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PHARMACOVIGILANCE SYSTEM IN INDIA IN COMPARISON WITH USA, EUROPEAN UNION AND FEW ASIAN COUNTRIES

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ABSTRACT: Though the anesthesia-related death of a 15-year-old Hannah Greener marked the beginning of pharmacovigilance 160 years ago, the science of pharmacovigilance was not established as a separate field until the wake of the thalidomide tragedy in 1960's. The World Health Organization (WHO) instituted International Drug Monitoring Program to internationalize the act of drug safety monitoring. Inspite of this, many countries, particularly the low and middle-income developing countries, found it difficult to implement a robust drug safety monitoring system in their country due to various technical and financial snags. India was able to establish its own pharmacovigilance system called Pharmacovigilance Program of India (PVPI) only in 2005. This article analyzes the hurdles and challenges faced by India during the implementation phase of the Pharmacovigilance program, and this article also compares the pharmacovigilance system of India with few other developed and developing countries.

INTRODUCTION: The history of pharmacovigilance dates back to over 160 years ago following the death of a 15-year-old Hannah Greener after administration of chloroform, a new anesthetic at that time, before a routine removal of an in-growing toenail [1]. Following the death of Hannah Greener, The Lancet formed a commission and invited physicians all over Britain and its colony countries to report deaths that are related to anesthesia. This formal reporting system was the precursor of today's Spontaneous Reporting System (SRS) [2]. In 1906, the US Federal Food and Drugs Act (USFDA) was passed in order to prevent adulteration and to misbrand of the food and medicines available in the market at that time.

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This could not, however, avoid the deaths of over one hundred people, in 1937, from diethylene glycol, a chemical used to dissolve sulphanilamide [3]. Thus, the Food Drug and Cosmetic Act of 1938 was made even stricter. It started banning drugs and foods with false advertisement claims and misbranding of ingredients. Perhaps the most catastrophic drug tragedy happened in 1959-61 that made the whole globe realize the need of a robust and scientific way of assessing and improving drug safety.

The Lancet again, in December 1961, published a case report of an Australian doctor, W. McBride, who first suspected a causal link between the fetal anomalies (Phocomelia) and the drug thalidomide [4]. West Germany registered the gravest effect of thalidomide tragedy, where the drug was available over-the-counter [5]. This major tragedy would have been avoided if the drug had been tested sufficiently before marketing. The World Health Assembly, in the wake of the thalidomide tragedy, requested the World Health Organization (WHO)

to develop satisfactory ways for monitoring adverse drug reactions (ADRs), especially delayed toxic effects of drugs already in use, and also to establish international monitoring centers for monitoring ADRs and to collate that information derived from national monitoring centers. This marked the birth of Pharmacovigilance as a separate branch of science. Pharmacovigilance can be defined as "a science of activities relating to the detection, assessment, understanding, and prevention of adverse drug reactions or any other drug-related problems [6]."

In reaction to these resolutions, a pilot project was started in Virginia USA in 1968 to assess the feasibility of that initiative. Within few years, the project was transferred to WHO Headquarters, Geneva, to become a formal program. The operational activities of the project were transferred to Uppsala, Sweden, between 1976 and 1978. A collaborating center was established with the support of Swedish Government, which is responsible for the operational activities of the program [7]. The board aim of this project is to develop an international system that aids in detecting previously unknown or poorly understood adverse effects of drugs. The Uppsala Monitoring Center (UMC) maintains a database of all reports of adverse effects and it presently contains over 9 million case reports [8].

Initially, the program was supported by 10 member countries, but currently, 150 countries have joined the WHO Drug Monitoring Program and have 29 countries as its associate members [8]. These member countries provide the vital information required for the database, thus globalizing the science of pharmacovigilance. The UMC supports the WHO Program for International Drug Monitoring (PIDM) by collecting, assessing and communicating information from member countries' national pharmacovigilance programs with regard to the benefits, harms, effectiveness and risks of drugs.

