Pharmacovigilance in Healthcare: A Comprehensive Review

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ABSTRACT:
Pharmacovigilance, the systematic science of monitoring, assessing, understanding, and preventing adverse effects and other drug-related issues, is a vital pillar of modern healthcare. This comprehensive review offers a detailed examination of pharmacovigilance, encompassing its historical progression, core objectives, and its profound impact on patient safety and healthcare quality. Starting with a historical overview, we trace the evolution of pharmacovigilance, highlighting the pivotal events and developments that have culminated in its current significance. We emphasize the core objectives of pharmacovigilance, elucidating how they directly contribute to the well-being of the public. Adverse drug reactions (ADRs), their classification, and the repercussions of ADRs on clinical practice and healthcare economics are thoroughly explored. The review then delves into the intricate processes that underpin pharmacovigilance, including data collection, signal detection, and risk assessment. The multifaceted roles of healthcare professionals, regulatory bodies, and pharmaceutical companies in these processes are elucidated. This review underscores the indispensable role of pharmacovigilance in ensuring medication safety, improving healthcare quality, and safeguarding the health and well-being of patients. It serves as a comprehensive resource for healthcare professionals, researchers, and policymakers in understanding and advancing this critical component of healthcare practice.
Keywords:Pharmacovigilance, Medication Safety, Adverse Drug Reactions, Healthcare Review, Drug Safety.

I. INTRODUCTION:

Medicines and vaccines have revolutionized disease prevention and treatment. Alongside their benefits, these products may also produce unintended and undesirable side effects. This is where pharmacovigilance comes into play, dedicated to identifying, evaluating, comprehending, and preventing any adverse effects or other medicine/vaccine-related issues. While rigorous clinical trials ensure the safety and effectiveness of all medicines and vaccines before approval, these trials involve a limited number of carefully chosen participants for a brief duration. Some side effects may only surface when these products are used by a diverse population, including those with other health conditions, over an extended period.[1]Hence, it is imperative to continuously monitor the safety of all medications throughout their utilization in healthcare.The European Medicines Agency (EMA) takes charge of overseeing the pharmacovigilance system within the European Union (EU) and manages various functions and procedures designed to bolster pharmacovigilance efforts across the EU.EU regulations mandate that every marketing authorization holder, national competent authority, and the EMA establish and maintain a pharmacovigilance system. This comprehensive EU-wide system thrives on collaboration between EU Member States, the EMA, and the European Commission. In certain Member States, regional centers operate under the guidance of the national competent authority to further reinforce pharmacovigilance efforts.[2]

Fig 1. Working of pharmacovigilance[3]

The primary objectives of pharmacovigilance in the pharmaceutical sector closely align with those of regulatory agencies, which is to safeguard patients from unforeseen drug-related risks, unveil underlying predisposing factors, dispel misleading safety signals, and gauge risk against benefit. Although the perspectives of companies and regulatory bodies may differ, they are increasingly fostering collaboration and information sharing. Notably, major pharmaceutical companies often possess well-equipped central pharmacovigilance units with extensive in-house expertise dedicated to ensuring the safety of their specific products.[4]

