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W H I T E P A P E R

Historical Perspective, Current Status and Newer Trends in Pharmacovigilance

THE REPORT

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1. Introduction

Pharmacovigilance, also known as drug safety, is a precise and dynamic clinical and scientific field. Clinical trials are conducted to evaluate the safety and efficacy of new drugs in humans under extremely controlled conditions and with a limited number of subjects. So there is always a chance that a new drug will behave differently in the real world patients with concurrent co-morbid conditions with polypharmacy or in long-term use in terms of safety, where these controlled conditions and limitations will no longer apply. Hence the practice of examining these safety concerns after post marketing is called pharmacovigilance.

Pharmacovigilance is now the activity of contributing protection of patient and public health through providing timely information about drug safety to patients, healthcare professionals, and the public; however, WHO also brought safety of herbal and traditional medicines, biological, and medical devices under the radar of pharmacovigilance. The World Health Organization (WHO) has succinctly defined this process as a "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem." Previously, detecting adverse effects and reporting them to drug manufacturers or regulators was a lengthy process that did not maintain timeliness.

As an illustration, consider teething gel, which was originally made available on the market in 1970. In 1980, patients began to voice concerns about potential negative consequences. The AE reporting system received the first adverse reaction report in 2004 after 34 years, and in 2014, the label was modified to include a warning signal for methemoglobinemia. Since its proactive inception following the thalidomide tragedy, this field has grown significantly and evolved into a multibillion dollar business, supported by strict regulations from various countries' regulatory authorities regarding the safety of marketed drugs and the globalization of pharmaceutical and biotechnological companies worldwide. Additionally, newer technologies have replaced the traditional pharmacovigilance system.

2. History of Pharmacovigilance

Our perception of what constitutes safe medicine has likewise evolved throughout time. In the past, physicians believed that the onset of an unfavourable effect was an indication that the drug was working and had reached its maximum therapeutic dose. However, it ought to be separated into two sections when referred to as a history of pharmacovigilance, pharmacovigilance before and after thalidomide tragedy. The Thalidomide disaster was the catalyst for the development of modern pharmacovigilance. A common antiemetic drug used by pregnant women to treat morning sickness in the late 1950s and early 1960s caused a

terrible adverse reaction in newborns, known as phocomelia, which is characterized by shortness of limbs.

(Photo Credit: Freepik/freepik)

2.1 Pre-Thalidomide Tragedy Pharmacovigilance

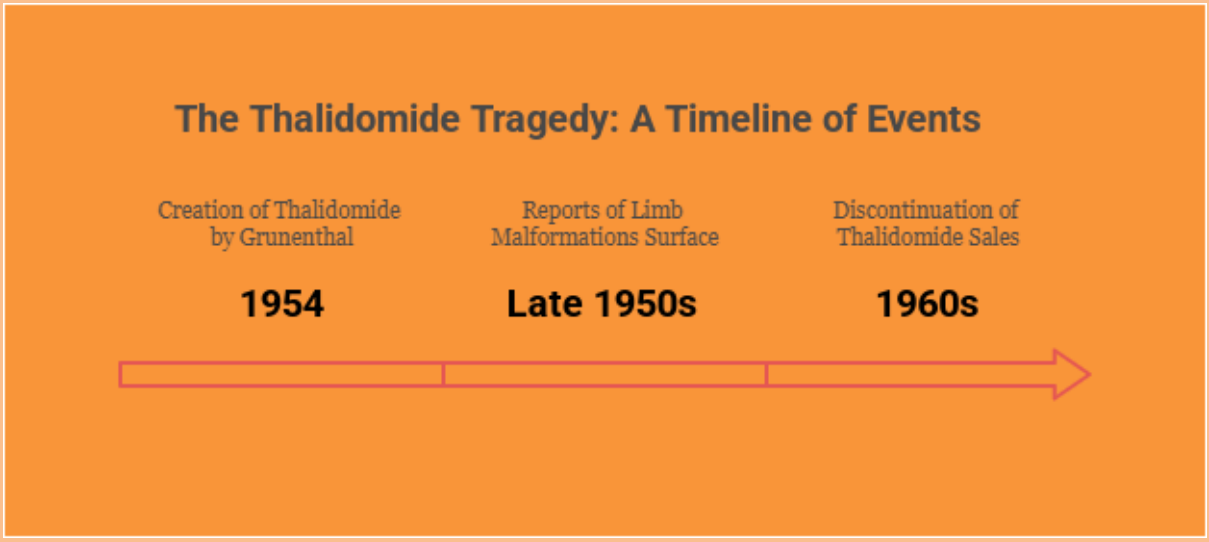
Before thalidomide tragedy, the regulators or governments were working submissively for safety of medicines, more precisely in reactive mode. The steps taken for drug safety or patient safety were merely the reaction to a particular event happened in history and not proactive step for minimising adverse effects before launch of medicine in to market.

A 15-year-old girl who had previously tolerated diethyl ether anesthesia well died in 1848 from chloroform anesthesia while undergoing surgery for an ingrown toenail. We can claim that spontaneous reporting began when The Lancet, a prestigious scientific research publication house at the time, urged physicians to record anesthesia-related deaths in Britain. The USA passed the Biological Control Act in 1902 to ensure the safety and purity of biological products, such as vaccinations and serums. Thirteen children died in 1901 after receiving tainted injections of diphtheria antitoxins, which sparked the creation of this act. In his 1906 book The Jungle, American journalist and author Upton Sinclair revealed the unhygienic practices and health risks in the meatpacking and pharmaceutical industries, which paved the way for the creation of the Food and Drug Act of 1906. This law forbade the

interstate sale of tainted food and pharmaceutical items, but it made no mention of the efficacy or safety of the medications.

