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Review Article

PHARMACOVIGILANCE/REPORTING ADVERSE DRUG REACTIONS: AN APPROACH TO ENHANCE HEALTH SURVEILLANCE AND EXTENDING MARKET SHARE BY MINIMIZING THE CHANCES OF DRUG WITHDRAWALS

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ABSTRACT

Any unintended response of a drug which; apart from the doses that cover therapy of a disease; includes lack of efficacy, overdose and its misuse can be termed as an adverse drug reaction. In this scenario, adverse effects of drugs are mostly shown which result in the withdrawals of block buster's molecules and finally lead to the sharp decline of the market share. So there is an immense need to keep a hawk eye on these suspected adverse reactions to enhance health surveillance as well as minimizing the chances of drug withdrawals from the market. Thus the whole exercise of reporting adverse drug reactions is administered through implementation of pharmacovigilance program that deals with timely identification of ADR and it's monitoring-i.e. Collecting data, assessment, and follow up action. The importance of Pharmacovigilance has been on the rise because the frequency of ADRs and the percentage of hospital admissions have been increasing day by day, which finally have led to decline the global market share of blockbuster drugs by numeral instances of the cases of recalls and in some more severity have resulted in drug related mortality and morbidity of patients forcing the companies to ultimately withdraw the drug. The article highlights the different approaches of reporting the adverse drug reactions for enhancing the health surveillance and strategic consent for the pharmaceutical industry to generate long term revenues by reducing the chances of drug withdrawals with special emphasis on the consequences of reporting and non-reporting of ADRs and due examples of drug reported ADRs & their recalls. The article also highlights the Pharmacovigilance program in the European Union, United States and India, strategies for reducing the ADRs and future aspect of Pharmacovigilance.

Keywords: Pharmacovigilance, Health Surveillance, Adverse Drug Reaction, Reporting, Non-reporting of ADRs.

INTRODUCTION

Globalization of the world economy and free trade has given birth to the unrestricted flow of information across the borders. People have become accustomed to the lifestyle of the other nations through different means of communications and they try to imitate them, resulting in the major change in their health habits and exposure to the newly discovered medicinal products that assure them of better health. The growing public awareness with global exposure has also heightened their expectations of safety and efficacy of the drugs. The flip side of globalization has resulted in an irrational drug consumption pattern, easy accessibility, overdose, increasing tendency of self-medication, multiple drug therapy and lack of an effective regulatory body which can only be counteracted by setting up of Pharmacovigilance centres to address the safety concern of the masses. The term Pharmacovigilance is the science and activities related to the detection, evaluation, understanding and prevention of adverse drug reactions and other related problems [1].

According to WHO, Pharmacovigilance is a set of practices aiming at the identification, understanding and assessment of the risks associated with drugs [2]. It starts from the pre-marketing phase of a new drug and continues beyond the post-marketing phase covering the entire life cycle of the product [2, 3]. There are a bunch of examples of drugs, which have been detached from the market owing to reported adverse effects. Rosiglitazone holds the first position in the market; other well-known drugs, including terfenadine, cisapride, phenylpropanolamine, rofecoxib, cerivastatin, Gatifloxacin, cisapride were withdrawn because of their adverse reactions [2]. It has been observed that an adverse reaction is the major cause of hospitalization and drug withdrawals proves expensive for the patients as well for the manufacturing companies. Though a new drug molecule has to undergo various clinical and non clinical trials yet the need of Pharmacovigilace becomes mandatory as the information generated from the clinical trial is not sufficient to evaluate the safety of the drug with regard to adverse drug reactions for its being limited to a few number of patients and the conditions for the use of medicines differ from that in clinical practice and for regular use by the patients. The main objective of Pharmaco vigilance/post market surveillance is to regulate and ensure the safety & efficacy after the entry of the new drug molecule into the market for the treatment of diseases of the general population with different medical conditions. Recently the concern of Pharmacovigilance has been widened to include herbals, medicines, blood products, biological products, medical devices and vaccines [2]. Every medication has potential adverse/side-effects. Also many medications have potential interaction with other substances. When a new drug is prescribed, there is an exponential increase of interaction. So, to prevent these types of adverse effects, there is also a need of skilled health care practitioners & other health care members who can select & prescribe the best & safest medicines according to the medical needs of the patients.

