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A Review on Comparison of Pharmacovigilance Systems in the Us, India, Australia

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ABSTRACT: The primary emphasis of pharmacovigilance is the collection, assessment, and reporting of adverse reactions through various methods. This plays an indispensable role in the pharmaceutical industry. The pharmacovigilance databases aid in the promotion of safe medication use and public health protection. This article gives a brief insight into the pharmacovigilance system in the USA, India, and Australia by relatively comparing them and highlighting the process involved in the reporting of pharmacovigilance. Pharmacovigilance is a field where communication is crucial and the exchange of information is done in a timely manner. The US and Australia have a very advanced well- established pharmacovigilance system.The most recent advancements in India are the national pharmacovigilance program and the pharmacovigilance program of India This article focuses mainly on these three countries detailing the slight differences in reporting the adverse events by the consumers.

KEYWORDS: Adverse reactions, Adverse drug reporting, data bases, Pharmacovigilance program,

I. INTRODUCTION:

The World Health Organization (WHO) defines pharmacovigilance (PV) as "the science and activities relating to the detection, assessment, understanding, and prevention of the adverse effects or any other possible drug-related problems [1].It is a structured activity in the professional health field with important social, and economic implications aimed at monitoring the risk/benefit ratio of drugs and improving patients' safety and quality of life.The discipline and science of pharmacovigilance have emerged as a result of increased awareness of adverse reactions [2]. Pharmacovigilance has to constantly adapt rapidly with new advancements in the medical field. Most adverse effects can be seen after the drug is marketed. Pre-marketed clinical trials are limited by short duration and small sample sizes. This fails to detect the adverse events in patients of different study grouppopulations. Dying with illness is inevitable but dying with medicine is undesirable.

WHY pharmacovigilance is essential:

Pharmacovigilance has begun formally in every country as a result of the thalidomide incident which remains a tragedy in history.Thalidomide was introduced in 1950 and widely prescribed as an allegedly harmless treatment for morning sickness and nausea for pregnant women. It became apparent in the 1960s that thalidomide treatment resulted in severe birth defects in children[3]. This resulted in countries having different regulatory authorities such as the US- Food and Drug Administration (FDA), India- Center for drug standards control organization (CDSCO), and Australia- Therapeutic goods administration (TGA) regulating adverse events.

In the current situation of the pandemic, to combat the COVID- 19, Vaccination is the most effective way to reduce deaths and severe illnesses from infection.

Like all medicines, COVID-19 vaccines may also cause certain side effects ranging from mild to moderate effects. People are aware as a result of effective good reporting practice i.e, Pharmacovigilance.

Adverse Reactions are common but they are preventable.

Some frequent definitions are:

1) Adverse Events:

Adverse events are defined as any untoward medical occurrence in a patient, consumer, or clinical investigation subject administered a medicine, which doesn't necessarily have a relationship with the treatment.

2) Adverse Reactions:

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An adverse reaction is a noxious and unintended response to a medicine.

An adverse reaction in contrast to an event is characterized by the fact that the sponsor, investigator, or reporter suspects there is a casual relationship between the medicine and the occurrence.

Adverse reactions are again divided into serious adverse reactions and non-serious adverse reactions:

A serious adverse reaction is any medical occurrence that in relation to medicine at any dose results in death or serious injury or life-threatening or patient hospitalization.

Non-serious adverse reactions are that don't meet any circumstances of serious adverse reactions.

3) Significant-Safety Issues:

A significant safety issue is a new safety issue or validated signal that is considered by a person in a relation to a medicine that requires urgent attention of a regulatory body.

Pharmacovigilance focused on drug surveillance programs and its process involves:

- Compile and report ADRs/ AEs
- Causality assessment and study of ADRs.
- Collect and combine the database
- Calculate the risk-benefit ratio and combine the results.
- Convey for safe use of drugs for consumers [4].