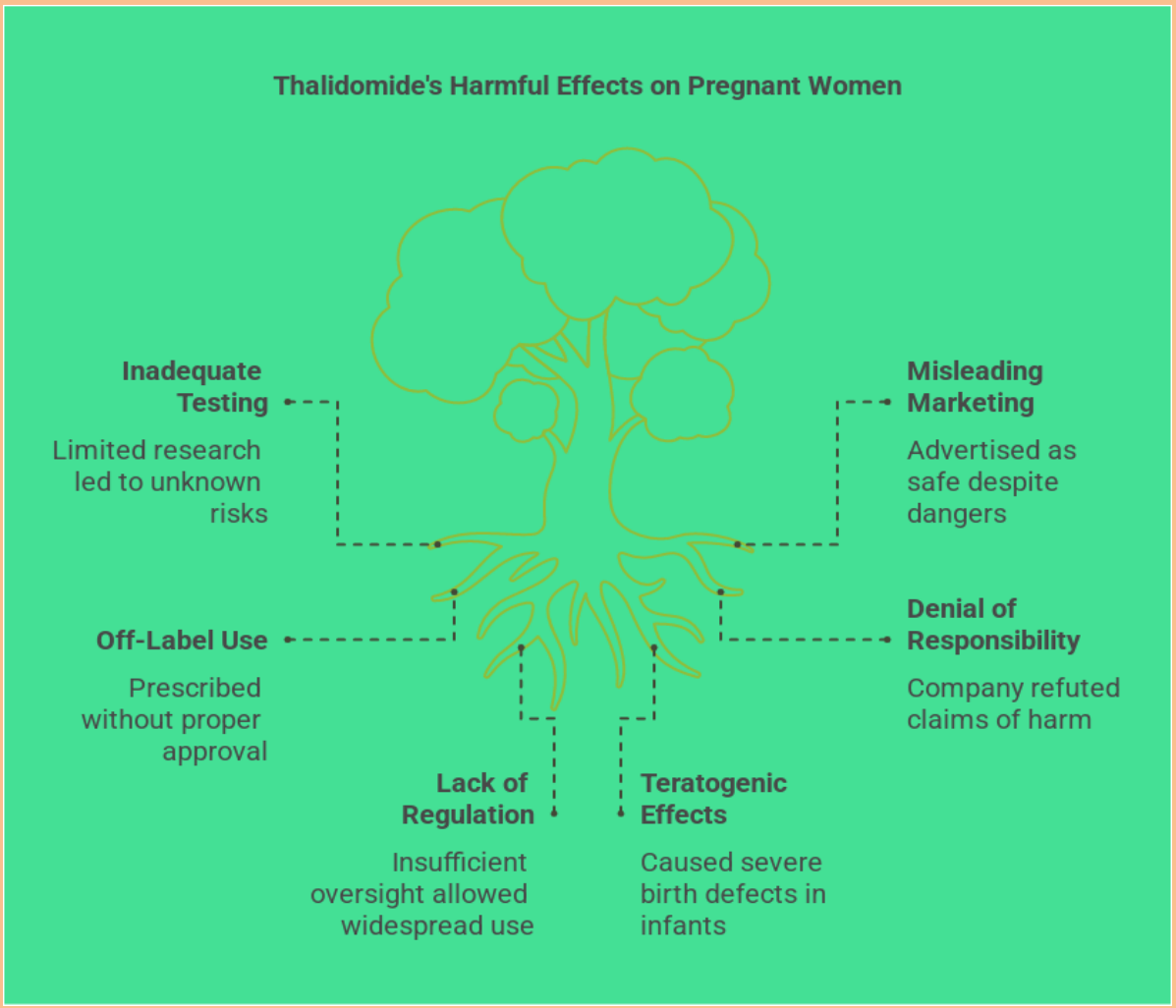
The next major disaster that rocked the world occurred in 1937 and claimed the lives of 105 people, including 35 children. One pharmaceutical business released a well established anti-infective medication sulphanilamide in novel liquid format. For many years, this medication's tablet and powder forms were safe and well-tolerated for streptococcal infections. New elixir form was formulated in raspberry flavour especially for children. Physicians reported numerous kidney failure-related deaths to the American Medical Association (AMA). Ethylene glycol was the toxic material that AMA extracted from this elixir. After that, unused products were recalled and only doctors were notified. At that time selling poisonous substance was not illegal but misbranding was. The sulphanilamide event was the major turning point which modified food and drug act into food, drug and cosmetic act (FDCA), enacted in 1938. FDCA was now responsible for regulation of dangerous medical product. FDCA was begun government's endeavour to assess risk benefit balance of medical product and started demanding for safety proof through New Drug Application (NDA). The second significant FDCA amendment, known as the Durham-Humphrey amendment 1951, divided medications into two categories: those that needed a prescription from a doctor and those that could be taken without one. The later were also dubbed over the counter (OTC) medications.

2.2 Thalidomide Tragedy

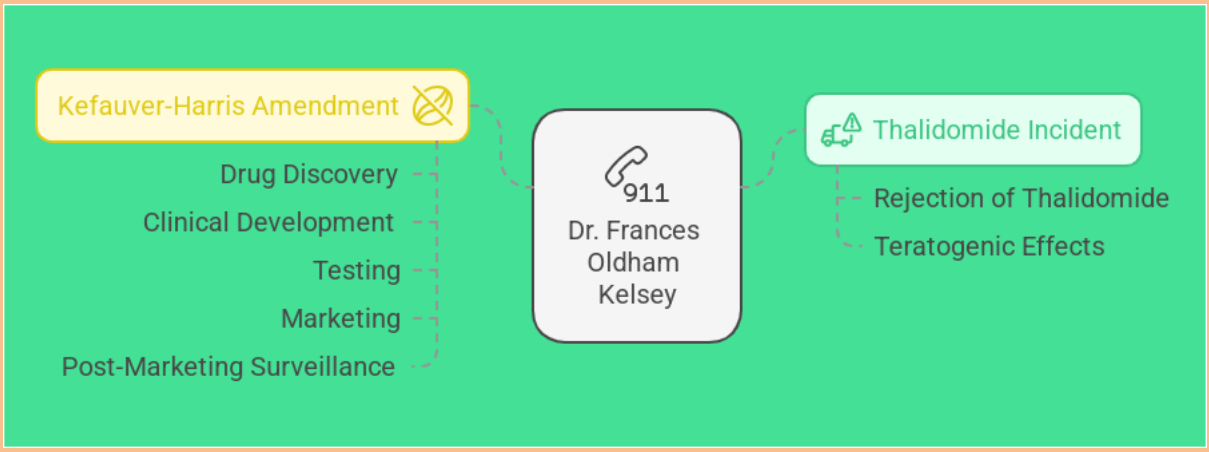


In the 1950s, the only non-barbiturate sedative on the market was thalidomide. In 1954, the German pharmaceutical company Grunenthal accidentally created it. Grunenthal conducted a brief clinical investigation on people for sedation following preclinical research on rats and discovered that it caused sleep in humans. Grunenthal advertised the medication as being