Therefore, health professionals play an important role in the detection and reporting the adverse drug reactions saving the precious lives of the patients. Not only health care professional, even hospitals, pharmaceutical industries & competent regulatory agencies across the world are the main partners of this Pharmacovigilance program. Not reporting of drug reactions or any apathetic attitude towards the gravity of the situation may lead to the massive spread of its adverse effects worldwide causing a huge loss to the company; at times bringing financial loss due to less cash flow as well as loss of good will whereas timely reporting to the regulatory mechanism through proper channel without letting it cause any further loss definitely saves the resources of the company as well as ensures safety and efficacy of the drug for which it had been intended. Thus pharmacovigilance program includes public awareness and education of patients and health care professional in reporting the adverse drug reactions so as to ensure better health care worldwide. This article covers various terms associated with Pharmacovigilance & adverse drug reactions as discussed in Table1 and puts special emphasis on the effects of ADRs on market share due to withdrawals of blockbuster molecules which lead to tremendous loss to the pharmaceutical industry. The article also highlights the various types of ADRs & consequences of reporting and non-reporting of adverse drug reactions with due examples of

reported ADRs & their recalls. The article also emphasises on the pharmacovigilance program in European Union, United States and India, strategies for reducing the ADRs and future aspect of pharmacovigilance programs.

Table 1: Terms related to pharmacovigilance & adverse drug reactions [4-6]

Term	Definition
Adverse Drug Reaction	It is any noxious, unintended and unexpected effect of a drug that occurs at a dose used in humans for prophylaxis, diagnosis, and therapy of a disease.
Side Effect	It is an unintended effect of pharmaceutical product which is related to pharmacological properties of a drug at normal dose.
Drug Recall	Recalls are actions taken by a firm to remove a product from the market. Recalls may be conducted on a firm's own initiative, by FDA request, or by FDA order under statutory authority.
Post Marketing Surveillance	It is the practice to monitor the safety concern of a drug or pharmaceutical device after it has been released in the market.
Periodic Safety Update Report	A systemic review of an internationally accepted global safety data which is available with the manufacturing unit of marketed drug for a specific period of time.
Prescription Event Monitoring	It is a system used to monitor ADRs in population. Prescribers are requested to report all events regardless of their being suspected adverse events for identified patients receiving a specific drug and also named as Cohort Monitoring System.
Spontaneous Reporting	A voluntary approach in which case reports of ADRs are voluntarily submitted from health professionals and pharma units to national regulatory Authority.
Vigi Base	It is also termed as WHO Global ICSR Database.
Vigi Flow	It is an ICSR management system of the Uppsala monitoring centre. It is web based & adheres to the ICH-E2B standard. It incorporates tools for report analysis &facilitates sending report to vigibase and for this it can be used as national data base for member countries in WHO program.
Vigimed	It is a mutual based conferencing facility involving member countries of the WHO Programme for International Drug Monitoring for fast communication of topical pharmacovigilance issues.
Vigi Search	Software to access ICSRs stored in the Vigi Base database.
WHO Drug Dictionary	It is an international classification of drugs providing proprietary and non-proprietary names of medicinal products used in different countries, together with all active ingredients.
Pani Flow	It is software used for collection and analysis of data in relation to vaccinations in apandemic situation.
Med DRA	It is the clinical validated international medical dictionary used by regulatory authority during regulatory process from premarketing to post marketing. It also classifies the adverse drug reaction endorsed by ICH.

Adverse drug reaction (ADR)