PHARMACOVIGILANCE IN US:

The Pharmacovigilance activities are regulated by the Office of Surveillance and Epidemiology (OSE) inthe Centre for drug evaluation and research (CDER), a branch of the FDA.

Spontaneous adverse events and medication error reports are submitted to the FDA. The reported activities and indications for use are coded using a medical dictionary for regulatory activities (MEDRA) [5].

The adverse events are reported using the FDA Adverse Event Reporting System (FAERS).

FAERS is a single centralized repository for spontaneous adverse event reports and is particularly helpful for identifying unrecognized adverse events that are not identified during clinical trials. FAERS data helps identify potential demographic groups and other factors that may contribute to product risks. However, FAERS is subjected to certain limitations such as reporting bias, underreporting, missing and incomplete data, and duplicate reporting. It is not possible to estimate the incidence of specific adverse events [6].

Direct to the FDA, reports are received through MED-WATCH, the FDA's safety information and adverse event reporting system. Med-Watch provides several reporting mechanisms for consumers, patients, and healthcare professionals.

Under the provisions of 21 CFR 314.80, an approved new drug application (NDA) or abbreviated new drug application (ANDA) is required to report each adverse drug event. These should be submitted quarterly for the first 3 years and annually thereafter.

Under this Act, post-marketing safety reports must be submitted to FDA for the following:

1) Expedited Reports: Both Serious and unexpected adverse events from all sources.

2) Non-Expedited Reports: Domestic spontaneous adverse events that are :

- Serious and expected
- Non-serious and unexpected
- Non-serious and expected

For serious, suspected adverse events, manufacturers must submit 15-day alert reports based on the literature articles and post-market studies.

Any person who is willing to report can voluntarily report the adverse event through Med-watch FDA FORM-3500. Consumers can report through Med-Watch FORM-3500B, in this form some specific instructions are given in filling the form.

The clinical reviewers in the CDER office systematically monitor the safety of all marketed drugs and therapeutically biological products that can prompt early signal detection of investigation of new and serious adverse events [7].

Adverse events reported in the USA [8] [9]:

Drug	Adverse event reported
Aspirin	Bleeding only
Mefdipine	Hypotension
Bosentan (Traclear)	Hepatotoxicity
Cisplatin	Renal Impairment
Raptiva	Brain infections and meningitis

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#CASE STUDY:

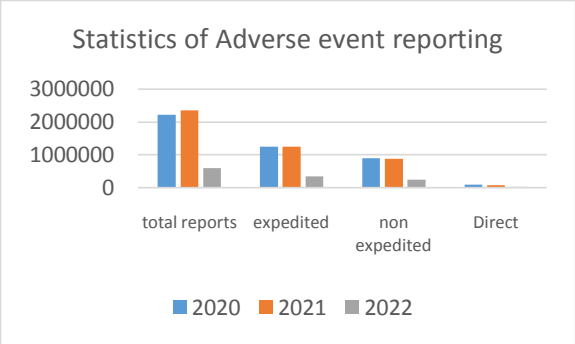
The drug Efalizumab was also known by the genericname Raptiva is used to treat psoriasis. The FDA received several adverse events reports of brain infections and meningitis regarding this drug. Later, the medicines were withdrawn from the market, due to its adverse effects.[10]

Statistics of adverse events reporting in the USA:

The adverse events are mainly reported in 3 main ways, they are:

1. Expedited- these areserious adverse reports that are not mentioned in the product label
2. Non-expedited- these are non-serious which can be either expected or unexpected.
3. Direct: these are submitted by the consumers and healthcare professional directly to FDA through the Med Watch.