entirely safe when sold over-the-counter. When doctors queried its action on foetus, Grunenthal answered 'unknown'. Peripheral neuropathy was the first significant side effect of thalidomide that long-term users reported experiencing. Grunenthal, however, refuted this assertion, stating that it was uncommon and reversible if halted. The practice of administering thalidomide to pregnant women for morning sickness was begun by an Australian doctor who found that the medication helped with morning sickness and began prescribing it off-label to his pregnant patients. Reports of newborn babies born with severe limb malformations, including shortness of both upper and lower limbs, and exhibiting the hallmarks of phocomelia began to surface in the late 1950s and early 1960s from 46 countries where thalidomide was marketed. Babies born to moms who had taken thalidomide during the second month of pregnancy were found to have these limb abnormalities. Additionally, doctors reported that these moms had used a teratogenic substance while pregnant. The Grunenthal denied any connection to thalidomide despite the terrible side effect that was suspected to be caused by the drug. However, they were forced to discontinue its sale in Germany, and it was later outlawed in the majority of nations.



2.3 Regulations after Thalidomide Tragedy



One incident that occurred prior to this tragedy illustrated the importance of stringent regulations requiring proof of safety for medications before they are put on the market. Dr. Frances Oldham Kelsey, a medical officer with the US FDA, rejected the proposal to market thalidomide in the United States when it was introduced as a sedative in other countries. Dr. Kelsey's decision was based on the fact that thalidomide had never been tested on pregnant women and that its teratogenic effects were unknown. Before approving their marketing proposal, Dr. Kelsey insisted that the manufacturer of thalidomide demonstrate its safety through scientifically sound testing and other complaints. This decision of Dr. Kelsey was later appreciated by American public and government of President John F Kennedy and awarded Dr. Kelsey with President's Award for her distinguished Federal Civilian Service.

Following the catastrophe, everyone realized how crucial it is to test products for safety and efficacy before releasing them onto the market. But the rules of many nations differed. The Kefauver-Harris Amendment 1962 was a 1962 amendment to the United States' Food, Drug, and Cosmetic Act. Using the code of federal rules 21 that are dispersed across the product's lifespan, the Kefauver-Harris amendment established the present framework for medication approval in the United States. This framework includes drug discovery, clinical development, testing, marketing, and post-marketing surveillance.

2.4 WHO-International Drug Monitoring

The World Health Organization (WHO) had taken coordinated international action to address the problem of drug safety shortly after the thalidomide tragedy. The 16th World Health Assembly adopted a resolution confirming the need for prompt action on reports of adverse drug reactions, and later in 1968, WHO initiated its pilot research project on International Drug Monitoring with the goal of creating a globally applicable system to monitor and detect adverse drug reactions that had not yet been identified. Through systemic post-marketing

surveillance through national pharmacovigilance centres of member states, WHO's central database of ADRs received data from patient files worldwide. This step implicated the science and practice of pharmacovigilance. The Uppsala Monitoring Centre in Uppsala, Sweden, currently coordinates international drug monitoring, and over 136 nations have joined as member states (WHO).

2.5 United Kingdom on Pharmacovigilance

In 1964, two years after the thalidomide catastrophe, the UK established a committee on drug safety (CSD), which was subsequently, renamed the Committee on Safety of Medicines (CSM). In order to do this, the government asked doctors and dentists around the United Kingdom for information on adverse medication reactions. The UK created a yellow card system for reporting purposes, and all doctors received these cards. The yellow card system was the colloquial name for this method. Under this system, pharmacists participated in 1997, nurses in 2002, and customers in 2005.

2.6 Japan

Under the "Re-examination System for New Drugs," which was established in 1967 by the Ministry of Health and Welfare of the Government of Japan, hospitals in Japan were asked to report any serious adverse drug reactions (ADRs) to the national pharmacovigilance system. In contrast to many other systems around the world, the Japanese government began rewarding reporting physicians with a small amount of cash as well.

3. Current Status of Pharmacovigilance

The current state of pharmacovigilance around the world has developed as a result of enduring the consequences of unanticipated historical incidents. Every nation had passed legislation pertaining to the safety and effectiveness of pharmaceuticals following the thalidomide tragedy, but a global platform was required to standardize the pharmacovigilance process, from reporting adverse drug reactions to benefit risk analysis and signal detection. Numerous organizations, including governmental, nongovernmental, and nonprofit groups, have previously taken steps to condense the pharmacovigilance system into a widely recognized standard procedure and incorporate it into the current system.

3.1 Council for International Organizations of Medical Science (CIOMS)

Established in 1949 by WHO and UNESCO, the Council for International Organization of Medical Sciences (CIOMS) is a nongovernmental, nonprofits organization that serves the scientific interests of the scientific biomedical community. Its mission is to advance public health by providing guidance on health research, including safety, ethics, and the

development of medical products. In 1977, CIOMS hosted a conference on the subject of Trends and Prospects in Drug Research and Development. The conference's predictions were that, as a stand-alone organization, CIOMS could be crucial in bringing together government and academic experts with policy makers from research-based pharmaceutical industries to discuss and make recommendations on particular issues. In order to establish coordination and standardization for reporting adverse drug reactions to regulators from the pharmaceutical industry, a working group of adverse drug reactions was formed in 1986. As a result, the international adverse drug reaction reporting form and a tried-and-true procedure were released for reporting ADRs from the pharmaceutical industry to the regulatory authorities of the USA, UK, Germany, and France. In the early 1980s, CIOMS began focusing on monitoring drug safety and reporting adverse drug reactions as part of its Drug Development and Use program, which it launched in partnership with the World Health Organization.

