

Objectives

Improvement of the patient care &the safety in relation to the use of medicines with medical &paramedical interventions remains to be an important parameter. The important objectives of the pharmacovigilance involve exhibiting the efficacy of drugs by monitoring their adverse effect profile for many years from the lab to the pharmacy, tracking any drastic effects of the drugs improving public health & the safety in relation to the use of medicines, encouraging the safe, rational & cost-effective use of drugs, promoting understanding, education & the clinical training in the pharmacovigilance & effective communication to the generic public. [14] In addition, providing information to consumers, the practitioners & regulators on the effective use of drugs along with designing programs & the procedures for collecting &analyzing reports from the patients & the clinicians conclude to the objectives of the pharmacovigilance studies. [13, 14]

Roles of Pharmacovigilance

The Pharmacovigilance has been widely accepted to possess a significant role in early observation of the risk associated with the drug. All the medicines are tested on a concerned small ratio of the

population before it is approved for the post-marketing surveillance. The Pharmacovigilancehas been known to possess various roles like identification, quantification & the documentation of drug-related problems & contribution towards reducing the risk of drug-related problems in healthcare systems &enhancement of the knowledge & understanding of factors & the mechanisms which are responsible for the drug related injuries. [15] However, in order to fulfill the various roles of the pharmacovigilance the interactions & the influence of many stakeholdersin society with the decision-making powers has been required, which include the politicians at national, regional & local levels, healthcare administrators, drug regulatory authorities, pharmaceutical companies, healthcare professionals like the physicians, dentists, pharmacists & nurses, the academic institutions, media representatives, health insurance companies patient group& the lawyers. [16]

Need of Pharmacovigilance

It is widely accepted that the clinical development of medicines is a complex process which require huge amount of time for its completion. Once a drug is marketed, it leaves the secure & the protected scientific environment of clinical trials & is free for consumption by the general public. At this point, most of the medicines will only have been tested for short-term safety & the efficacy on a limited number of carefully selected individuals. Hence, the need of pharmacovigilance arises which include securing the early detection of new adverse reactions or the patients subgroups of exceptional sensitivity &introducing certain measures in order to manage such risks. Moreover, it is essential that new and medically still evolving treatments are monitored for their effectiveness & the safety under real-life conditions after being marketed. Furthermore, more information is generally needed about use in specific population groups like children, pregnant women and the elderly, about the efficacy and safety of chronic use in combination with other drugs. Numbers of adverse effects, drug-interactions and risk factors have been reported later in the years of drug release.[17]

PHARMACOVIGILANCE PROGRAMME

The national pharmacovigilance system plays an important role in increasing public awareness of the drug safety. However, the minimum requirements for a functional national pharmacovigilance system are required which include a national pharmacovigilance center with the designated staff, stable basic funding, clear mandates, well defined structures , roles & collaborating with the WHO programme for the international drug monitoring & the existence of a national spontaneous reporting system with a national individual case safety report (ICSR) form, a national database or system for collating & managing the adverse drug reaction reports, a national pharmacovigilance

advisory committee able to provide the technical assistance on causality assessments, risk assessments, risk managements, case investigations & a clear communication strategy for routine communication & crises communication. [18-20] However, the national pharmacovigilance system has been known to exhibit the various functions which include, promoting the pharmacovigilance in the country inAnkurRohilla,[21] order to collect & manage the adverse drug reaction, reporting of medication errors &suspected substandard drugs, collaborating & harmonizing with existing adverse reaction collection activities within the country, identifying signals of medicine safety, undertaking assessment of the risk & options for the risk management, identifying the possible quality problems in medicines resulting in the adverse reactions, supporting the identification of medicine quality issues, providing effective communication on aspects related to the medicine safety, applying resulting information from the pharmacovigilance for the benefit of public health programmes, individual patients & the national medicines policies & the treatment guidelines, developing & maintaining the drug utilization information & identifying issues associated with unregulated prescribing & dispensing of the medicines. [22, 23, 24]

