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The Complexities of Pharmacovigilance Challenges and Opportunities

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Abstract
Pharmacovigilance, the science of detecting, assessing, and preventing adverse effects of medicines is crucial for patient safety and public health. Despite facing challenges such as adverse events, data analysis complexity, and limited resources, advancements in technology and global collaboration provide opportunities for growth and innovation. Improve methods to evaluate drug safety, availability of real-world data, advanced methods such as machine learning approaches and other technical tools the opportunities in Pharmacovigilance have increased. This review discusses the current state of pharmacovigilance, challenges, opportunities, and future directions for enhancing patient safety and public health.

Keywords
Artificial intelligence, Drug safety, pharmacovigilance, Patient safety, Risk management, Real world evidence.

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INTRODUCTION
In 1974 the concept of pharmacovigilance (PV) was first proposed in France. Pharmacovigilance is essential for protecting patients from harm and promoting public health. Despite its importance, Pharmacovigilance faces challenges that hinder its effectiveness. In2002 WHO explicitly defined (PV) pharmacovigilance, the science of detecting, assessing and preventing adverse effects of medicines, plays a crucial role in protecting health. As the pharmaceutical industries continuous involve, pharmacovigilance faces numerous adverse events, complexity, of data analysis, and limited resources, however, advancements in technology, increased focus on patient safety and global collaboration present opportunities for growth and innovation, this review aims to explore the current state of pharmacovigilance, discussing challenges and opportunities and highlighting future direction for enhancing patient safety and promoting public health. Today the scope of drug safety surveillance is costly and is becoming increasingly complex because the safety of medicine is related not only to its pharmacological property but also to how it is used in actual practice and to the integrity of the products quality throughout the supply chain while medication errors and product quality concern have always been important aspect of drug safety surveillance, their integration into pharmacovigilance system has increased in recent years [1].

PV also covers drug safety problems such as drug substance abuse, drug quality, reactions to excipients [2]. PV monitors drug safety events during the whole drug 'life cycle' (pre-marketing, post marketing and any recall or withdrawal from market). The PV focuses on the direction of ADR calculation of risk benefit ratio and circulation of information to the health care professionals, pharmaceutical companies and the public. PV should be empowered in every country to establish a rack strong healthcare system and to provide a rational and individualized treatment to patients [3].

PROBLEMS OF PHARMACOVIGILANCE
1. Underreporting

Poor reporting of adverse events due to incomplete safety information generated. Healthcare professionals, patients, and even the manufacturing companies may fail to report ADRS due to several reasons include lack of awareness, time constraint, and fear of legal liability [https://drug-card.io]. Generally, previous studies carried out among the HCPS showed a broader range of reasons for underreporting, fear, indifference, diffidence, ignorance, complacency, lack of security, unavailability of the reporting form, laziness, motivational factors, and monetary compensation. Approximately 90% of adverse events remain unreported (WHO) of serious adverse events that occur only 1-10% are reported (FDA) [https://linkspringer.com].

2.Data quality

Low quality of data, making it challenging to draw meaningful inferences or conclusions from safety data. Even considering the constraints associated with spontaneous reports, quality management of data can make this source of information more meaningful. Even though under reporting cannot be cured in this way, the influence of negative value of incomplete reports is another serious problem of pharmacovigilance, can be diminished by this [https://pubmed.ncbi.nlm.nih.gov.in].

Inconsistent formatting oftentimes uses different formatting, so these inconsistencies can result in major data quality issues working with different forms of measurement can cause similar issues. -70% of pharmacovigilance data is of poor quality (PWC)-30% of adverse event reports are incomplete (EMA).

3.Complexity

Complex data analysis and signal detection, requiring advanced analytics and expertise. Identifying potential safety signals amid the vast amount of data Collected is complex. Pharmacovigilance system uses advanced tools and algorithms to detect early signals of events which could lead to previously unrecognized ADRS. Reports on adverse events may be challenging due to the variability in clinical terminologies and response among patients. Signal to noise identification becomes challenging because one needs to separate significant and meaningful pattern in a multidimensional dataset. 100 million adverse events reports received annually (WHO) Safety signals 50,000 detected annually (FDA) [https://firsteigen.com].

4.Resource constraints

There is limited funding, personnel and technology which hampers effective pharmacovigilance. The biggest challenge that the pharmacovigilance system faces is that there is a lack of consistent reporting requirements across different regions and healthcare systems. Inconsistent reporting standards make data collection difficult, making it a tough assignment to compare and analyse safety information in the global platform. Pharmacovigilance resource limitations arising from constraints in resources effective pharmacovigilance requires dedicated resources including human resources, sophisticated technology and investment in money. Pharmacovigilance teams need more resources 50% of the companies. Companies spend less than 1% of the budget on pharmacovigilance. The "World of Pharmacovigilance" (pharmaceutical executive).
[https://www.pharmacovigilanceanalytics.com].