The purpose of the second working group was to investigate the potential of a globally accepted method for creating safety update summaries. Regulatory bodies needed these safety reports on a regular basis to assess how well the medicine performed in the market in terms of post-marketing safety. Therefore, the standard format that these periodic summaries must report to regulators in was provided by CIOMS working group II. In 1992, the CIOMS-II report on medication safety updates was released. The most crucial component of useful information for medical professionals regarding the product's risks and benefits was the regulatory approval of the pharmaceutical product. Without such a standardized format and set of guidelines, it is believed that there would be differences and inconsistencies between nations and manufacturers. The proposal from the CIOMS-III working group addressed the clinical safety labelling standards and the creation of the company's core data sheet. In 1994, the CIOMS-III report on CCDS of pharmaceuticals was released. The CIOMS-IV working group meeting resulted in a guideline for the medicinal product's benefit-risk analysis. Through CIOMS IV, the working group anticipated that regulatory agencies and pharmaceutical corporations would adhere to the systematic approach provided by the CIOMS-IV working group.

3.2 International Council for Harmonization (ICH)

EFPIA organized a meeting in Brussels in April 1990 that resulted in the creation of the International Council for Harmonization, formerly known as the International Conference on Harmonization. At first, it was made up of industry professionals and regulatory bodies from

the USA, Japan, and Europe. The ICH was in charge of developing several guidelines regarding the efficacy, safety, and quality of new pharmaceuticals.

Following the establishment of ICH, it became apparent that using distinct terms for adverse drug reactions at various phases was challenging, expensive, and time-consuming. The Medical Dictionary for Drug Regulatory Activities (MedDRA), the most sophisticated adverse drug reaction terminology, was created in response to this need and is now used by pharmaceutical companies for regulatory purposes pertaining to ADRs.

The rule E2A provided recommendations on how to handle quick reports of adverse drug reactions (ADRs) during clinical development stages as well as standard terminology for clinical safety reporting. While E2C explained periodic benefit risk evaluation, E2B explained electronic transmission of ICSR. Post-marketing expedited reporting rules and definitions were outlined in the E2D guidelines. Early post-marketing pharmacovigilance planning efforts for new medications were outlined in E2E guidelines, with a primary focus on the pharmacovigilance plan that must be submitted with a license application. Reports on development safety updates are handled by E2F.

3.3 Good Pharmacovigilance Practice

The European Medicine Agency was established in 1995 to guarantee the safety, efficacy, and quality of pharmaceuticals sold within the European Union (EU). For this reason, the European Union has established Good Pharmacovigilance Practice (GVP) recommendations regarding the safety of pharmaceuticals. The sixteen modules from I to XVI address the main pharmacovigilance procedure guidelines. These guidelines provide comprehensive information about the pharmacovigilance system that holders of marketing authorizations for pharmaceuticals must adhere to if they wish to sell their goods in any EU member state. The first seven modules of this new pharmacovigilance legislation were released in July 2012, and it was later enlarged to its present sixteen modules.

Major processes under pharmacovigilance activities at the MAH level make up each GVP module. According to GVP, MAH should submit to EMA the Risk Management Plan (RMP) under module V and the Periodic Safety Update Report (PSUR) to assess the benefit-risk ratio of the marketed medicine under module VII. Module VII explained that after MAH received approval to market the drug in the European Union or European Economic Area, PSUR should submit six monthly for the first two years, then annually for the next two years, and finally three times a year after that. The phrase Periodic Benefit-Risk Evaluation Report

(PBRER) has more recently taken the place of PSUR (ICH-E2C guideline). Eudravigilance is used to report all ADRs in the EU region.

3.4 USA

The Code of Federal Regulation Title 21 part 314 governs post-marketing adverse drug reaction reporting in the United States. Section 314.80 governs FDA approval applications for new drug marketing. The FDA Adverse Event Reporting System (FAERS) receives the information from the FDA. For reporting purposes, ADR Form 3500A or 3500B is utilized. Mandatory reporting from regulated industries uses the former, whilst voluntary reporting from consumers and healthcare professionals uses the latter. Med Watch has been used for online reporting. The Center of Drug Evaluation and Research (CDER) or the Center of Biologics Evaluation and Research (CBER) evaluated the reported adverse drug reactions. Through the Periodic Adverse Drug Experience Report (PADER), the MAH is required to send a periodic report to the FDA detailing the risk-benefit analysis of their medication marketed in the United States. The report must be submitted quarterly for the first three years, and then yearly after that.

3.5 India Initiatives to Strengthen Pharmacovigilance

The Pharmacovigilance Programme of India (PvPI), which was introduced in July 2010, was the third attempt to establish pharmacovigilance in India, following two previous attempts in 1986 and 2005. The 2010 system's framework includes four regional centers, one National Coordination Center (NCC), and 22 ADR monitoring centers, the majority of which are located in government teaching medical colleges. At the program's inception, All India Institutes of Medical Science (AIIMS), New Delhi, served as the NCC. The NCC was moved to its present site at the Indian Pharmacopoeia Commission (IPC), Ghaziabad, Uttar Pradesh, later in April 2011. ADR monitoring has recently expanded to 250 locations throughout India, including district hospitals, corporate hospitals, ICMR research centres, and government and nongovernment medical schools. This time, pharmacovigilance has been successfully implemented in India thanks to the efforts of Indian scientists to reach out to healthcare professionals at the local level. In order to help the Central Drug Standard Control Organization (CDSCO) make decisions regarding the safety of marketed medications, this program aims to gather unprompted reports of adverse reactions from patients and healthcare professionals caused by medications marketed in India. The data is then sent to the Uppsala Monitoring Center (WHO-UMC). IPC is currently a WHO-Collaborative Center for Regulatory Services and Pharmacovigilance in Health Programs.