National Programme of Pharmacovigilance

The experience of products, safety &the efficacy is limited to its use in the clinical trials which are not reflective usually of practice conditions as they are limited by the patient numbers & the duration of trial as well as by the highly controlled conditions in which Clinical Trials are conducted before the product is being marketed. The condition under which the patients are studied at the pre- marketing phase does not reflect necessarily the way; the medicines will be used in the hospital or in the general practice once it has been marketed. Information about rare but the serious chronic toxicity, adverse drug reactions, use in special groups e.g. pregnant women, children, elderly & the drug interactions is often incomplete or may not be available. Certain ADR's may not be detected until the very large numbers of the people have received the medicine. The Pharmacovigilance is therefore one of the important post-marketing tools in ensuring the safety of pharmaceuticals & related health products.

i. Assessing the risks & benefits of the medicines in order to determine if any, what action, is necessary to improve their safe use.

ii. Providing information to users to optimize the safe & effective use of the medicines

iii. Monitoring the impact of any action taken.

National pharmacovigilance centers are responsible for:

a. Promoting the reporting of the adverse reactions

b. Collecting case reports of the adverse reactions

c. Clinically evaluating case reports

d. Collecting, analyzing& evaluating patterns of the adverse reactions

e. Distinguishing signals of the adverse reactions from noise

f. Recommending or taking regulatory action in response to findings supported by the good evidence

g. Initiating the studies to investigate the significant suspect reactions

h. Alerting prescribers, manufacturers & the public to new risks of the adverse reactions

i. Sharing their reports with the WHO Programme for International Drug Monitoring.

National centres have plays a significant role in increasing the public awareness of issues relevant to the safety of medicines. As a result, in some countries, the pharmacovigilance is increasingly being seen as much more than the regulatory activity as it also has a major part to play in the clinical practice &development of public health policy. These developments are partly attributable to the fact that many national & the regional centres are housed within the hospitals, medical schools or poison & the medicine information centres &is in collaboration with a Medicines Regulatory Authority [MRA]. The scope of activities of national centres has expanded to include the communication of information about the benefits, harm & the effectiveness of medicines to the practitioners, patients & the public. The Central Drugs Standard Control Organization [CDSCO] is initiating a countrywide pharmacovigilance programme under the aegis of the DGHS the Ministry of Health & Family Welfare, and Government of India. The programme shall be coordinated by the National Pharmacovigilance Centre at CDSCO. The National Centre will operate under the supervision of the National Pharmacovigilance Advisory Committee to recommend the procedures & the guidelines for regulatory interventions. [25]

TERMINOLOGY

Individual Case Safety Report (ICSR)

A report that contains the information describing the suspected adverse drug reaction which is related to the administration of one or more medicinal products to the individual patient. [26]

Medical error

“An unintended act either of commission or omission or one that does not achieve itsintended outcomes.” [27]

Table:1; Terminology's used in Pharmacovigilance

Term	Definition	Reference
Adverse event	The adverse event can be defined as any un toward medical occurrence that may be present during the treatment with the drug but which do not necessarily have the relationship with its use.	**28**
Safety signals	The Safety signal means to a concern about an excess of the adverse events compared to what would be expected to be associated with the products use that can arise from the post marketing data and the other sources, such as the pre clinical data and the events that are associated with other products in the same pharmacological class.	**29**
Post marketing surveillance	The Post-marketing surveillance is the practice of monitoring the safety of the pharmaceutical drug or a device after it has been released in the market.	**30**
Adverse drug reaction	An adverse drug reaction is any unwanted, unintended & undesired effect of the drug, which occurs at the dose used in the human for diagnosis, prophylaxis, therapy or modification of the physiological functions.	**31**
Clinical trials	The Clinical trials are the sets of tests in the medical research and the drug development that generates safety and efficacy data for health interventions [For e.g., drugs, diagnostics, devices, therapy protocols].	**32**

Terms commonly used in drug safety:

The Pharmacovigilance has its own unique terminology that is necessary to understand. Many of the following terms are used within this article

Dechallenge and Rechallenge refers to the drug being stopped & restarted in the patient, respectively. The positive dechallenge has occurred, for e.g., when an adverse event resolves or abates completely following the discontinuation of the drug. The positive rechallenge occurs when the adverse event re-occurs after the drug has been restarted. Dechallenge & rechallenge play an important role in determining whether the causal relationship between an event & the drug exists.