Historical Evolution of Pharmacovigilance-

Around 170 years ago, the practice of pharmacovigilance began, even though it wasn't explicitly termed as such during that era. This important activity within the healthcare field, with significant social and economic implications, was designed to assess the risk-to-benefit ratio of drugs, enhance patient safety, and improve overall quality of life. In this discussion, we delve into the key milestones in the history of pharmacovigilance, from its early days when clinicians sent letters or warnings to renowned scientific journals, to the present time, marked by sophisticated electronic registries and data management.[5]
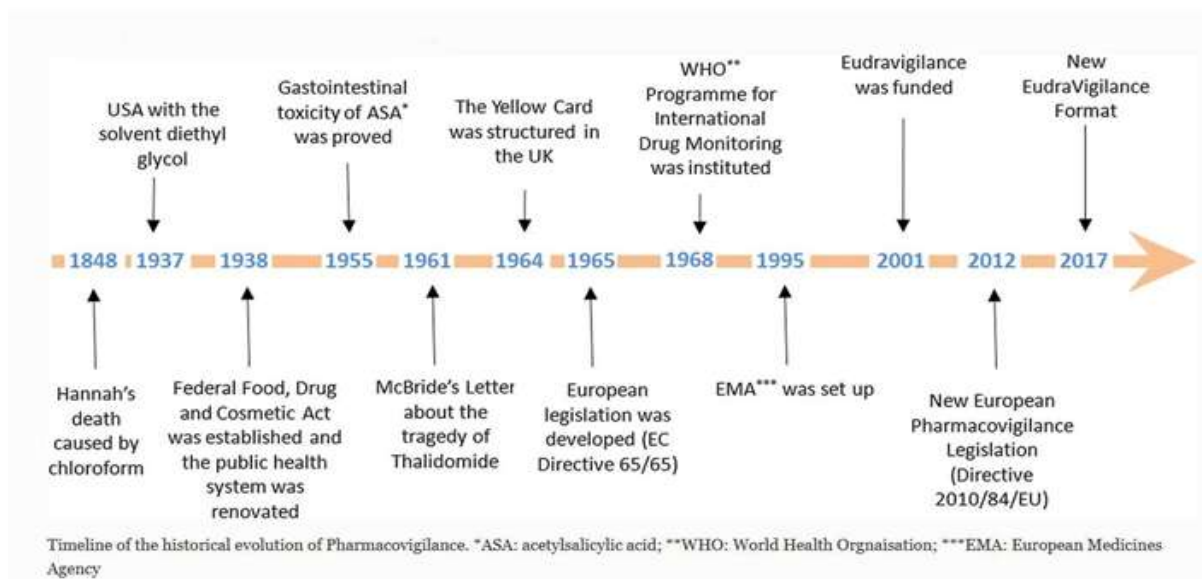

Timeline of the historical evolution of Pharmacovigilance. *ASA: acetylsalicylic acid; **WHO: World Health Orgnaisation; ***EMA: European Medicines Agency

Fig 2. Historic Timeline of Pharmacovigilance[6]

The evolution of pharmacovigilance and development- Over time, people have shown a growing interest in the safety and effectiveness of the medicines they use. The evolution of pharmacovigilance can be traced through key events in its history:

1848: Tragedy strikes as fifteen-year-old Hannah Greener dies under chloroform during surgery.

1937: A toxic sulfanilamide elixir causes harm to over a hundred people in the USA.

1938: The United States Congress passes the Federal, Drug and Cosmetic Act.

1955: Acetylsalicylic acid is linked to gastrointestinal diseases.

1961: Dr. William McBride's letter in "The Lancet" highlights thalidomide's impact on fetal development.

1964: The UK introduces the Yellow Card scheme for reporting adverse drug reactions.

1965: Council Directive 65/65/EEC is established.

1968: The World Health Organization initiates the Programme for International Drug Monitoring.

1995: The European Medicines Agency is founded.

2001: The EudraVigilance database is launched.

2012: Directive 2010/84/EU amends pharmacovigilance guidelines.

2017: The new EudraVigilance system comes into operation.[7]

Goals and Objectives of Pharmacovigilance-

The main goal of pharmacovigilance is to ensure the safe and effective use of healthcare products. This is achieved by promptly sharing safety information with patients, healthcare providers, and the public. Ultimately, pharmacovigilance plays a vital role in safeguarding patients and upholding public health.[8]

Fig 3. Goals of pharmacovigilance[9]

Objectives- The main objectives of pharmacovigilance include assessing drug effectiveness through long-term monitoring of their adverse effects, from the lab to the pharmacy. This process aims to identify any severe drug-related issues, ultimately enhancing public health and safety in the realm of medication usage. Furthermore, pharmacovigilance promotes the safe, rational, and cost-effective use of drugs, along with fostering education, clinical training, and effective

communication. The ultimate objective is to provide valuable information to consumers, practitioners, and regulators about optimal drug usage. This is achieved through the development of programs and procedures for collecting and analyzing reports from both patients and clinicians.[10]

In line with the definition of pharmacovigilance, as outlined by the EMA, the core objectives embedded in the applicable EU legislation for pharmacovigilance encompass two pivotal aspects:

- Preventing harm caused by adverse reactions in humans resulting from the use of authorized medicinal products, whether used within or outside the terms of marketing authorization, or through occupational exposure.