Adverse drug reaction monitoring is a process of continuous monitoring of undesirable effects suspected to be associated with the use of medicinal products. ADR reporting covers all pharmaceutical products, biological, herbal drugs, cosmetics and medical devices. It is defined as "Response to a drug which is noxious, unintended and which occurs at doses normally used for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function" [3]. Adverse drug reactions are classified into various categories on the basis of frequency and its type as discussed in tabal 2. Every medication has potential adverse/side-effects, but the issue is reporting of these ADRs. As we know that the cost of treatment of these ADRs is very high and for the developing countries, it is not easy, even to afford medicines, so how come a patient afford the cost of adverse drug reactions. Recently, an increase in ADRs is being noticed in tandem due to multiple drug therapy, availability of new drugs in the market, irrational use of medicine, self-medications & absence of any effective regulatory bodies. These adverse drug reactions can be prevented by creating awareness among the professionals and the masses, strict adherence to the law enforced by the regulatory bodies and last but not the least is the reporting of ADRs itself and their compilation. The information so compiled helps to identify the faults of the drug dose, administrations, dosage form etc. If these ADR are reported in time, then it will help the patients & will definitely prevent the similar incident happening again at global level, in turn, saving huge losses to the company and the nation in terms of money and valuable manpower and making them independent on the socioeconomic front as well. Pharmacovigilance system is being geared more towards delivering effective risk management strategies and reducing the chances of adverse drug reactions. For this, different countries adopt different modern techniques of reporting ADRs including e-reporting system in their spontaneous reporting to communicate these issues globally. Examples of such systems include the yellow card scheme in UK, managed by the Medicines and Health care products Regulatory Agency (MHRA), MED Watch in US, managed by the Food and Drug Administration (FDA) and the Uppsala monitoring centre in Sweden, which is the base for the WHO programme for international drug monitoring [7].

Consequences of not reporting & reporting of adverse drug reactions

To understand this simple but very crucial phenomenon let us think about the consequences of not reporting ADRs and benefits of reporting to the concerned authorities one by one. In the first instance we take up the case of not reporting ADR. Suppose a doctor prescribes three tablets a day (as recommended by the manufacturer after following the due obligations) to a patient suffering from a particular disease. The patient returns after few days with symptoms worth reporting ADR. But the doctor, at his/her own level changes the medication and, though keeps an eye on the patient, does not report the matter to the concerned regulatory agency.

Fig. 1: Consequences of not reporting of adverse drug reaction [10]

ADR may not be reversible or may escalate into severe consequences. In the long run, this ADR may spread out in different parts of the world with the same symptoms as no professional

engaged in prescribing the doses takes pain in reporting the matter to the concerned agency. Such a casual approach may prove fatal to the large population and at times be cost effective and result into loss of valuable man power. At last medicine, despite promising ingredients to cure the disease, is discarded and the other alternatives are searched upon. Fig. 1 describes the consequences of non-reporting of adverse drug reaction which ultimately leads to the withdrawals of blockbuster drug molecules.

Table 2: Classification of adverse drug reaction [8, 9]

Based on frequency of occurrence		
Category	**Frequency**	**Example**
Very common	>10%	Dizziness, fatigue, tiredness, difficulty in concentration
Common (frequent)	>1% and<10%	Sedation, memory problems, Depression
Uncommon (infrequent)	>0.1% and<1%	Ataxia, somnolence, skin rash
Rare	>0.01% and<0.1%	Stevens Johnson syndrome, nephrolithiasis (topiramate)
Very rare	<0.01%	Aplastic anemia (phenytoin), glaucoma (topiramate)
Based on type of adverse drug reactions		
Type	**Description**	**Examples**
Type A (Augmented)	Predicted, Dose dependent, severity increases with increase in dose	Hypotension by beta-blockers & hypoglycaemia caused by insulin
Type B (Bizarre)	Unpredictable, rare, idiosyncratic, mechanisms are unknown, unrelated to the dose	Hepatitis caused by halothane & aplastic anaemia caused by chloramphenicol
Type C (Continuous drug use)	Irreversible, unexpected, unpredictable	Tardive dyskinesia by antipsychotics &dementia by anticholinergic medications
Typed D(Delayed)	Delayed occurrence of ADRs	Corneal opacities after thioridazine & ophthalmopathy after chloroquine
Type E (End of Dose)	Withdrawal reactions	Seizures on alcohol or benzodiazepines withdrawal
Type F (Failure of therapy)	Therapeutic failure of drug	Accelerated hypertension because of inefficient control

In the second instant, ADR is religiously reported by the medical professionals to the concerned regulatory agencies. Prescription and patients' complain of adverse effects are taken due care of and are reported to the concerned authorities by the professionals worldwide prescribing it. Each one makes an approach to the regulatory authorities. The compiled ADRs are sent to W. H. O. All these information is shared with the manufacturer by these regulatory agencies.