Benefitsis commonly expressed as the proven therapeutic good of the product but it should also include the patient's subjective assessment of its effects.

The Causal relationship is said to exist when the drug is thought to have contributed or caused to the occurrence of an adverse drug reaction.

• The **Risk** is a probability of the harm being caused usually it is expressed as the percent or the ratio of the treated population.

• The **Control group** is the group of individual patients that is used as the standard of comparison within the clinical trials. The control group may be taking a placebo [in which there is no active drug is given] or where the different active drugs are given as the comparator.

• The **Effectiveness** is a extent to which the drug works under clinical practices that is real world circumstances.

•The **Temporal relationship** is said to be exists when an adverse event occurs when the patient is taking the given drug. Though the temporal relationship is absolutely necessary in order to establish the causal relationship between a drug & the Adverse Event, the temporal relationship does not necessarily in & of itself prove that the event was caused by the drug.

•The **Efficacy** is a extent to which the drug works under clinical trials that is under ideal circumstances.

• The **Harm** is the extent & nature of the actual damage that could be or has been caused.

• The **Implied causality** refers to spontaneously reported Adverse Event cases where a casualty is always presumed to be positive unless the reporter states otherwise.

• The **Individual Case Study Report** [ICSR] is the adverse event report for an individual patient.

• The **Life threatening** refers to the adverse event that places the patient at the immediate risk of death.

• The **Event** refers to the adverse event.

•The **Phase** refers to the 4 development phases: I - Early on in the drug's development the small safety trials are done; Phase II - For both safety & efficacy the medium-sized trials are carried out; Phase III - It includes key [pivotal] trials that is large trials & Phase IV - Typically for the safety reasons the large, post-marketing trials are carried out. There are also intermediate phases designated by the ‘a’ or ‘b’ for example Phase IIb.

• The Risk factor is the attribute of the patient that may increase the risk of that patient developing an event that may be or may not be drug-related. For example, the obesity is considered the risk factor for the number of different diseases & potentially the ADRs. Others would be the higher blood pressure, diabetes possessing the specific mutated gene for e.g., mutations in the BRCA1 & BRCA2 genes increase the propensity to develop the breast cancer.

• The **Triage** refers to the process of placing the potential adverse event report into one of the following 3 categories: i) non-serious case; ii) serious case; or iii) no case [minimum criteria for an Adverse Event cases are not fulfilled].

• The **Signal** is the new safety finding within safety data that requires further investigation. There are 3 categories of signals: i) The confirmed signals where the data indicate that there is the causal relationship between the drug and the Adverse Event ii) refuted [or false] signals where post investigation the data indicates that no causal relationship exists & iii) unconfirmed signals which

require further investigation [more data] such as the conducting of the post-marketing trials to study the issue.[33]

PHARMACOVIGILANCE METHODS

As per International Conference on Harmonization Efficacy Guidelines 2 (ICHE2E) guidelines, the pharmacovigilance methods can be categorized as:

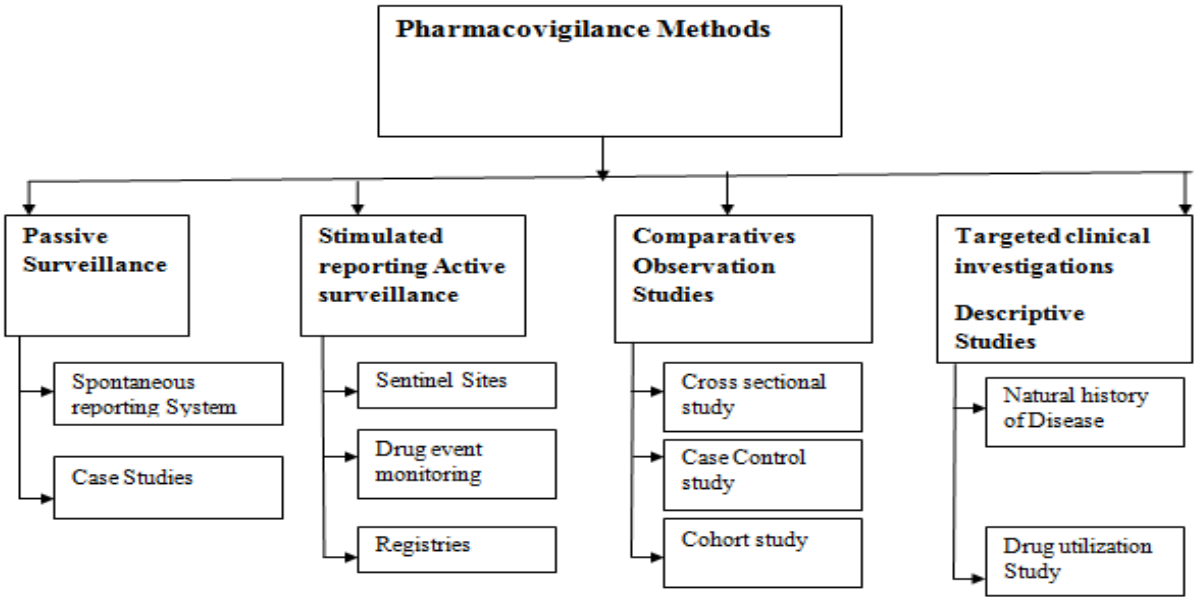

Figure1: Different Pharmacovigilance Methods

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

Spontaneous reporting systems

Recording and reporting clinical observations of a suspected ADR with a marketed drug is known as spontaneous or voluntary reporting[34]. There are subtle differences between countries but the principles are the same. The national system based on this in the UK is the 'Yellow Card' scheme, where doctors, dentists, and recently, hospital pharmacists are encouraged to report all suspected reactions to new medicines and serious suspected reactions to established medicines. Safety of medicines is commonly monitored through spontaneous reporting systems [35]**.** Standardized forms are used for reporting of suspected adverse reactions to the regulatory authorities by medical professionals, including physicians, pharmacists, nurses and in some countries, by consumers. The reports are of 'suspected' adverse reactions, and a reporter does not have to confirm the association between drug and effect. [36] Spontaneous reports are more likely to be effective where products are regulated as medicines and also where products are supplied by health professionals, who are well informed in the use of this reporting system. Consumers may not be aware of the importance of reporting adverse effects.[37] Spontaneous reporting of adverse drug reaction and adverse events is

an important tool for gathering the safety information for early detection, case reports collected by such system represent the source of information providing the lowest level of evidence and highest level of uncertainty regarding casualty.[38] Spontaneous reporting has advantages in that it is available immediately after a new product is marketed, continues indefinitely and covers all patients receiving the drug. It is the most likely method of detecting new, rare ADRs and frequently generates safety signals which need to be examined further.[39] The main limitations are the difficulty in recognizing previously unknown reactions, particularly events that are not usually thought of as being ADRs and under-reporting, which is variable, sensitive to reporting stimuli and difficult to quantify. It usually does not confirm hypotheses; although situations exist where spontaneous reporting data alone allow conclusions that a signal indeed represents a true ADR. [40]

Prescription-event monitoring (PEM)

PEM is a non-interventional, observational cohort form of pharmacovigilance. PEM studies are cohort studies where exposure is obtained from a centralized service and outcomes from simple questionnaires completed by general practitioners. [41] Follow-up forms are sent for selected events. Because PEM captures all events and not only the suspected ADRs, PEM cohorts potentially differ in respect to the distribution of number of events per person depending on the nature of the drug under study. This variance can be related either with the condition for which the drug is prescribed (e.g. a condition causing high morbidity will have, in average, a higher number of events per person compared with a condition with lower morbidity) or with the drug effect itself. [42]. When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamics and pharmacokinetics studies might be conducted to determine whether a particular dosing instruction can put patients at an increase risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore specific studies to investigate potential drug-drug interactions and food-drug interactions needs to be conducted based on the pharmacological properties and the expected use of the drug in general practice. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.[43]

Risk Management

The Risk Management is the discipline within the Pharmacovigilance that is responsible for the signal detection & the monitoring of the risk-benefit profile of the drugs. Other key activities within the areas of the Risk Managements are that of the compilation of Risk Management Plans

[RMPs]& aggregate reports such as the Periodic Safety Update Report [PSUR], Periodic Benefit Risk Evaluation Report [PBRER]& the Development Safety Update Report [DSUR].