More recently, in March 2016, the Indian government made changes to its schedule Y in accordance with the 1945 Drug and Cosmetic Act. Clinical trial requirements and recommendations are included in Schedule Y. Pharmacovigilance guidelines have been provided to MAH who wish to promote their product in India under the recently updated Schedule Y. Previously not required, this guideline requires the MAH to set up a pharmacovigilance system at the MAH level in order to report all adverse drug reactions (ADRs) of their product to PvPI. The PSUR filing timetable, which is the same as EMA, is also outlined in Schedule Y. For the purpose of reporting adverse drug reactions, PvPI has created a suspected adverse drug reaction form in English for healthcare professionals and in ten regional Indian languages for consumers or non-healthcare professionals. These forms are available for download on the Indian Pharmacopoeia Commission website or in person at any ADR Monitoring Center in the nation.

4. New Trends in Pharmacovigilance

The field of pharmacovigilance has significantly changed throughout time as a result of numerous international rules and regulations. Drug manufacturers are able to see more and more ways to gather as much information as possible about the safety of their products thanks to strict regulations. They are also able to use more and more cutting-edge technologies to speed up the process and lessen the pressure to meet regulatory bodies' various requirements, which has resulted in more high-quality work being produced.

4.1 Social Media

The pharmacovigilance community has a long history of using the Internet. Through Med Watch in the USA, Med Effect in Canada, and the Yellow Card system in the EU, adverse effects can be reported directly to the FDA. In their module VI, the EU GVP guidelines also addressed the use of the internet for literature searches in order to monitor potential adverse events. The usage of social media, including Facebook, Twitter, and more recently WhatsApp, has grown significantly among individuals worldwide during the past seven to eight years. In contrast to the conventional PV system, social media stands out as the new avenue for reporting adverse medication reactions. Social media provides a more patient-focused platform for reporting adverse drug reactions, analyzing, and tracking safety information. It permits and facilitates direct connection between the patient and the healthcare professional. It has been noted that members of online communities frequently tell friends and relatives about their negative medication experiences. Another benefit of this adverse event monitoring channel is that the online shared data acts as documented evidence,

allowing for the tracking of the reporter's identity and the authentication of the adverse experience. Additionally, the data remains online for a longer period of time unless and until the reporter deletes it. Additionally, it makes it possible to identify adverse experiences caused by specific drugs by tracking down adverse events online using relevant terms: pharmaceutical combination.

Researchers from the FDA and WHO-UMC conducted a retrospective investigation on the assessment of Face book and Twitter to identify safety signals. Product event pairs were used to capture 935246 posts in total for this investigation. Researchers contrasted these posts with the FDA's most recent signals. According to the study, two social media messages that were in line with recent FDA safety alerts were shared. One of these two postings was shared prior to the FDA detecting the signal from FAERS, but the second post was shared first. Social media as a PV tool should be carefully evaluated and assessed in terms of meaningfulness and impact on result, even though it has advantages over the conventional approach of detecting bad events.

4.2 Mobile App and Toll free number

With the help of various apps, a mobile phone can now perform numerous functions with a single click. This feature is currently being used by many authorities worldwide to streamline the ADR reporting procedure. Although the UK's Yellow Card system was established many years ago to report ADRs, its mobile app for ADR reporting was released in July 2015. People in the UK can now use the Yellow Card Mobile App 35 to immediately report ADRs to the regulating body. In order to expedite ADR reporting to the Pharmacovigilance Program of India, the Indian Pharmacopoeia Commission released its mobile app in May 2015, two months prior to the UK's mobile app debut. PvPI has also introduced a toll-free number, 1800-180-3024, for immediate ADR reporting to regulatory bodies in addition to its mobile app. PvPI employees at the National Coordination Center oversee a toll-free number, and the information about ADRs is thereafter sent to the closest ADR monitoring center in that area. In this manner, HCPs at the ADR monitoring center visit the reporter to obtain medical validation if the ADR was reported by a non-healthcare professional.

(Photo Credit: Freepik/freepik)

4.2.1 WEB RADR

The company that developed the adverse drug reaction reporting mobile app, WEB RADR, has created the HALMED app for reporting in Croatia, the LAREB app for reporting in the Netherlands, and the yellow card app for the UK. Additionally, WEB RADR developed apps for Burkina Faso, Zambia, and other African nations.

4.3 Outsourcing

Over the past ten years, outsourcing some of the job has become commonplace in the pharmaceutical sector. By 2024, the pharmacovigilance industry is expected to grow to a value of $8 billion USD. By outsourcing, the pharmacovigilance sector can perform sophisticated PV processes from a trained pharmacovigilance team at a contractor's location without having to hire these experts directly. These outsourcing firms provide comprehensive pharmacovigilance services, such as risk management, medical affairs, regulatory affairs, and case processing. Pharmaceutical corporations are the ones who wish to outsource. While some pharmaceutical companies outsource the entire pharmacovigilance process, others outsource only a portion of it (ICSR processing), with the remaining portion being handled internally, especially at their global or national headquarters. These outsourcing businesses are mostly knowledge process outsourcing (KPO) enterprises, full-service CROs, specialty

contract research organizations, and individual consultants. These businesses can handle challenging PV projects since they have specialized personnel and strong technologies.