Manufacturer plans a strategy with the production and marketing units to overcome the ADRs [10]. All the previous data of clinical trial and laboratory reports are reviewed and the committee comes to the conclusion to perform repeated clinical trial to find out the risk associated with the drug. The results and reports of this clinical approach reveal that the dose should be reduced from three tablets a day to two tablets a day. The company changes the labels and notifies the medical professionals in this regard. The resultant ease of professionals and patients' satisfaction becomes the due advantage of reporting ADRs along with minimal risk of withdrawal and maximum contribution in the market share. Tabal 3 describes the classical examples of blockbuster drug molecules with reported adverse drug reactions along with the reasons for the recall.

Table 3: List of classical examples of drug reported adverse drug reactions & drug recalls [11, 4]

Generic name	**Year**	**Country**	**Reason for recall**
Astemizole	1999	U. S, Malaysia, Multiple non specified markets	Arrhythmias due to interactions with other drugs
Amineptine	1999	France, US	Hepatotoxicity & dermatological side effects
Alatrofloxacin	2006	Worldwide	Liver toxicity and death
Alpidem	1995	Worldwide	Serious hepatotoxicity
Benoxaprofen	1982	Germany, Spain, U. K, U. S	Liver & Kidney failure and gastrointestinal bleeding
Bunamiodyl	1963	Canada, U. K, U. S	Nephropathy
Cisapride	2000	US	Risk of fatal cardiac arrhythmias
Cerivastatin	2001	US	Risk of rhabdomyolysis
Chlormezanone	1996	European Union, U. S, South Africa, Japan	Hepatotoxicity, Steven-Johnson Syndrome & Toxic Epidermal Necrolysis.
Efalizumab	2009	Germany	Increased risk of progressive multifocal leukoencephalopathy
Flosequinan	1993	U. K,U. S	Increased mortality at higher doses
Fenfluramine	1997	European union, U. K, U. S, India, South Africa, others	Cardiac vascular disease and pulmonary hypertension
Grepafloxacin	1999	Germany, UK, U. S others	Cardiac repolarization
Lumiracoxib	2008	Worldwide	Liver damage
Methaqualone	1984	South Africa (1971), India (1984), United Nations (1971-1988).	Risk of addiction and overdose
Phenformin & Buformin	1977	France, Germany, US	Lactic acidosis
Phenacetin	1975	Canada, Germany, Denmark, U. K,U. S	Risk of cancer and kidney disease
Phenylpropanolamine	2000	Canada, US	Haemorrhagic stroke
Propoxyphene	2010	Worldwide	Increased risk of heart attacks and stroke.
Pemoline	1997	Canada, U. K	Hepatotoxicity

Rofecoxib	2004	US	Risk of myocardial infarction and stroke
Rosiglitazone	2010	Europe	Increased risk of Cardiovascular diseases & heart attacks.
Thalidomide	1961	Germany	Teratogenicity
Ticrynafen	1980	Germany, France, U. K, U. S others	Liver toxicity & death
Triazolam	1991	France, Netherlands, Finland, Argentina, U. K others	Psychiatric adverse drug reactions, amnesia
Temafloxacin	1992	United States	Allergic reactions and cases of haemolytic anaemia
Tolrestat	1996	Argentina, Canada, Italy others	Severe hepatotoxicity
Terfenadine	1997-1998	France, South Africa, Oman, US	Prolonged QT interval & ventricular tachycardia
Tolacapone	1998	European Union, Canada, Australia	Hepatotoxicity
Temazepam	1999	Sweden and Norway	Diversion, abuse, and high rate of deaths due to overdose.
Troglitazone	2000	US. Germany	Hepatotoxicity
Trovafloxacin	1992	Germany, U. K, U. S & others	Haemolytic anaemia, Kidney liver dysfunction.
Thioridazine	2005	Germany, UK	Cardio toxicity

Pharmacovigilance program in European Union, United States and india

European Union

Pharmacovigilance program in the European Union is being run in coordination with European Medicines Agency (EMA) and is conducted by the National Competent Authorities (NCAs). EMA maintains & develops the Pharmacovigilance data base involving all the suspected ADRs of medicinal products including medical devices in the European community. The data processing network and management system is called Eudravigilance [12]. Eudravigilance was established in 2001, and currently contains adverse reaction reports of authorized and licensed medicines across Europe, including those noticed during the process of clinical trials. This information is shared by national competent authorities. From July 2012 onwards, the role of Eudravigilance has been expanded: It has become the only window to receive all Pharmacovigilance information for authorized medicines used for human beings in the European Union. Companies and Member States report reactions directly to Eudravigilance which immediately notifies all Member States electronically. The database is accessible to member states and the European Commission, and is also partially open to healthcare professionals and the public (patients).