Causality Assessment

One of the most important & challenging problems in the Pharmacovigilance is that of the determination of the causality. The Causality refers to the relationship of the given adverse event to the specific drug. The determination of Causality [or assessment] is often difficult due to the lack of clear-cut or reliable data. While one may assume that the positive temporal relationship might 'prove' a positive causal relationship this is not always the case. Indeed, the 'bee sting' AE—where the AE can clearly be attributed to the specific cause- is by far the exception rather than the rule. This is because of the complexity of the human physiology as well as that of the disease & illnesses. By these calculations, in order to determine the causality between an adverse event & the drug one must first exclude the possibility that there were other possible causes or contributing factors. In addition, if the patient is on a variety of the medications it may be the combination of these drugs which causes the Adverse Events& not anyone individually. There have been a variety of recent high profile cases where the AE lead to the death of an individual. The individuals were not overdosed by taking any one of the many medications but the combinations there appeared to cause the adverse event[AE]. Thus it is more important to include in one's AE report not only the drug being reported but also the patient was taking all other drugs. For instance, if the patient was to start Drug X & then 3 days later was to develop the Adverse Event one might be tempted to attribute blame the Drug X. However, the patient's medical history would need to be reviewed to look for possible risk factors for the AE before doing that. In other words, did the AE occurs with the drug or due to the drug. This is because the patient on any drug may develop or be diagnosed with the condition that could not have possibly been caused by the drug. This is especially true for the diseases like cancer which develops for an extended period of time, being diagnosed in the patient who has been taken the drug for the relatively short period of time. On the other side, certain adverse events such as blood clots [thrombosis] can occurs with certain drugs with only short-term exposure. The determination of risk factors is an important step of confirming or ruling-out the causal relationship between an event & the drug. Often the only way to confirm the existence of the causal relationship of an event to the drug is to conduct the observational study where the incidence of the event in the patient population taking the drug is compared with the control group. This could be essential to determine if the background incidence of the event is less than that found in a group taking the drug. If the incidence of an event is significant statistically is higher in the 'active' group versus the placebo group [or other control

group], it is possible that the causal relationship may exist to the drug, unless other confounding factors may exist.

Signal Detection

The signal detection [SD] involves the range of the techniques [CIOMS VIII]. The WHO defines the safety signal as; 'Reported information on the possible causal relationship between an adverse event and the drug, the relationship being unknown or documented previously incompletely'. Usually more than the single report is to be required to generate the signal, depending upon the event & the quality of the information available. The data mining pharmacovigilance databases is one of the approach that has become increasingly popular with the availability of the extensive data sources & inexpensive computing resources. The databases [data sources] may be owned by the pharmaceutical company, the drug regulatory authority, or the large healthcare provider. Individual Case Safety Reports [ICSRs] in these data sources are retrieved and converted into the structured format & the statistical method [usually the mathematical algorithm]is applied to calculate the statistical measures of the association. If the statistical measure crosses an arbitrarily set threshold, the signal is declared for the given drug associated with the given adverse events. All the signals deemed worthy of the investigation requires further analysis using all the available data in an attempt to confirm or to refute the signal. Additional data may be needed such as a post-marketing observational trial if the analysis is inconclusive. The SD is an important part of the drug use & safety surveillance. The aim of SD is to identify the ADRs that were considered previously unexpected & to be able to provide guidance in the labeling of product's as to how to minimize the risk of using a drug in the given population of patient.