4.4 AUTOMATION: Artificial Intelligence, Machine Learning and Natural Language Processing

Artificial Intelligence (AI), machine learning, and natural language processing—more specifically, cognitive computing—have been hot topics in pharmacovigilance over the past year. Good pharmacovigilance practice regulations require that pharmaceutical companies take further steps and take a proactive approach to patient safety. Drug manufacturers rely on their websites, forums, inbound emails and calls, and scholarly literature for safety signals in pharmacovigilance. However, in practice, a signal might be found in posts on Facebook and Twitter, in independent patient forums and blogs, in comments posted on WordPress, and on YouTube and Pinterest. It was estimated that 10–17% of ADRs were overlooked because pharmaceutical companies were unable to identify ADRs through these routes. AI began to show up in the press as a solution to this sea of possibilities. AI is now starting to change the capabilities of human teams. AI and natural language processing can now filter and clean data by eliminating erroneous and irrelevant information. It can decipher human languages and analyze everything from brief tweets to lengthy WordPress pages. Machine learning algorithms allow software to watch and adjust to teams, just as human teams communicate and share data. Meaningful data is ultimately provided to the user with the choice to share results with the team and submit adverse events to the regulatory processor for immediate action. It was thought that this most recent technology could provide precise results from searches on the entire internet and social media platforms in just ninety seconds, and those red flags would alert supervisors to significant and dangerous issues. Because it lowers case processing costs and improves data quality, this is currently seen as the true game changer in pharmacovigilance. Despite all of AI's benefits, some people are skeptical about its reliability. Although they enjoy the concept of AI, pharmaceutical companies are worried that automation won't yield the same results as traditional case processing. Therefore, everyone in the pharmacovigilance community is currently waiting to see how AI will affect pharmacovigilance.

4.5 Global Harmonization

Although worldwide recommendations led by the FDA, ICH, and EMA have advanced the majority of pharmacovigilance processes, there is still a lack of full harmonization, and some nations still enforce their own laws and regulations for the processing of safety data. This has

led to a need to harmonize the entire process in order to streamline pharmacovigilance on a global basis. This includes harmonization goals that specify data ownership at the international level, patient safety, and the regulations required for information sharing on a global scale. The FDA and EMA have made one step in this approach with the creation of "Cluster." The FDA defines Cluster as the frequent joint meetings between EMA and other regulatory agencies outside the EU to examine matters pertaining to a certain product's safety. The industry, regulators, and patients will all gain from this new global harmonization trend since it will make international data sharing quicker, simpler, and more efficient.

4.6 Vaccine Pharmacovigilance

The vaccination industry is evolving quickly, raising questions about its safety. In the past, affluent nations were the first to adopt vaccines, while low- and middle-income countries (LMIC) followed several years later. The situation is now different; some vaccinations, like the meningococcal vaccine and the candidate vaccines for dengue and malaria, may be introduced in LMIC first, while newly developed vaccines, like the rotavirus vaccine, were introduced in LMIC fairly soon after they were launched in industrialized nations. Given the resource-constrained environment for vaccination safety in LMICs, pharmacovigilance will become essential. The World Health Assembly presented the Global Vaccine Safety Blueprint, a vaccine safety strategy, in The Global Vaccine Action Plan in 2010, marking the start of the WHO's ten-year vaccine campaign. Every nation in the world will have at least a rudimentary capacity for vaccination safety according to this model. The strategy plan for enhancing vaccine safety efforts worldwide is contained in this document. The Global Vaccine Safety Initiative (GVSI) was established to carry out this plan. The eight objectives of this GVSI are designed to promote and develop a holistic approach to vaccine pharmacovigilance in all LMICs. 1) Adverse event following immunization (AEFI) identification 2) Safety signal investigation are the eight goals. 3) Communication about vaccine safety 4) Instruments and techniques 5) Regulatory structure 6) Technical assistance and instruction 7) International analysis and reaction 8) Public-private information sharing.

4.7 Active Pharmacovigilance: *Sentinel Initiative*

As we previously noted, worldwide pharmacovigilance changed from a reactive to a proactive posture following the thalidomide catastrophe. However, in 2008, the FDA believed that its attempts to gather safety information from clinical trial and spontaneous reporting were insufficient to take action on medications sold in the United States. Therefore,

the United States of America established the Sentinel Initiative initiative in 2007 along with the Mini Sentinel Initiative, which was its pilot version. Through a nationwide electronic system for tracking the safety of FDA-approved medications, the FDA is actively seeking safety data under this effort, which is known as "Active Pharmacovigilance," as opposed to "Passive Pharmacovigilance." Instead of replacing the current post-marketing surveillance system, our Sentinel System will supplement it. A comprehensive picture of safety concerns pertaining to FDA-approved medications is provided by this mix of passive and active surveillance. The FDA and all pharmacovigilance drug regulators across the world will benefit from this trend of active pharmacovigilance.

4.8 Pharmacogenomics-Personalised Medicine

When it comes to the safety and effectiveness of pharmacological therapy in two distinct persons, differences in the hereditary and non-inherited features of genomes are significant. Pharmacokinetics or pharmacodynamics may be associated with these genetic differences. During clinical development, it is challenging to identify populations with either increased or decreased response to medication due to genomic changes because, as was previously noted, the new drug was only administered to a very small number of patients under extremely stringent settings. Determining which population has a particular genotype and phenotype will help with therapy customization, reducing risk and boosting medication effectiveness. On the other hand, in addition to the positive clinical outcome, the patient will also gain financially since more appropriate medication will be administered rather than trying them on unnecessary drugs. The European Medicine Agency's Committee for Medicinal Products for Human Use (CHMP) established several important guidelines for the application of Pharmacogenomics in pharmacovigilance. Pharmacovigilance will benefit from this Pharmacogenomics trend since fewer adverse events will be reported, but there will be a greater need for high-quality data.

4.9 Pharmacovigilance Quality Assurances (PhVQA)

Pharmacovigilance system audits for MAH were formerly contracted out to an outside service provider. However, the growing number of audits suggests that this is not a wise financial move. Presently, MAH is required to conduct both internal and external audits, with two to five audits per year, as mandated by EMA through GVP modules and Pharmacovigilance System Master File (PSMF). Additionally, PSMF incorporated open corrective action preventive action (CAPA) for the audit's top important findings. Along with

audits, this new procedure also covers other tasks including data integrity, change controls, deviations, inspection remediation / CAPA, and CAPA effectiveness, among others.