- Promoting the secure and efficient utilization of medicinal products, with a primary focus on delivering timely safety information regarding these products to patients, healthcare professionals, and the general public.[10]
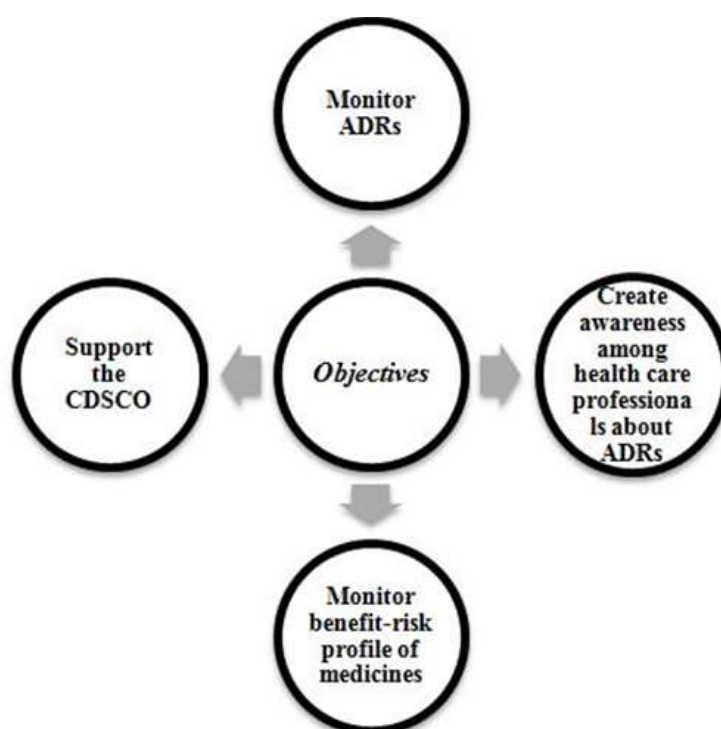

Fig. 4 Objective of pharmacovigilance [11]

Adverse Drug Reactions (ADRs)-

An Adverse Drug Reaction (ADR) refers to harm or injury caused by taking a medication. These reactions can occur after a single dose, with long-term use of a drug, or as a result of using multiple drugs, whether as a combination or separately. The study of ADRs has given rise to its own scientific discipline known as Pharmacovigilance (PV), defined by the World Health Organization (WHO) as 'the science and activities related to identifying, assessing, understanding, and preventing adverse effects and other issues related to drugs.[12]Medication-related harm encompasses more than just Adverse Drug Reactions (ADRs). Non-adherence, the act of not taking prescribed medications, is another form of medication-related harm. Non-adherence to

medications can have severe consequences, including death and other adverse outcomes. It's important to note that Adverse Drug Reactions (ADRs) involve the use of medication.[13]

Adverse drug events can occur during drug therapy, but they may not necessarily be directly caused by the drug. In contrast, an adverse drug reaction is directly linked to the drug and occurs when the drug is used as intended.

Drug reactions can be categorized into several types:

- Type A: These are dose-related reactions, meaning adverse effects can occur at either normal doses or in cases of overdose. Examples include conditions like serotonin

syndrome or the anticholinergic effects of tricyclic antidepressants.

- Type B: Non-dose-related reactions, where any exposure to the drug can trigger a reaction. Allergic or anaphylactic reactions fall into this category.
- Type C: These reactions are both dose and time-related. They may occur due to dose accumulation or prolonged drug use, such as adrenal suppression with corticosteroids.
- Type D: Time-related reactions that result from prolonged use of a drug that doesn't tend to accumulate. An example is tardive dyskinesia from antipsychotic medications.
- Type E: Withdrawal reactions, stemming from the undesired effects of discontinuing the drug, such as opiate withdrawal.
- Type F: Unexpected failure of therapy, where a drug either increases or decreases in efficacy undesirably. Examples include decreased drug clearance by dialysis or decreased antibiotic effectiveness due to resistance.[14]

Far-reaching impact of ADRs on clinical practice and healthcare economics-The World Health Organization has defined pharmacovigilance as 'the science and activities related to identifying, assessing, understanding, and preventing adverse effects and other issues related to drugs' . These 'drug-related problems' encompass adverse drug reactions (ADRs), which are unintended injuries or complications arising from iatrogenic drug-related causes, potentially leading to hospitalization, disability, or even death. The risk of ADRs is an inherent part of all drug therapies and is influenced by various factors, including dosage, administration frequency, genetics, and pharmacokinetics in special populations like pediatrics, the elderly, and individuals with hepatic or renal impairments. Given their high occurrence and potentially severe consequences, ADRs can significantly impact clinical practice both in terms of patient care and economic implications. This review aims to investigate the impact of ADRs in clinical practice, considering both clinical and economic aspects.[15]