Risk Management Plans

The Risk Management Plan (RMP) is the documented plan that describes the risks [adverse drug reactions and potential adverse reactions]that is associated with the use of the drug & how they have being handled [warning on the drug label or on the packet inserts of the possible side effects which if it is observed the patient should inform his physician or the pharmacist or the manufacturer of the drug or the FDA]. Once the drug has been marketed the overall goal of the RMP is to assure the positive risk-benefit profile. The document is required to submit in the specified format with all the new market authorization requests within the European Union. Though it is not necessarily required that RMPs may also be submitted in countries outside the EU. The risks described in the RMP fall into one of the following 3 categories: Unknown Risks, Identified Risks and Potential Risks. Other measures described within an RMP are the measures that the Market Authorization Holder usually to minimize the risks associated with the use of the

drug, the pharmaceutical company has to undertake. These measures mainly focus on the product's labeling and the healthcare professionals. In fact, the risks that are documented in the pre-authorization RMP will necessarily become part of the product's post-marketing labeling. Hence the drug, once authorized, may be used in the ways not originally studied in the clinical trials, this potential 'off-label use', and risks associated to it, is also described within the RMP. RMPs would be very lengthy documents, in some cases it would be running hundreds of pages & in very rare cases, up to the thousand pages long. In United States, under certain conditions, the FDA may require the company to submit the document called as Risk Evaluation & the Mitigation Strategies for the drug that has the specific risk that FDA believes requires Mitigation. While not as comprehensive as the RMP, the REMS can require the sponsor to perform the certain activities or to follow the protocol, referred as Elements to Assure the Safe Use [ETASU], [44] to assure that the positive risk-benefit profile for a drug is maintained for the conditions under which the product is being marketed.

Risk/Benefit Profile of Drugs

The Pharmaceutical companies are required by the law in most of the countries to perform the clinical trials, testing of new drugs on people before they are made generally available. This occurs after the drug has been pre-screened for its toxicity, sometimes using the animals for the testing. The manufacturers or his agents usually select a representative samples of patients for whom the drug has been designed -at most a few thousand – along with thecomparable control group. A control group may receive the placebo or another drug, often a so-called 'gold standard' that is the 'best' drug marketed for the disease.

The main aim of clinical trials is to determine the:

a) if the drug works and how well it will work

b)if it has any adverse harmful effects,

c) if it does more good than the harm, and how much more? If it has a potential to harm, how probable and how serious willit harm?

The clinical trials when done in general, tells a good deal about how well the drug works & what potential harm it may cause. They provide the information that should be reliable for the larger populations with the same characteristics as that of trial groups - age, gender, state of health, ethnic origin etc. The variables in the clinical trial are specified and controlled, but the clinical trials can never tell you the whole story of the effects of the drug in all the situations. The fact is that nothing could tell you the whole story, but the clinical trial must tell you enough "Enough" being determined by legislation and by contemporary judgments about the acceptable balance of the

benefits & harms. Ultimately, when the drug is marketed it may be used in patient populations that were not studied during clinical trials [children, the elderly, pregnant women, patients with co-morbidities not found in the clinical trial population, etc.] & the different set of warnings, precautions or contraindications [where the drug should not be used at all] for the product's labeling may be necessary in order to maintain a positive risk/benefit profile in all known populations using the drug. [45]

PHARMACOVIGILANCE: REPORTING AND FUNCTIONING

To fulfill the pharmacovigilance obligations for its marketed products as per regulations, a pharmaceutical company in India has to essentially carry out activities such as collection which included expedited reporting of the serious unexpected adverse reactions and preparations. [46] A typical setup for pharmacovigilance studies, people involved on various levels, organizational units and their functions are given as Figure. 2.