Pharmacovigilance In India: It is estimated that Indian pharmaceutical industries could account for about 3.5% in value of the international pharmaceutical industry. By the end of 2020, it is expected to grow to US$55 billion and to US$100 billion by 2025, thus developing as the sixth largest pharmaceutical market worldwide [9].

Branded generics constitute about 80% of the market share, and New Chemical Entities (NCEs) are also being known in the nation, also subsequently emerging as a significant crossroad for clinical research as well as various outsourcing programs [10, 11]. With a population of around 1.3 billion and various ethnicities, diverse ailment occurrence sequence, and the existence of different structures of medicine, it is indisputably vital to have a unified pharmacovigilance system in the country [12]. The problem of ADRs globally is high and accounts for significant morbidity, mortality and expense to patients.

Pharmacovigilance plays a role in developing public health policy and enhancing patients' health and safety [13]. To create a unified pharmacovigilance system in the country, The Pharmacovigilance Program of India (PvPI was started on 14th July 2010 with the All India Institute of Medical Sciences (AIIMS), New Delhi, as the National Coordination Centre (NCC). The program initially had 22 ADR monitoring centers (AMCs), including AIIMS, New Delhi so as to monitor ADRs all over the country. On 15th April 2011, the NCC was transferred from AIIMS to the Indian Pharmacopoeia Commission (IPC), Ghaziabad, for proper implementation of the program. The main aim of the program is to generate independent data on the safety of drugs and to match it with global drug safety monitoring standards.

Many clinicians in the country felt that this program may doubt their efficiency in prescribing medicine and were apprehensive about it [14]. The PvPI is working hard to overcome this challenge and constantly finding out ways to overcome the problems behind [15]. The program also aims to build a trust between the physician and the patient, thereby increasing the safety of the patient and gaining the confidence of the people in the health system of the country.

The mission of PvPI is to safeguard the health of the Indian population by ensuring that the benefit of medicines outweighs the risks associated with their use [16]. The PvPI consolidates the information collected in the form of Individual Case Safety Reports (ICSRs) from the AMCs, Health Care Professionals (HCPs), pharmacists, and other non-HCPs (medical colleges and hospitals, medical/

central/autonomous institutes or corporate hospitals not enrolled under the PvPI) **Fig. 1**. It analyses the data obtained and uses the inferences to recommend informed regulatory interventions. Simultaneously, it informs the HCPs and end-users about the risks associated with the medicines. In addition to this, the PvPI also strives to identify substandard medicines and errors arising from prescribing, dispensing, and administration to ensure better patient safety. PvPI also tries to reduce other challenges like counterfeit drugs, antimicrobial resistance, and surveillance during mass vaccinations and other national programs.