It is mandatory for the individual marketing authorization stake holders to submit all the received ADRs in electronic form except in exceptional circumstances whereby the reporting obligations of the various stakeholders are defined by EEC legislation. table 4 describes the few terms related to the Pharmacovigilance program of the European Union. Good Pharmacovigilance Practices that apply to marketing-authorization holders, the European Medicines Agency and medicines regulatory authorities in EU Member States is a set of measures drawn up to facilitate the performance of Pharmacovigilance in European Union. fig. 2 highlights the different modules of good Pharmacovigilance practice in European Union member states.

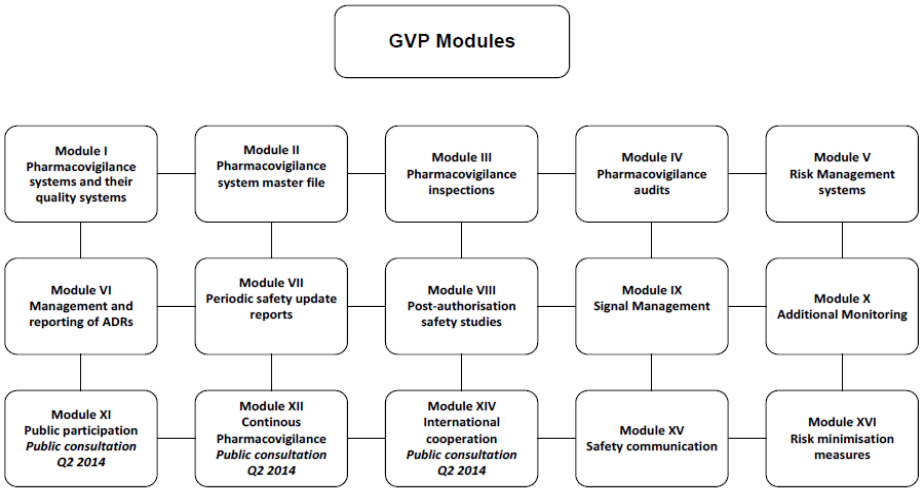

Fig. 2: Good pharmacovigilance module of European Union [13, 14]

The Pharmacovigilance program of the European Union has special emphasis on risk management plan. For market authorization of new drug molecule in European Union manufactures have to submit the risk management plan. It concerns with complete scrutiny of the safety specifications including identification of potential risks along with important missing information. It also accommodates the post authorization efficacy evaluations when previous efficacy data have to be revised at length due to variant findings of the disease or the clinical methodology [13]. It also ensures planning and formation of Risk Management Agency (RMA) and its timely implementation. It includes:

- Product overview.
- The safety specifications which should be a summary of the identified risks, important potential risks, and important missing information. It will form the basis of the evaluation of the need for risk minimization activities and where appropriate, the risk minimization plan.
- The Pharmacovigilance plan that proposes actions to address the identified safety concerns and includes also the post-authorization safety studies.

- Post-authorization efficacy studies: when previous efficacy evaluations have to be revised significantly due to new understanding of the disease or the clinical methodology, the marketing authorization holders shall initiate and manage a post-authorization efficacy study.
- Risk minimization activities and an evaluation of its effectiveness.
- Summary of the risk management plan which consists of its key elements and the specific focus on risk minimization activities.