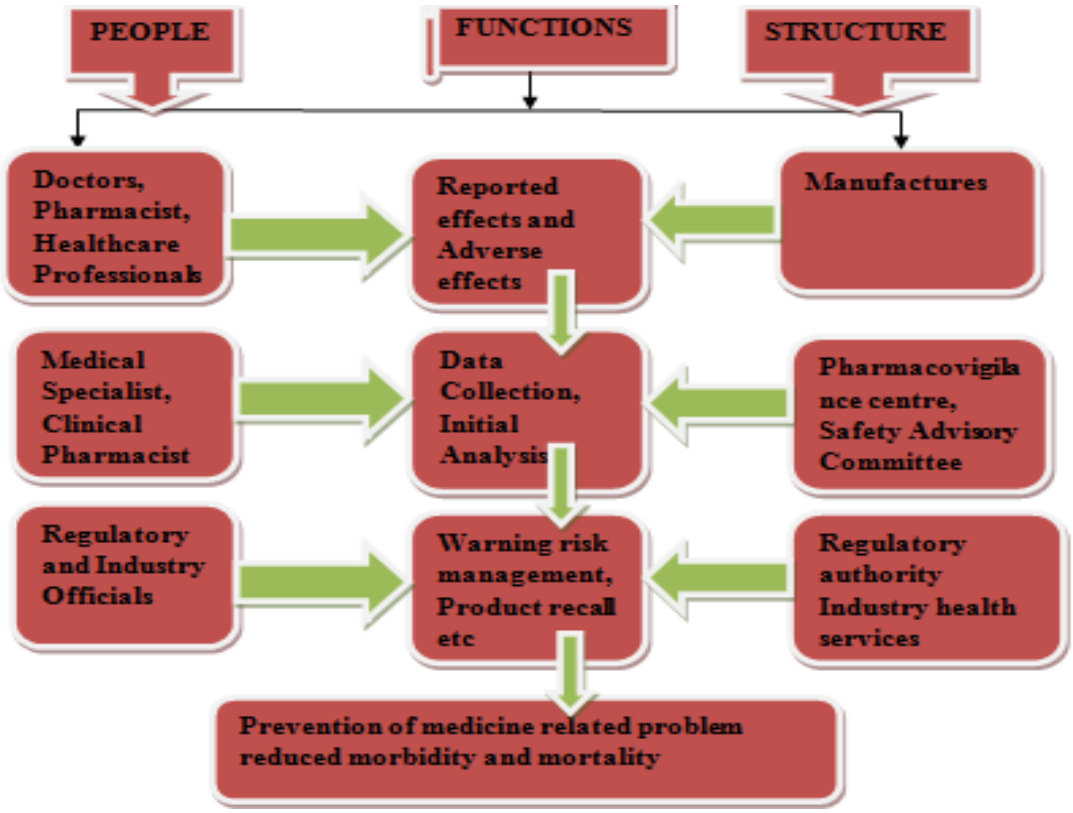

Figure 2: A typical pharmacovigilance setup: People involved, functions & structure

Detection and reporting

The Physician plays an important role in pharmacovigilance. This is because the physician is the first person to who the patient will come with the symptoms; but also to suspect an adverse drug reaction. [47] The healthcare professionals or the marketing authorization holder reports the suspected adverse drug reaction which is related to one or more medicinal products, to the national

competent authority [the pharmacovigilance center]. The Reports are made in written form [for e.g. by using report forms], by electronic or by telephone or by any other way that is approved. [48] The Reports are collected and then validated by the pharmacovigilance centre & are usually entered into the database. The Serious reactions should be handled with the higher priority. The database is used to identify the potential signals and analyze the data in order to clarify the risk factors, the apparent changes in reporting profiles.[49]**.** A typical ADR reporting form is given.

Case report collection and validation

This concerns the collection and the validation of the primary data that is the data transmitted from the reporter to the competent authority. For the validation and the management of the reports that are transmitted electronically, the specified operational procedure should be followed.[50] The pharmacovigilance spontaneous report concerns the single case as one patient, one identifiable reporter, one or more of the suspected reactions, and one or more of the suspected medicinal products. In accordance to the European Directives and Regulations, only the serious cases reported by healthcare professionals will be received on an expedited basis.[51]

PHARMACOVIGILANCE IN INDIA

The need

Though in India the clinical trials is being conducted & started in 1996 in the global market, year of landmark for the industry was 2005. The clinical trials studies are structured, supervised where the efficacy & the safety of a new drug or therapy are tested in an effort to develop new treatments that will help those afflicted with the targeted condition. For conducting the global clinical trials, India is looked upon as a better choice.[52] Indian clinical market provides an opportunity of availability of highly educated talents, large patient populations, lower operations cost, a wide spectrum of disease & a favourable economic &the intellectual property environment. In the current time, the clinical research industry has grown around the world at an unbelievable rate with the pharmaceutical industry. The main survival amount of the pharmaceutical companies is innovation through introducing the new drugs in the market. [53] For the approval, well organized, supervised & structured clinical trials have to be essentially conducted as per ICH GCP guidelines in accordance with the defined rules of the country in which the trial is planned.[54] It is very essential as the patients are studied during condition of the phase of pre-marketing which do not necessarily reflect the way the medicine will be used in the hospital or in general practice once it is marketed**.** [55]