Pharmacovigilance Processes-
Pharmacovigilance isthe simple process of monitoring drug safety. Within the pharmaceutical industry, it stands as one of the most critical departments. Before delving into the details of this process, let's consider some essential facts. The pharmacovigilance department, often referred to as the Safety Team, collaborates with various sectors, including Regulatory, Clinical, and Non-clinical, in the pharmaceutical industry. This team holds the continuous responsibility of monitoring the safety of medicinal products for human use. Beyond monitoring product safety, they play a crucial role in composing regulatory documents for new Marketing Authorization Holder (MAH) applications. Pharmacovigilance is not a straightforward process; it's a complex system that ensures the safety of medicinal products for all involved in drug development, marketing, and administration. The exchange of such data is a multifaceted process involving multiple stages. As defined by the World Health Organization (WHO), pharmacovigilance encompasses the 'detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.
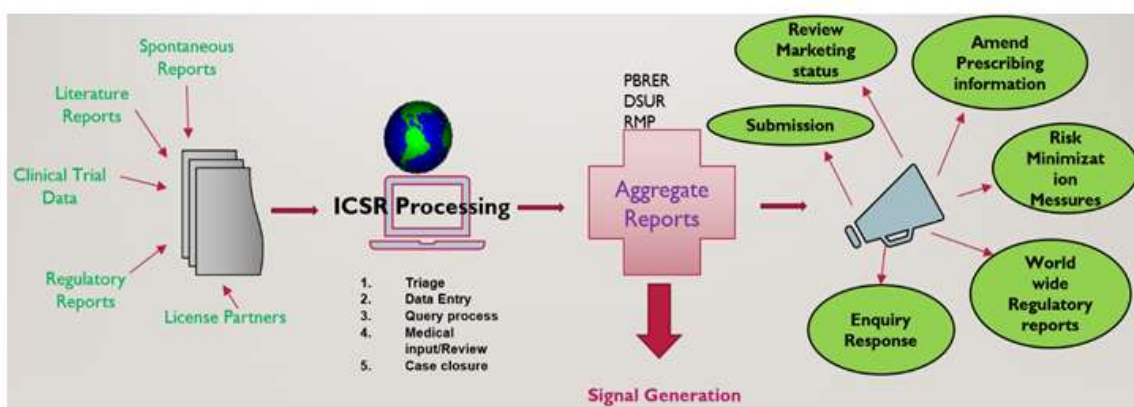

Fig 5. Pharmacovigilance process overview [16]

As per the definition pharmacovigilance process are classify into four type-

1. Pharmacovigilance process (stage 1); detection and collection of individual case safety reports (icsrs)
- Solicited sources - received as a result of targeted data collection (i.eestablish a channel to collect the adverse effects)
- Unsolicited sources - received without request or spontaneous in nature

2. Pharmacovigilance process (stage 2); assessment
- Triage
- Data entry
- Query process
- Medical input/review
- Case closure

3. Pharmacovigilance process (stage 3): understanding the drug safety profile

4. Pharmacovigilance process (stage 4): prevention of adverse global regulatory framework[16]

Data Sources and Reporting-

An exploration of the sources of pharmacovigilance data, encompassing spontaneous reporting systems, clinical trials, and electronic health records. We address the challenges of data collection and reporting.The following is a non-exhaustive list of data sources for use in the realm of pharmacovigilance analytics:[17]

Adverse Event (AE) / Adverse Drug Reaction (ADR) case reports:
- Reports generated by companies, covering the entire life cycle of medicinal products, from clinical development to post-market.
- Data from Health Agency databases like FAERS, EudraVigilance, and Vigibase.

Studies:
- Nonclinical studies.
- Clinical trial data, including research in unapproved populations or for off-label indications.
- Observational studies, real-world data, and registries.
- Systematic reviews, meta-analyses, outcomes research, and comparative effectiveness and safety research.

- Health economics analyses.

Scientific literature:
- Published scientific literature and reports from abstracts, including information presented at scientific meetings.
- Unpublished manuscripts.

Active surveillance systems:
- Sentinel systems or sentinel sites for ongoing monitoring.

Market access and market research:
- Data on product usage and drug utilization.
- Patient support programs.