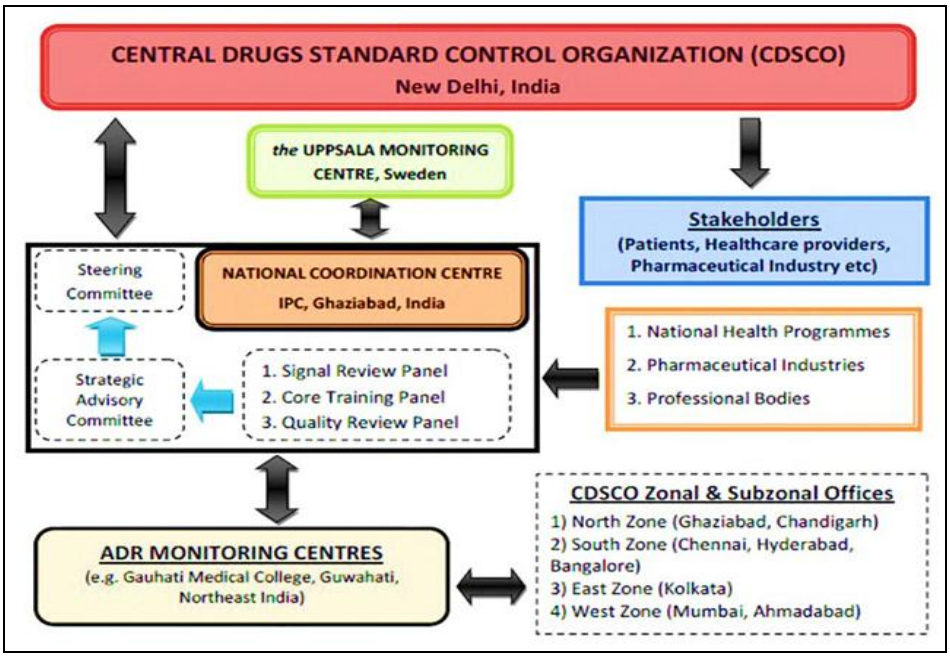

FIG. 1: PVPI ORGANIZATIONAL STRUCTURE

The NCC-PvPI is also actively involved in providing training to existing professionals in pharmacovigilance along with young healthcare professionals regarding the basics and regulatory aspects of pharmacovigilance around the year.

The NCC-PvPI IPC was also launched as a WHO Collaborating Centre for Pharmacovigilance in Public Health Programs and Regulatory Services on 30 October 2017, at the IPC in Ghaziabad.

International Aspects of Pharmacovigilance: There are differences among countries (and even regions within countries) in the occurrence of ADRs and other drug-related problems. This may be due to differences in diseases and prescribing practices; genetics, diet, traditions of the people; drug manufacturing processes used which influence pharmaceutical quality and composition; drug distribution and use including indications, dose and availability; the use of traditional and complementary drugs (*e.g.* herbal remedies) which may pose specific toxicological problems, when used alone or in combination with other drugs.

Data derived within the country or region may have greater relevance and educational value and may encourage national regulatory decision-making. Information obtained in one country (*e.g.* the country of origin of the drug) may not be relevant to other parts of the world, where conditions may differ. Therefore, drug monitoring is of tremendous value as a tool for detecting ADRs and specifically in relation to counterfeit and substandard quality products. ADR monitoring ensures that patients should obtain safe and efficacious products [17].

Pharmacovigilance in the United States of America [18]: The United States of America has one of the most stringent approval processes in the universe. The USFDA is the national public health agency that takes care of the regulatory aspects of drugs in the USA and is responsible for ensuring the safety of all marketed medical products. The USFDA encourages both recognition and voluntary reporting of serious adverse events by healthcare professionals in order to ensure safe and effective availability of medical products such as drugs, biologics, medical, radiation-emitting devices and

special nutritional products (e.g. medical foods and dietary supplements). The USFDA also makes the reporting of adverse events by the manufacturers compulsory. Therefore, adverse event reporting is voluntary by healthcare professionals and consumers whereas it is mandatory by manufacturers, packers and distributors of FDA-approved drugs and biological products. FDA's Med Watch Adverse Event Reporting Form (3500), a single page voluntary reporting form was launched in 1993 by the FDA commissioner so as to reporting all AEs associated with all medical products except vaccines.

Another form FDA (3500A) for launched for mandatory reporting. In addition, the Med Watch program was tasked with facilitating, supporting, and promoting the voluntary reporting process. In 1998, the Med Watch program implemented an online version of the voluntary FDA 3500 form for reporting via internet (www.fda.gov/medwatch). In addition, Med Watch provides a toll-free 800-phone number, 1-800-FDA-1088, for reporters who wish to submit a report verbally. Vaccines are the only FDA-regulated human use medical products that are not reported on the Med Watch reporting form. These reports are sent to the Vaccine Adverse Event Reporting System (VAERS) on the VAERS-1 form, available by calling 1-800-822-7967 or from the website (www.fda.gov/cber/vaers/vaers.htm).

The received reports are evaluated by safety evaluators, most of them are clinical pharmacists. After confirmation of a "signal" the FDA can initiate various regulatory actions, the extent and rigor of which depend on the seriousness of the AE, the availability, safety, the acceptability of alternative therapy and the outcome of previous regulatory interventions. Regulatory authorities use interventions such as boxed warning, restricted use or distribution of the drug, name or packing changes, a "Dear Health Care Professional" letter and rarely withdrawal of the drug from the market.