According to FDA, the statistics of the adverse event reported in the last 3 yearsis given as follows [11]:



PHARMACOVIGILANCE IN INDIA:

The National coordinator Centre (NCC)-Pharmacovigilance program of India (PVPI) took many efforts to the enhancement of Pharmacovigilance programs in India. PVPI was launched in the year 2010. In terms of telecommunications and the internet, India is a well-connected country. So, PVPI has launched the toll-free helpline number (1800-180-3024) on October 11th, 2013, and an android application on May 15, 2015, for faster reporting.As India is a multi-linguistic nation, consumer reporting forms are prepared in vernacularlanguages and are available 24x7 on the official website.At present 150 adverse drug reaction monitoring centers (AMCs) are functioning and reporting adverse reactions to NCC by spontaneous reporting system through Vigiflow (a web-based system developed by WHO).India's existing system for monitoring ADRs relies on voluntary reporting by healthcare professionals as its main source of information and is encouraged to report by submitting the Suspected Adverse Drug Reaction reporting form for Healthcare professionals (RED Form) available onthe CDSCO website.Pharmaceutical companies are key to connecting in the chain of pharmacovigilance. It is mandatory for Marketing Authorization Holders (MAH) to submit Periodic Safety Update Reports (PSURs) to CDSCO twice a year for consecutive 2 years and yearly once thereafter, this helps to collect safety data for ongoing products.To strengthen patient safety and direct consumer reporting NCC-PVPI has launched the "Medicines Side Effect Reporting Form for Consumer" (BLUE form). Patients or his/her representative are encouraged to report either through Blue Form or can directly call NCC through helpline numbers.The language used in the consumer form is very simple and understandable by amateurs and can easily report in non-technical terms. NCC-PVPI has released the first version of the Blue form in different languages such as Hindi, Oriya, Gujarati, Bengali, Kannada, Tamil, &Malayalam. The objective of NCC-PVPI is to encourage the crucial role of consumers/patients in enhancing thereporting of Adverse Events without any language barrier.The pharma companies maintain databases of all adverse drug reactions reported to them via consumers and healthcare professionals.Pharma companies should be held accountable for reporting ADRs after the drug has been released into the market and even during clinical trials.Companies should take ethical considerations into account when reporting ADRs during clinical trials and even after post-marketing of the products [12].

Examples of adverse events reported in India:

#CASE STUDY:

Lamivudine a HIV drug is approved by CDSCO. Based on ADR reports on the medicinal products PVPI has evaluated the basis of individual case study reports (ICSR) and recommended that

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CDSCO take necessary actions. The CDSCO has recommended that the adverse event hearing loss should be mentioned in the package insert [13].

PHARMACOVIGILANCE IN AUSTRALIA:

Drug safety in Australia is regulated by the office of Medicines safety and monitoring (OMSM), a branch of the administration of the Therapeutic good (TGA). TGA is responsible for assessing and monitoring activities to ensure therapeutic goods are available in the market at acceptable standards. Good Pharmacovigilance Practices (GPV) are to be followed.One must comply with any reporting requirements of adverse events stipulated as a condition of registering the therapeutic goods in the Australian Register of therapeutic goods (ARTG) under subsection 28(5) (e) of the Therapeutic goods Act 1989 and Regulation 15A of the Therapeutic Goods regulation.Adverse events were formerly reported to the TGA by submitting a blue card by physicians. Physical copies of these cards are no longer available. Anyone can report the adverse events throughthe Australian adverse Drug Reporting system. Alternatively, these reports can be made via telephone, mail, post, and fax.Clinicians and the general public are free to report. However, sponsors of both registered and listed pharmaceuticals are required by the law to disclose to the TGA any suspected adverse events.The Australian Register of therapeutic goods administration (TGA) includes Pharmacovigilance guidelines for sponsors of medicines. The sponsor must nominate a person in Australia to be in charge of the Pharmacovigilance reporting requirements of the medicines.The sponsor must provide the necessary details such as name, contact number of the Australian Pharmacovigilance contact person within 15 calendar days of the first entry of sponsor medicines.The significant safety issues and serious adverse events should be reported within less than 72 hours and less than 15 calendar days respectively. Under subsection 28 (5) (ca) of the act records must be maintained according to reporting requirements, Pharmacovigilance activities of the drug, and the safety of the medicines. The records must be maintained up to at least 10 years after removal from ARTG for registered medicines[14].Even the most extensive research and during clinical trialsare done before the medicine is first marketed every possible adverse event cannot be identified. Hence black triangle scheme is introduced in Australia. The goal of the "Black Triangle scheme" is to make it easy for practitioners and patients to recognize new medications as well as medicines that are used in unusual ways. A comparable scheme is currently placed across European Union including in the United Kingdom.This scheme encourages both the health care professionals and the consumers to report the suspected adverse events.The black triangle symbol and accompanying text will appear on the Product Information (PI) and Consumer Medicines Information (CMI). The black triangle symbol will appear for 5 years, starting from the date of the supply. The Australian Adverse Drug Reactions reporting system receives all data reported to TGA.The data is also sent to VIGIBASE, the World Health Organization's global database of adverse drug reactions. These databases are analyzed to detect signals which may identify previously unrecognized safety problems, an increased frequency or severity of adverse events, or patient groups that are particularly sensitive to adverse events [15].