Healthcare-related data:
- Administrative and claims data from health insurers.
- Clinical data, including vital signs and laboratory test results.
- Electronic health records and electronic medical records.
- Hospital data.
- Medicare data.

Internet:
- Information from marketing authorization holder-sponsored websites.
- Data from internet search engines.
- Insights from patient forums and social media channels.

Other sources:
- Information shared by licensing partners, sponsors, or academic institutions/research networks.
- Product quality investigations.
- Data obtained from regulatory authorities.
- Information collected from wearable devices.
- Ad-hoc reports generated by company field teams and medical requests for information related to potential benefits or risks.[18,19]

Global Regulatory Framework-

This section provides insights into the regulatory landscape of pharmacovigilance, highlighting key regulatory agencies and their responsibilities in monitoring drug safety.
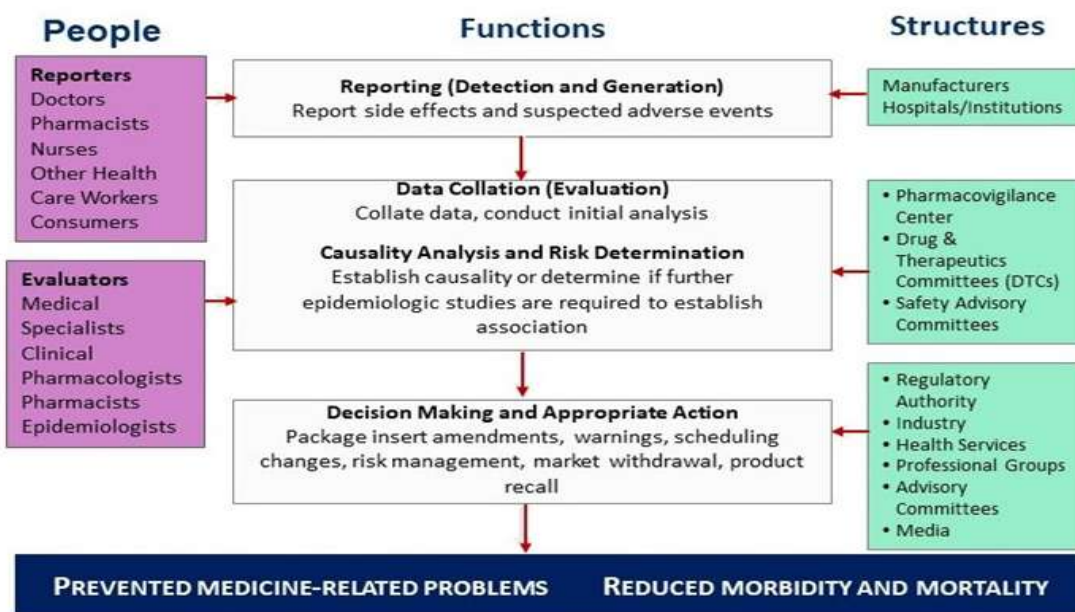
Fig 6. A Functional Pharmacovigilance System[20]

Australia- In compliance with regulatory frameworks, the Therapeutic Goods Administration (TGA) has instituted a pharmacovigilance system aimed at gathering and appraising data pertaining to the risk-benefit ratio of registered medicinal products. The TGA maintains an ongoing vigilance over the safety profile of products within Australia, promptly responding when required. Oversight is conducted through the Adverse Drug Reactions Advisory Committee (ADRAC). The guidelines encompass comprehensive information on adverse reaction reporting and specific reporting prerequisites for unique circumstances.

Brazil-The National System of Pharmacovigilance, overseen by the Pharmacovigilance Unit (PVU) under the Health Products Post-Marketing Surveillance Department (HPPMSD), plays a vital role in drug safety in Brazil. The significance of this initiative was underscored by a tragic event in 2000 involving meglumine antimonite, resulting in serious lesions for over 300 patients. This incident catalyzed the development of drug monitoring processes in Brazil. In 2001, the Ministry of Health (MoH) established the Brazilian National Drug Monitoring Centre (NDMC) through Decree 696, an initiative integrated into the PVU's activities to provide a legal framework for its expanded operations.