Pharmacovigilance in United Kingdom [19]: The medicines and Healthcare Products Regulatory Agency (MHRA) in association with the Commission on Human Medicines (CHM) runs the yellow card system in the United Kingdom (UK). The yellow card system is used to collect information on adverse drug reactions from healthcare professionals (HCPs) and lay citizens. The CHM, originally known as the Committee on Safety of Drugs, was established way back in 1964 after the thalidomide tragedy. Over half a million reports have been collected using the Yellow Card System since then. Only doctors and dentists were allowed to use the Yellow Card Scheme when it was first introduced. Eventually, all HCPs and lay citizens were allowed to use the scheme.

The filled yellow cards have to be either submitted directly to the MHRA or to one of its five Regional Monitoring Centers (RMC). Yellow Cards can also be obtained by writing to the MHRA or one of its five RMCs, British National Formulary (BNF), the Nurse Prescriber's Formulary, the Association of the British Pharmaceutical Industry Compendium of Data Sheets, and summaries of product characteristics and from the Monthly Index of Medical Specialties Companion and. An electronic form of Yellow Cards was introduced a couple of decades back in 2002 and can be downloaded from www.yellowcard.gov.uk. The pharmaceutical companies in the United Kingdom have a statutory obligation to report all suspected serious ADRs.

All suspected and doubtful reactions have to be reported using a Yellow Card. All the medical products, new drugs, and vaccines when they are first introduced into the market has to be intensively monitored in order to confirm the risk/benefit profile of the product. Those products will be labeled with an inverted black triangle, and HCPs are encouraged to report all suspected ADRs that occur because of the use of all black triangle products and further information about the black triangle scheme can be found on the MHRA website at www.mhra.gov.uk. Moreover, the patient themselves can submit a Yellow Card.

Pharmacovigilance in Australia [20]: Therapeutic Goods Administration (TGA) in Australia has established a pharmacovigilance system for the purpose of collection and analysis of information relevant to the risk to benefit balance of registered medicinal products. The TGA constantly monitors the safety profile of all the medicinal products available in Australia and, if required, takes appropriate action. Contrary to the global practice, here in Australia, the sponsor (the sponsor of

registered medicines registered with Drug Safety and Evaluation Branch of Australia) is responsible for reporting suspected adverse reactions to the TGA. The sponsor should report all unexpected and expected reactions occurring within Australia in an expedited manner.

The sponsors are not required to submit any reactions that occurred in foreign countries on an expedited basis, but the action taken by a foreign regulatory agency, including the basis for such an action, should be submitted to the TGA within 72 h. A sponsor will provide copies of foreign adverse reaction reports along with the basis for the action taken, if any.

If an individual spontaneous ADR is encountered, then a sponsor will be allowed up to 15 days to confirm and follow up the details before submitting an individual serious ADR report to the TGA. All the suspected increase in frequency of an ADR should be notified to the TGA on an expedited basis. All other reports can be reported in a Periodic Safety Updated Report (PSUR) on request.

Pharmacovigilance in China [21]: Pharmacovigilance in China is developed in four stages as shown in the figure below. After 20 years of rigorous development, a stable, mature regulatory system has been established in China.

The administrative levels of pharmacovigilance in China are four-fold national, provincial, municipal, and county. The ADR monitoring and assessment are carried out at each level.

The Department of Drug and Cosmetics Surveillance (DDCS) of the China state's Food and Drug Administration (CFDA) monitors the manufacturing, supply, distribution, and utilization of drugs, cosmetics, and special drugs or formulations.

It also monitors the implementation of ADR monitoring regulations, GMP, GSP, and 'Good Agricultural Practice' (GAP), and it responds promptly to safety issues. The Center for Drug Re-evaluation, the National Centre for ADR Monitoring (NCADRM) is affiliated to CFDA, and it aids in the decision-making based on a risk-benefit analysis.

Pharmacovigilance in Japan [22-25]: Over 10,000 patients got infected with hepatitis C after hepatitis C infected blood products were used in pregnant women in Japan between 1971 and 1990, which rocked the whole country. As a result, the Japan government tightened the regulations pertaining to pharmacovigilance in the pharmaceutical industry. Those blood-derived coagulant products were used to stop haemorrhaging after childbirth.