The development

India joined the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden in 1997. For the monitoring of the ADR's three main centers were identified, mainly based in teaching hospitals: the National Pharmacovigilance Centre located in the Department of Pharmacology & All India Institute of Medical Sciences [AIIMS], New Delhi & two WHO special centers in Mumbai (KEM Hospital) & Aligarh [JLN Hospital, Aligarh Muslim University].[56] The ADRs of the medicines which are in market for sell in OTC counter are monitored by these centers. This attempt was unsuccessful therefore again from 1st of January 2005 the WHO-sponsored & World Bank-funded the National Pharmacovigilance Program for India was formulated [57]. The National Pharmacovigilance Advisory Committee based in the Central Drugs Standard Control Organization (CDSCO), New Delhi over seen the National Pharmacovigilance Program established in January 2005. Two zonal centers are the South &West zonal centre (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM located in the Department of Pharmacology, AIIMS, New Delhi), were also established to collate information from all over the country & send it to the Committee as well as to the Uppsala Monitoring centre in Sweden [58]**.** The chronological developments in the field of the pharmacovigilance with special reference to India are given as Table 2.

Table:2; The Chronological developments in the field of the pharmacovigilance with special reference to India are as follows:[59]

Year	Event
1747	First reported clinical trials by James Lind, proving the effectiveness of lemon juice in preventing scurvy
1937	Death of 107 children due to sulfanilamide toxicity
1950	Aplasticanemia reported due to chloramphenicol
1961	Global disaster due to thalidomide toxicity
1963	16th World Health Assembly recognize important to rapid action on ADR's
1968	WHO pilot research project for international drug monitoring
1996	Clinical trials of global standards started in India
1997	India joined WHO Adverse Drug Reaction Monitoring Program
1998	Pharmacovigilance initiated in India
2002	67th National PharmacovigilanceCenter established in India.
2004-05	National Pharmacovigilance Program launched in India
2005	Conduct of structured clinical trials in India
2009-10	PVPI initiated

INTERNATIONAL COLLABORATIONS

The principles of international collaboration in the field of the pharmacovigilance is the main basis for the World health organization International Drug Monitoring Programme, through which over the 100 members nations have the systems in place that encourages the healthcare personnels to

report and record the adverse effects of the drugs in their patients. The UMC [Uppsala Monitoring Centre] which is located in the Uppsala, in Sweden, is a field name for the World health organization Collaborating Centers for the International Drug Monitoring. The Uppsala Monitoring Centre works by assessing, collecting& communicating the information from the member countries the national pharmacovigilance programs in regards to the benefits, harms, effectiveness and risks of the drugs.[60] The CIOMS that is the Council for the International Organizations of the Medical Sciences, through its Working Groups, is the globally-oriented think tank that provides the guidance on the safety of drug related problems. CIOMS is the part of World Health Organization and the prepared reports are used as the reference for developing the future policies of drug regulatory and the procedures. [61]

THE INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE (ISOP)

The International society of the pharmacovigilance is the international non-profit scientific organization which aims to foster the pharmacovigilance in both educationally & scientifically& enhances all aspects of the safe and the proper use of the medicines, in all the countries.[62] In 1992 it was established as the European Society of thePharmacovigilance.[63]

CONCLUSION

The Pharmacovigilance plays an important role in meeting the challenges posed by the ever increasing range & potency of medicines. So after the appearance of the adverse effects & the drug toxicities, it is necessary that these must be reported, analyzed & communicated to the general public having the knowledge to interpret the necessary information. Though the important amount of information regarding the effective use & adverse reactions has been collected but the necessary information required will be more for effective drug use in specific categories like children and elderly peoples. Also it is important to improve the communication between the health professionals and public to understand the benefits & risk of the medicines.

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