India-The National Pharmacovigilance Advisory Committee (NPAC) serves as the overseeing body for monitoring the performance of numerous zonal, regional, and peripheral centers. It operates as the 'Review Committee' for this program and offers recommendations for potential regulatory actions based on the pharmacovigilance data collected from these centers. The establishment of Zonal Pharmacovigilance Centers (ZPC) and Regional Pharmacovigilance Centers (RPC) further reinforces this effort.Under the purview of the Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare, Government of India, the Central Drugs Standard Control Organization (CDSCO) is taking the lead in launching a nationwide pharmacovigilance program.

Jordan-The Jordanian Pharmacovigilance Center (JPC) was founded in January 2001 through a collaborative effort with the Sweden International Development Agency (SIDA) and the Higher Council for Science and Technology.

Kenya-In Kenya, there is currently no existing pharmacovigilance system, but there are preparations for a protocol and pilot project to establish a unit following a similar framework.

Malaysia-In Malaysia, the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC), operating as a sub-committee of the Drug Control Authority (DCA), is responsible for reviewing reports of suspected drug reactions in Malaysia. The National Drug Safety Monitoring Centre (NDSMC), serving as the secretariat for

MADRAC, was officially recognized as the 30th member of the WHO's safety monitoring centers in 1990.[21]

Challenges and Future Directions-
This section addresses the challenges faced by pharmacovigilance, from underreporting to data quality, and presents future directions and innovations in the field.Systematically analyzing voluntarily submitted data, which involves numerous drugs, medical conditions, and events per report, presents well-documented challenges. This is compounded by the absence of a research protocol, randomization, or a control group of individuals receiving placebos. Another significant challenge lies in establishing the criteria for triggering an alert, deciding when a signal is sufficiently credible to necessitate further investigation, and when a signal should be escalated to indicate a potential safety concern.[22]Although pharmacovigilance systems have made notable advancements over the past few decades, they encounter a shared set of persistent challenges in drug safety surveillance, spanning five core and interconnected areas.

- engaging the public
- collaboration and partnerships
- incorporating informatics, adopting a global approach
- assessing the impact of efforts[23]

Future direction-Technological progress has opened up new possibilities for the integration of novel biomarkers into electronic medical record (EMR) databases. To identify adverse drug reactions (ADRs) in patients at various disease stages, a comprehensive approach would involve combining disease-specific biomarkers with the conventional EMR parameters. Successful clinical utilization of pharmacogenomic data hinges on the formulation of clinical guidelines to ensure uniform interpretation and prescribing practices. This also entails the creation of evidence-based information repositories and the implementation of educational programs to support informed decision-making.[24]

Emerging Technologies-
A look into how emerging technologies, such as artificial intelligence and big data analytics, are transforming pharmacovigilance. The potential for these innovations to enhance signal detection and data analysis is explored.

Artificial Intelligence (AI)- The rapid expansion of healthcare data in recent years, with even more growth anticipated due to the widespread adoption of digital tools for patient data collection, has paved the way for the application of artificial intelligence (AI) methods to enhance drug safety assessment. In particular, the field of clinical research has increasingly recognized the value of information extraction using natural language processing (NLP) and text mining techniques to extract meaningful insights from the vast, largely unstructured data sources available. In the context of pharmacovigilance, text mining and NLP methods serve as valuable tools for gathering information on adverse drug reactions (ADRs) and drug-drug interactions from diverse textual sources, offering essential support to researchers and clinicians in their ongoing efforts to monitor and ensure drug safety.[25]
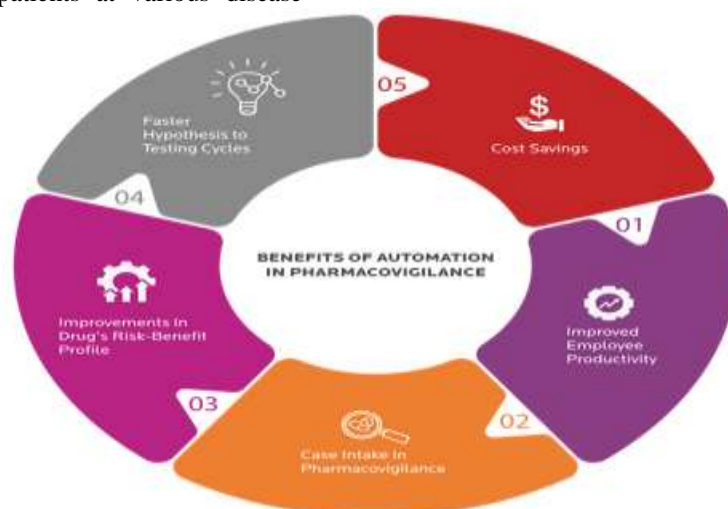