The saddest part is that the products continued to be used in Japan even after their withdrawal in the US in 1977. A law was passed in 2008 after the patients sued the government and the pharmaceutical companies. The law granted compensation to all who were affected and a special committee was also set up to investigate on what went wrong. In 2010, a final report was made which condemned the pharmaceutical administration in Japan and the report also made some recommendations to curb such events in the future, which paved the way for the establishment of pharmacovigilance in Japan. Not long after, the burden of pharmacovigilance was placed on MAHs, the regulatory agency (the Pharmaceuticals and Medical Devices Agency, acronym PMDA), the Ministry, healthcare professionals, and even ordinary citizens. There remains a strong focus on infections in safety reporting. The regulatory agency makes recommendations, but the final decisions for Marketing Authorization Applicants (MAAs), re-examinations, and re-evaluations are taken by the Ministry. The PV inspections are not conducted by the agency, but the agency distributes relief funds to patients who have suffered ADRs.

Pharmacovigilance in Germany [26, 27]: The current pharmacovigilance framework of Germany is largely harmonized into the European Union (EU) and ICH framework. The history of pharma-covigilance in Germany dates back to 1950s when a German pharmaceutical company Grunethal manufactured a sleeping pill called Contergan, which was available over-the-counter. Contergan was also prescribed by a German physician to expectant mothers to combat morning sickness. Contergan contained an active ingredient called thalidomide, as it is widely known in non-German speaking countries. Between 1950s and 1960s, the drug led to around 5000 babies born with severe limb and other organ deformations in former West Germany.

After this tragedy, testing of pharmaceuticals was made compulsory in 1964 for the first time in West Germany. The forerunner for the current competent authority, the Institute for Pharmaceuticals (Institute for Arzneimittel), was formed in 1975. The purpose of this institute was to review the quality, efficacy, and safety of all pharmaceuticals.

A major revision of the Medicinal Products Act happened in 1976 called "Arzneimittelgesetz", acronym AMG. When another tragedy involving the administration of HIV infected blood products to haemophiliacs struck Germany, Federal Health Agency in 1994 was dissolved, and the responsibilities were split between three new independent organizations; the Federal Institute for Drugs and Medical Devices, the Robert Koch Institute and the Federal Institute for Consumer Health Protection and Veterinary Medicines.

CONCLUSION: The Drug Controller General of India has shown its commitment to ensuring the safe use of drugs by establishing the National Pharmacovigilance Program. The challenges in the implementation of better pharmacovigilance in the country due to nonavailability of trained staff in pharmacovigilance, lack of training of healthcare professionals in drug safety and ADR reporting, lack of expertise, *etc*., should overcome by Indian regulatory body via knowledge-based systems. For an effective pharmacovigilance system to be functional and efficient, all the stakeholders need to be alert and attentive throughout the lifecycle of a medicinal product in the market.

The healthcare professionals, patients, and pharmaceutical companies should report ADRs by own selves and actively participate in the pharmacovigilance system of the country. The system needs to be reviewed timely to face future challenges. Ultimately, effective pharmacovigilance will facilitate the competent pool of data from all sources, transformation of significant data into information with authorization of the country to use this information, enhancing the trends of medicine use in their countries, and enable to make judicious therapeutic judgments on the usage of the medicine.

The progression of pharmacovigilance cannot occur in inaccessibility; rather, it must be part of a larger effort to improve global clinical research and development and reform the regulatory system. The PvPI has strived tirelessly to achieve its goals. These continued efforts have resulted in remarkable achievements within a period of 6 years. Despite its achievements, the program intends to continue with the same fervour to meet its challenges, like creating awareness and inculcating the reporting habit in the country's population, with special attention to disease-specific ADRs. It is noteworthy that monitoring generic drugs and biosimilars is becoming a major challenge. The regulatory authorities must address these challenges in a harmonized manner with the best pharmacovigilance practices.

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