4.10 Non Interventional Studies/ Observational Studies

Over the past few years, there has been a greater interest in non-interventional research in pharmacovigilance. The GVP module VIII, post-authorization safety study, is where non-interventional studies that follow the marketing of pharmaceuticals first appeared. As the name suggests, there is no patient therapy intervention in this trial. The only thing the researcher did for this study was watch patients being treated in a clinical environment and record different things that happened while they were being treated. There was no recommendation or alteration of treatment. NIS was tasked with monitoring the medication's effectiveness and safety once it was put on the market. Questionnaires, interviews, or study-specific blood collection may be used in NIS. When making decisions regarding the safety of medications, MAH or regulators can use this data as evidence.

4.11. Medical Device Pharmacovigilance

The process of tracking and assessing the safety of medical devices over the course of their lifetime is known as medical device pharmacovigilance. In recent years, the laws around medical devices have been greatly strengthened by all international regulatory bodies, making it mandatory to monitor and report any adverse occurrences involving these devices.

5. Conclusion

Since its inception following the thalidomide tragedy, global pharmacovigilance has advanced significantly in terms of quality, speed, and the development of new techniques and technology. The thalidomide disaster was the true turning point in the history of pharmacovigilance, even though it had been established many years earlier and was demonstrated by a few isolated incidents that occurred in the past. Pharmacovigilance gained attention due to strict restrictions on drug safety, and the pharmaceutical sector worked tirelessly to meet all safety data requirements in order to prevent product rejection. During this process, numerous governmental and nongovernmental organizations developed their own rules and regulations to streamline the pharmacovigilance procedure on a worldwide scale. Pharmaceutical firms began utilizing cutting-edge techniques and new technologies for monitoring and detecting adverse drug reactions in order to monitor the performance of their products in real time and expedite regulatory procedures. Global pharmacovigilance is being carried forward by these new tendencies, which have also made the procedure increasingly accurate.

7. References

1. Jeetu G, Anusha J. Pharmacovigilance: A worldwide master key for drug safety monitoring. J Young Pharm 2010; 2(3): 315-320.

2. Dave VS. Current trends in pharmacovigilance. J Pharmacovigilance 2013; 1(2): 1000e104.

3. European Medicine Agency. Guidelines on good pharmacovigilance practices (GVP). Introductory cover note EMA/213497/2017.

4. WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. World Health Organization, Geneva 2004.

5. Lichtenfeld I. The past, present and future of pharmacovigilance. dddmag.com/drug safety 2016 March 17.

6. Young S. FDA warns about benzocaine baby pain gel. cnn.com 2012 June 1st.

7. Jones JK, Kingery E. History of Pharmacovigilance. Elizabeth B. Andrews and Moore N Editors. Mann's Pharmacovigilance. 3rd ed. John Wiley and Sons, Ltd 2014. p. 11-24.

8. Knight III PR, Bacon DR. An unexpected death Hannah greener and chloroform. Anaesthesiology 2002; 96:1250–3.

9. DeHovitz RE. The 1901 St Louis incident: The first modern medical disaster. Pediatrics 2014; 133 (6): 964-65.

10. McIntyre A. Upton Sinclair's *The Jungle*: The legal and social impact of classic novel. Food Regulation in the United States 2008 Feb 02. P-1-11.

11. Ballentine C. Taste of raspberries, taste of death the 1937 sulphanilamide incident. Sulphanilamide disaster, FDA consumer magazine June 1981.

12. A history of the FDA and drug regulation in United States. FDA Centennial 1906-2006.

13. Ridings JE. The thalidomide disaster, Lessons from the past. Barrow PC editor. Teratogenicity Testing: Methods and Protocols, Methods in Molecular Biology, Vol 947. Humana Press; 575-86.

14. Fintel B, Samras AT, Caria E. The thalidomide tragedy: lessons for drug safety and regulation.

15. Sen A. Thalidomide tragedy revisited. Pharma Bio World 2013 September.

16. Hamburg M. 50 years after thalidomide: Why regulation matters. FDA Voices 2012 February 02.

17. Rice EL. Dr. Frances Kelsey: Turning the thalidomide tragedy into food and drug administration reform. Research Paper; 2007: p-1-25.

18. World Health Organization. The importance of pharmacovigilance, safety monitoring of medicinal products. The Uppsala Monitoring Centre WHO collaborating centre for international drug monitoring; 2002.

19. The medicines and healthcare products regulatory agency. Medicines and Medical Devices Regulation: What you need to know; April 2008.

20. Post marketing surveillance of drugs. Chapter 4 Pharmaceutical regulation in Japan.

21. CIOMS. Benefit risk balance for marketed drugs: evaluating safety signals. Report of CIOMS working group IV. Geneva; 1998.

22. CIOMS. Organization, Activities, Members. Geneva; 1994.

23. Cortez A. Introducing the International Conference on Harmonization Guidelines into the World Trade Organization: A Strategy to Remove Technical Trade Barriers for Pharmaceutical Products. MACD Project; spring 2002.

24 ICH Harmonization for better health. Understanding MedDRA, medical dictionary for drug regulatory activities. . International Conference on Harmoniization of technical requirements for registration of pharmaceuticals for human use. ICH Secretariat; 2013.

25. World Health Organization. International Conference on Harmonization (ICH): pharmacovigilance activities. WHO Drug Information; 16(1): 2002: p-11-12.

26. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH Harmonised tripartite guideline. Pharmacovigilance Planning (E2E); 2004 November 18.

27. European Medicine Agency. Pharmacovigilance risk assessment committee. Rules of procedure. 2013 March 03.

28. Yes leading in regulatory solution. Recent development in pharmacovigilance from regulator perspective.

29. Post marketing reporting of adverse drug experiences. 21 C.F.R. Sect. 314.80 (2017).

30. Suke SG, Kosta P, Negi H. Role of pharmacovigilance in India: An Overview. Online Journal of Health Informatics 2015; 7(2): 1-34.