Examples of Adverse events reported in Australia:

Drug	Adverse event reported
Sodium-Glucose co-transposer 2 inhibitors	Diabetes ketoacidosis
Risperidone	Cerebrovascular events with Dementia
Denosumab	QT interval prolongation and Hypocalcaemia
Proton pump inhibitors	Acute interstitial nephritis
Oral contraceptives	Bowel disease.

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#CASE STUDY:

Denosumab is used to treat osteoporosis have an adverse effect QT interval prolongation and

Hypocalcaemia. This is issue was identified by the TGA during the assessment of adverse events reported relating to this medicine.[16] .The adverse event was mentioned in the product information. And then, it was labelled in the special precautions and contraindications.[17]

Comparison of Pharmacovigilance in the US, INDIA,and AUSTRALIA [18] [19] [20]:

PARAMETER	US	INDIA	AUSTRALIA
Regulatory Authority Pharmacovigilance responsible body	FDA CBER, CDER	CDSCO NCC, PVPI	TGA OMSM
Guidelines followed	21 CFR314.80; 314.98 Pharmacovigilance assessment	Schedule Y of drug and cosmetics Act 1940, Rule 1945	Therapeutic goods act, 1989.
Process for reporting	Through Med-Watch and online through FAERS	ADR Reporting in AMCs or through mail or through the phone.	Australian adverse event reporting system
Types of different ADR reporting	Two forms: 1) Form 3500 2) Form 3500B	Suspected Adverse reporting form for Health care professionals- (RED form) Medicine side effect reporting for consumers- (BLUE from)	Not mentioned
Serious Adverse event reporting database	Within 15 days of occurrence through FAERS	Within 24 hours of occurrence	Within 72 hours of occurrence
PSUR Submissions	To CDER for drug products To CBER for biologics	To DCGI and PVPI	To TGA
Data lock point	70/90 days	30 days after the last reporting period	70 days/ 90 days.

II. CONCLUSION:

Pharmacovigilance is well-established in all countries. Based on the reports the regulatory authority can take a action such as adding a warning to the drug's label or taking off the drug from the market.In the USAthere is a robust innovative mobile application called MedWatch. It is easily accessible to the consumers for reporting adverse events. Underreporting is not a problem in the USA.In Australia, the black triangle scheme plays a significant role in reporting adverse events by the physicians to the regulatory body. Consumers also report through the website. In India, the main challenge is underreporting by the consumers due to inadequateawareness. Also, the Indian PV system is still lacking robustness and needs improvement. Due to a lack of training programs, lack of scientific knowledge, and language barriers, a lay person can't report to the regulatory authority. Through better PVsystems we get to know about the drug interactions, contraindications, co-morbidities interactions and we can save millions of lives.

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