Table 4: Terms related to pharmacovigilance in European Union [12, 13]

a. Direct patient reporting (DPR)
It refers to the possibility for patients to directly report the suspected ADRs to authorised agency. DPR already exists in several countries of European Union, but the system is rather different. It is a tool to encourage "spontaneous reporting" by patients and consumers of suspected adverse drug reactions. "Spontaneous" means that a patient, losing no time, himself takes the initiative in reporting a reaction.
b. Black symbol
Products containing new active substances are identified for 5 years by a black symbol on the medicine packaging/patient information leaflet. If the product is subject to additional monitoring this period can be extended. Additional monitoring means that the reports database is checked more often to detect any signals as early as possible.
c. European public assessment report (EPAR)
A scientifically based assessment report published by the European Medicines Agency for each medicine that has been granted a centralised marketing authorisation in the European Union.
d. Marketing authorisation
To place a medicine in the market in the EU, a company must obtain a marketing authorisation. Once the application is submitted, the competent authority examines the risk-benefit balance of the medicine, assessing its safety, quality and efficacy. There are several routes to apply for EU marketing authorisation e. g. centralized procedure, decentralized procedure, national authorization procedure or mutual recognition procedure.
e. National competent authorities (NCAs)
These are national agencies responsible for the evaluation and monitoring of medicines at national level.
f. Pharmacovigilance master file
Marketing authorisation holders (companies, either manufacturers or importers of medicines) keep and maintain a master file containing a detailed description of the pharmacovigilance understanding which they use for one or more medicinal product in a declared location.
g. Periodic safety update reports (PSURs)
These reports aim at giving updates on the safety of a product from the experience acquired worldwide. These must contain a summary of data that could reveal risk-benefit balance of a medicine, a scientific evaluation, and data related to volume of sales, prescription and exposure of the population. For products placed in the market these have to be submitted twice a year for the1st 2 years, yearly for the next 2 years and thereafter at the interval of 3 years. The agency and the European Commission will maintain a repository of these reports and can make it available to national authorities.
h. Urgent union procedure
This is an alert procedure which has to be triggered by either the Commission or a Member State, if there are serious concerns related to the medicine, including a new contraindication or change in the dosage recommendation. The EMA will publicly announce the procedure, and give information on the product concerned upon the receipt of scientific information. The European Commission can ask member states to take temporary urgent measures.
i. Signal
Reported information on a possible causal relationship between an event (either adverse or beneficial for the patient) and a drug; the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.
j. Summary of products characteristics (SPC)
This is a summary submitted with the application for marketing authorisations which sets out the details of the use of the product including the therapeutic indication, dosage, how to administrate, contraindications, precautions for use etc., and its composition.

United States

The Centre for Drug Evaluation and Research (CDER) and the Centre for Biologics Evaluation and Research (CBER) of the USFDA monitor and review safety information throughout the life cycle of the medical product right from application for market authorization, its approval and after the entry of the drug in the market. The routine Pharmacovigilance activities in the US i.e. compliance with applicable post-market requirements under the FDCA and USFDA include post-marketing surveillance and risk assessment. The Pharmacovigilance plan describes efforts beyond the routine post-marketing spontaneous reporting and is designed to enhance and expedite the sponsors' acquisition of safety information [12]. The sponsors have to develop a Pharmacovigilance plan for products for which serious safety risks have been identified post-approval and/or already identified safety risks need more evaluation or risk populations have not been adequately studied. Under the USFDA guidance the different phases of the risk assessment and risk management for industry are divided into three parts: pre marketing risk management, post marketing Pharmacovigilance & pharmaco epidemiologic assessments; and risk evaluation & mitigation strategies [15].

Pre marketing risk management

The sponsor/manufacturer is responsible for promptly reviewing all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any sources; foreign or domestic sources, or from any clinical or epidemiological investigation, or from animal or in-vitro studies. The sponsor is responsible for notifying FDA and all participating investigators in written about Investigational New Drug (IND) safety report of all serious and unexpected serious risk from clinical trials or any other sources that have not previously been reported to the agency by the sponsor. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in the light of previous, similar reports or any other relevant information. Each IND safety notification must be submitted electronically or on an FDA Form 3500A. Foreign events may be submitted either on an FDA Form 3500A or if preferred on a Council for International Organization of Medical Science (CIOMS) Form Reports from animal, in-vitro, clinical or epidemiological studies shall be submitted in a narrative format and shall bear prominent identification of its contents, i.e. 'IND Safety Report' and must be transmitted to the FDA's responsible centre for the review of IND [15].