31. Biswas P. Pharmacovigilance in Asia. J Pharmacol Pharmacother 2013; 4:7-19.

32. Ghewari PS, Salunkhe SS, Bhatia NM,Kileedar SG. Strategies and current scenario of Pharmacovigilance in India. Journal of Advanced Drug Delivery 2014; 1(3); 122-134.

33. Kalaiselvan V, Thota P, Singh GN. Pharmacovigilance Programme of India: Recent developments and future perspectives. Indian J Pharmacol 2016; 48: 624-8.

34. Pharmacovigilance Programme of India. PvPI reaches out to rural masses with the perspective of safeguarding the health of the poor; pharmacovigilance now has remote districts in its expanse. Newsletter Pharmacovigilance Programme of India 2017; 7(19).

35. Gupta V, Kaur K, Sharma R, Kaushal IG, Kaushal S. Pharmacovigilance: Current schedule Y perspective. J Adv Res Pharm Sci Pharmacol Interv 2016; 1(1&2): 26-32.

36. 3 Trends in the Global Pharmacovigilance Market. Future market insight 2016 Jan 14. 37. Sikdar S, Souttou A. The current challenges in dealing with adverse event reports from social media. 26th Annual Euro Meeting; 2014 March 25-27; Vienna, Austria.

37. Brennan W. Industry trends shaping the future of pharmacovigilance. C3i solutions 2015 Nov 15.

38. Sciformix Corporation. The impact and use of social media in pharmacovigilance. Westborough MA.

39.Pierce CE, Bouri K, Pamer C, Proestel S, Rodriguez HW, Le HV et al. Evaluation of Facebook and Twitter Monitoring to Detect Safety Signals for Medical Products: An Analysis of Recent FDA Safety Alerts. Drug Saf 2017; 40:317–331.

40. Pharmacovigilance programme of India. Newsletter 2015; 5(12).

41. WEB RADR. Theme 2: Using mobile technology for real-time pharmacovigilance. WEB RADR stakeholder Event. 2017 Sept 7.

42. Houyez F. Web-RADR: Use of mobile applications for ADRs reporting & social media data mining. Eurordis PCWP-HCPWP meeting EMA. 2015 March 4.

43. Outsourcing Trends in Pharmacovigilance.

44. Williams A. Hot trends in pharmacovigilance. QuintilesIMS blog 2017 January 19.

45. Stepping in to the future of pharmacovigilance The what why and how of knowledge process outsourcing. Parexel white paper.

46. Global market insight. Pharmacovigilance Market will grow at lucrative CAGR to cross $8 billion by 2024. Industry Today 2017 September 20.

47. Pitts P. 21st Century Pharmacovigilance and the Role of Artificial Intelligence. Morning Consult 2016 October 6.

48. Bataller C. Case Study: Pharmacovigilance Monitoring Adverse Drug Reactions. Coming of age of artificial intelligence Disruption, transformation ahead. Accenture. p-8-10.

49. Automation in Pharmacovigilance Data Processing – Do You Trust Artificial Intelligence?ArisGlobal 2017 May 16. 51. Sherlock A, Adolf C. Artificial Intelligence as an Aid to Pharmacovigilance. PharmaExec.com 2017 March 12.

50. Alsayed I. An integrated pharmacovigilance model to meet the new regulatory trends. Parexel white paper.

51. Kumar V. Challenges and Future Consideration for Pharmacovigilance. J Pharmacovigilance 2013; 1 (1): 1-3.

52. Issued by Strategic priority group of the global vaccine safety initiative (GVSI): Global Vaccine Safety Initiative 2013-2014 Annual Report. World Health Organization; 2015. Report No.: WHO/EMP/RHT/SAV/2015.2.

53. Maure CG, Dodoo AN, Bonhoeffer J, Zuber PLF. The Global Vaccine Safety Initiative: enhancing vaccine pharmacovigilance capacity at country level. Bull World Health Organ 2014; 92:695–696.

54. Global Vaccine Safety Global Advisory Committee on Vaccine Safety. World Health Organization; 2017 June 7-8.

55. US Food and Drug Administration. The Sentinel Initiative. US department of health and human services. Centre for drug evaluation and research. Office of medical policy.

56. European Medicines Agency. Guideline on key aspects for the use of Pharmacogenomics in the pharmacovigilance of medicinal products. 2015 September 24.

57. Ehmann F. Personalised Medicine 2020 –Regulatory Aspects and Early Dialogue. EHFG-Forum 4 "Personalised Medicine 2020" – 2014 October 2, Bad Hofgastein, Austria.

58. Wertheimer A. The Impact of Personalized Medicine on Pharmacovigilance. J Pharmacovigilance 2015; 3 (1).

59. Swaminathan M. Pharmacovigilance QA (PhVQA) - The next big thing in Pharmacovigilance. Linked in 2016 July 16.

60. Prepare for the unexpected. Quanticate the clinical data expert.

61. McCully S. Conducting non-interventional studies in Europe attempts at clarity lead to increased complexity. Inventive Health Clinical 2015 January.

62. Companies encouraged to seek scientific ad-vice for PASS. What's new in pharmacovigilance QPPV update 2016 (1).

63. Sapkota B, Palaian S, Shrestha S et al, Materiovigilance in Perspective: Understanding Its Concept and Practice in the Global Healthcare System. Ther Innov Regul Sci. 2023 Apr 27; 57(4):886–898

64. Sapkota B, Palaian S, Shrestha S, Ibrahim MIM. Materiovigilance in Perspective: Understanding Its Concept and Practice in the Global Healthcare System. Ther Innov Regul Sci. 2023 Jul; 57(4):886-898. doi: 10.1007/s43441-023-00514-4. Epub 2023 Apr 27. PMID: 37106236; PMCID: PMC10139667.

65. Medical Device Reporting (MDR): How to report Medical Device Problems, US Food and Drug Administration, published on 28 Aug 2024.