Fig 7. Benefits of AI & Automation in Pharmacovigilance[26]

Big Data Analytics-Extracting information from drug safety reports and medical literature is traditionally a labor-intensive process. However, in the digital age, researchers are exploring the potential of big data to revolutionize the study and monitoring of drug safety. Many developed countries are increasingly adopting automated drug safety surveillance based on extensive databases, employing electronic methods to systematically analyze vast amounts of information. This approach holds the promise of uncovering data patterns that can reveal new adverse drug reactions not easily detectable through conventional screening methods. This commentary delves into the realms of big data, artificial intelligence, and the utilization of social media, shedding light on how 'big data' plays a crucial role in evaluating the safety of both new and orphan medicines.[27]
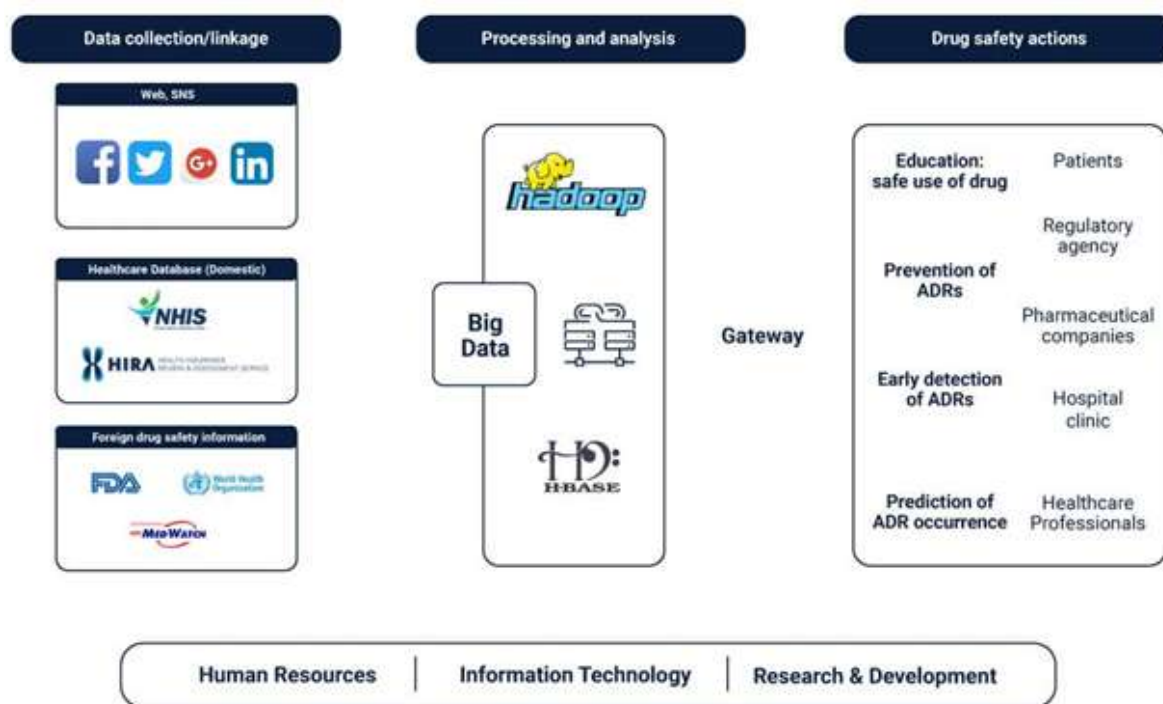

Fig 8. Big data approaches in pharmacovigilance[28]

II.   CONCLUSION:

In conclusion, this comprehensive review has delved into the intricate world of pharmacovigilance within healthcare, shedding light on its vital role in ensuring the safety of medicinal products. We have explored its historical development, core objectives, and its ever-expanding significance in modern healthcare. From the detection and assessment of adverse drug reactions to the prevention of potential risks, pharmacovigilance stands as a formidable guardian of patient well-being.Furthermore, we have discussed the evolution of pharmacovigilance in the context of technological advancements, emphasizing its growing reliance on data analysis and emerging technologies. While the challenges it faces are undeniable, such as data quality and the need for global harmonization, the potential for innovation and improved safety outcomes is evident.

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