Post-marketing pharmacovigilance and pharmaco epidemiologic assessments

All the scientific and data gathering activities related to the detection, assessment, and evaluation of safety signals that come

under the preview of the Pharmacovigilance program in the US include:

- Safety signal identification,
- Pharmacoepidemiologic assessment and safety signal interpretation
- Pharmacovigilance plan development.

Risk management plan/risk evaluation and mitigation strategies (REMS)

FDA has authority to guide manufacturers to implement special risk management programs called Risk Evaluation and Mitigation Strategies (REMS). If the Secretary, in consultation with the office responsible for reviewing the drug and for its post-approval safety, concludes that a risk evaluation and mitigation strategy is necessary to ensure that the benefits of the drug outweigh the risks of it, then the applicant having an approved application for new drug or for abbreviated new drug or for a biological medicinal product has to submit REMS. The proposed REMS must be submitted within 120 days of the FDA notification or within another reasonable time approved by FDA [15]. Risk Management is an iterative process throughout the product's life cycle and consists of:

- Assessing product's benefit-risk balance;
- Developing and implementing tools to minimize its risks while preserving its benefits;
- Evaluating tool effectiveness and re-assessing the benefit-risk balance;
- Making adjustments as appropriate to the risk minimization tools to further improve the benefit-risk balance.

India

The Legislative requirements of Pharmacovigilance in India are guided by the specifications of Schedule Y of the Drugs and Cosmetics Act 1945. In1978, to make the Pharmacovigilance and surveillance bear more fruitful results, the Uppsala Monitoring Centre (UMC) in Sweden was set up. The Uppsala Monitoring Centre is authorised to receive the data about adverse drug reactions across the world, especially from countries that are members of the WHO including India [12]. Any adverse report sent by the co-ordinating centre of a member country to Uppsala Monitoring Centre is entered in the WHO International Database. ADRs from different countries are evaluated, analysed (based on the study of supporting evidences) and communicated to the members depending on the gravity of the situation. In 1997, India joined the WHO Programme for International Drug Monitoring managed by the Uppsala Monitoring Centre, Sweden. Department of Pharmacology, AIIMS New Delhi and KEM Hospital Mumbai were identified as national and WHO centres respectively. The NPVP was guided 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 centres (located in the Department of Pharmacology, AIIMS, New Delhi) collated information from all over the country and send it to the Committees as well as to the Uppsala Monitoring Centre in Sweden. Three regional centres report to Mumbai centre and two to New Delhi. Recognizing the need to implement effectively the National Pharmacovigilance Program (NPVP) AIIMS and CDSCO, in late 2009, formulated a programme, now rechristened as the Pharmacovigilance Programme for India (PVPI), to be operational w. e. f 14 July 2010, with the All India Institute of Medical Sciences, New Delhi as the National Coordination Centre for monitoring Adverse Drug Reactions (ADRs) and 21 other centres covering almost every part of the country. The centre was finally shifted from the All India Institute of Medical Sciences, New Delhi to the Indian Pharmacopoeia Commission Ghaziabad for administrative reasons [16]. Tab. 5 describes the role of different regulatory agencies for health surveillance in India.

Table 5: Role of regulatory agencies for health surveillance in india [4, 12, 17]

Agencies	Role of agencies
Drug Controller General of India (DCGI)	Implementation the National PharmacovigilanceProgrammein India.
Central Drugs Standard Control Organization (CDSCO)	Operates under the supervision of National Pharmacovigilance Advisory Committee to recommend procedures and guidelines for regulatory interventions.
Indian Council of Medical Research (ICMR)	Credit to bring out the 'Ethical guidelines for Biomedical Research on Human Subjects'.
Ministry of Health and Family Welfare (MHFW)	An autonomous body for setting of standards for drugs, pharmaceuticals and healthcare devices and technologies in India.
National Pharmacovigilance Advisory Committee (NPAC)	NPAC oversees the entire Pharmacovigilance Programme &the performance of various Zonal, Regional and Peripheral Centres and performs the functions of "Review Committee" for this program. The NPAC also recommends possible regulatory measures based on pharmacovigilance data received from various centres.
Central Bureau of Narcotics (CBN)	Closely monitors all clinical trials which require additional narcotics compliances relating to storage, import-export quotas and movement of the investigational drug.
Department of Biotechnology (DBT)	Provides product evaluation and validation through support for field trials for agriculture products and clinical trials for health care products.

What can be done to decrease adverse drug reaction?

The simplest way of decreasing the ADRs is the rational use of medicines by prescribing lower doses and prefers not to use multiple therapies in the very first stage of medication. Health professionals/medical staff like nurses or pharmacists plays a major role in monitoring drug therapy prescribed by the medical practitioners. They provide information to patients about medications and their rational use & also monitor the health and progress of patients in response to medication/drug therapy to ensure its safe and effective use. Health professionals should periodically be educated about adverse reactions and should be encouraged to report the same. Even some industries have also started taking part in pharmacovigilance program and have taken an initiative by setting up a separate cell and self-online reporting system to counteract any adverse effects of their products. Even the safety information of pharmaceutical products is communicated to doctors by pharmaceutical companies in the form of 'dear doctor letters'. According to the U. S. Food and Drug Administration (FDA), Dear Healthcare Professional letters (also known as Dear Doctor letters) or pieces of advice is mailed from the pharmaceutical production units or distributors to physicians and other healthcare professionals to convey important product safety information [18]. Even patient information leaflets by pharmaceutical companies and newsletters of pharmacovigilance centre & WHO provide updated information concerning to the safe use of medicine. But the need of the hour is timely updating of all the professionals engaged in this holy business. Linking pharmacovigilance with academics can play a

major part in the decrease of ADRs. For this medical council should take an initiative to make pharmacovigilance a part of academics and be taught to the students of medical professions. The aim of linking pharmacovigilance to the academics is to educate the medical students about the role and responsibilities of health professionals towards the community and the profession itself so that they can understand the importance of the rational and safe use of drugs and also the importance of the pharmacovigilance program. The pharmacists and other healthcare workers should participate in spontaneous ADR reporting, during post-marketing observation of drugs used in public. The knowledge and training of the health care members will definitely generate the quality of reporting and minimize the cases of ADRs.

Future aspects

Pharmaceutical market is moving towards the generic trends and the global pharmaceutical market is expected to reach at nearly $1.6 trillion by 2020but the growth rate of developing the new chemical entity is relatively very low in comparison to the generic market [19]. This generic trend ultimately leads to the flow of more cash in the hands of the pharmaceutical industry which is going to be ultimately used for the development of new drug molecules. But the challenging issue industry is facing today is the high investment in the R&D segment and the uncertainty associated with the success of their molecule in the market. Some of the drugs fail to show the desired effect on a large population and some may be recalled from the market due to reported adverse drug reactions incurring severe losses. Even companies are not able to overcome these huge losses which ultimately lead to decline the global market share and a tremendous loss to the market [20]. High investment in R&D and enhanced medical facilities to fulfil the medical needs of the patients demand pharmacovigilance activities to incorporate the spontaneous reporting of ADRs which ultimately leads to ensure the patient's health and reduce the chances of drug withdrawals at times saving the revenue.

CONCLUSION

Every medication has potential adverse/side effects. Also many medications have potential interaction with the substance. The one and the only way to counteract these exponential interactions and steal a march is to form a strong regulatory authority with set guidelines, a network for spontaneous reporting and rational use of the drugs. Pharmacovigilance, empowered with regulatory mechanism, has proved itself in detection, evaluation, understanding & prevention of ADRs and the related problems ranging from very common to very rare. Any slackness in timely reporting of ADRs may prove fatal to the large population, at times, be cost effective and may lead to the untimely recall of the otherwise genuine drug. Hence various agencies across European Union and USA including India have set up different bodies to monitor the pharmacovigilance program. WHO and Uppsala at the international level compile all the reported incidents of ADRs and issue the necessary guidelines. Pharma companies at their level also take the initiative to reduce the chances of drug withdrawals by sharing the safety information & updates of their own products and direct online reporting of ADRs. The efficient & spontaneous reporting not only reduces the chances of drug withdrawals but also meets the patient's compliance and enhances the health surveillance.

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CONFLICT OF INTERESTS

Declared None

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