5.Regulatory heterogenicity

Diverse requirements from different regulatory bodies, which make it difficult to operate a pharmacovigilance activity in the global platform. There are 50+ regulatory agencies in the world. WHO 20+ different reporting formats. EMA.

6. Patient engagement

There is less patient engagement and part involvement in the pharmacovigilance activity. 50% patients are unaware of the process of pharmacovigilance. Patient view 20% of patients report ADR events (FDA) at times patients may resist taking part in their health care decision similarly, the healthcare professionals may also resist the encouragement to include patients in the process of healthcare due to patients preference and lack of knowledge, interest. Partial and inadequate availability of records can raise challenges to patient involvement [https://resource.ddregpharma.com]. The patient may have a significant role in pharmacovigilance since they may provide useful feedback about their experience with medication [https://resource.ddregpharma.com].

7. Technology adsorption

Show adoption of new technologies, hindering efficient and effective pharmacovigilance. 80% of companies have embraced AI/ML (pharmaceutical executive) 50% of companies use outdated technology (PWC). Technology adsorption and integration – the uptake machine learning, and blockchain, are difficult from infrastructure, expertise and regulatory compliance, where stakeholders need to invest in training, resources, and governance frameworks. [https://gyanocunsulting.medium.com].

Technology uptake is the process by which People or organizations adopt and use the new technologies involves learning and adapting to new technologies. Technology adoption is affected by performance expectancy effort expectancy facilitating condition and social influence [https://www.ncbi.nlm.nih.gov].

8. Data sharing

Meager data sharing and collaboration, data integration access is only available for a few. 50% of the firms share information with their associates (PWC) 20% of the firms share information with regulatory agencies (EMA). Data take long before being collected Availability may only delay the timely detection of adverse drug reactions (ADRS) and other drug safety issues; Evolve standardized data formats and schemas: development of standardized formats and schemas for data collection and storage can streamline the integration process, while reducing data latency [https://www.tcs.com]. Issues business must consider while deciding to share their data two of the major ones are concern about opening them themselves up to liability and other costs and worries about losing the value of confidential business information [https://www.propharmagroup.com].

9. Signal detection

Trouble in detecting safety signals, especially for rare events. 50%of safety detected through manual review (FDA). 20%of safety signals detected through AI/ML (pharmaceutical executive). Signal detection and management in pharmacovigilance necessities the continuous monitoring of individual case safety reports (ICJR) to identify case reports of adverse events (AE) that are worthy of further study traditionally, signals are detected either qualitatively or quantitatively [https://www.propharmagroup.com].

Common challenges in signal detection:

- Data quality and integration
- Timely decision making
- Global regulatory compliance
- Technical advancement [https://typest.I.o].

10.Connectivity

Inadequate communication of safety information to all customers/stakeholders, including patients and healthcare professionals. 50% of patients were given inappropriate safety information as observed by the patient view. 20% of healthcare professional was given inappropriate safety information as stated by the FDA. Communication problem refers to the problems or hindrances that surface while exchanging information or idea between people or organizations [https://study.com]. Lack of knowledge or information Relating to the subject matter, unaware of cultural difference, lack of Motivation. The proper usage of communication tools and attitude. The proper communication in the field of pharmacovigilance ensures drug and vaccines are safe enough and capable of advancing public health. It ensures the right time is taken with the right action to take place to be able to eliminate maximum risk to the patients [https://www.clinskill.com].

ONGOING CHALLENGES

All pharmacovigilance systems share a common set of ongoing challenges in drug safety surveillance in five principal interrelated areas:

1.Engaging the public

Pharmacovigilance is, first and foremost, about and for patients and the practitioners who care for them. As drug safety surveillance systems move into the future, they must continue to listen to patients and practitioners and to equip them with relevant and actionable information on the safety and safe use of medicine. Which are the best ways of doing that still is unknown. The establishment of previously unknown adverse effects of medicines is a central concern of pharmacovigilance. For decades, the foundation of drug safety surveillance has been based on reporting by patients and practitioners of suspected adverse drug reactions.

2.Collaboration and partnership

Pharmacovigilance is a collaborative effort. Because of the broad scope, pharmacovigilance systems cannot fulfil their role in isolation from other agencies for public health. On the contrary, pharmacovigilance systems should form partnerships that provide supportive expertise and an ability to implement all-encompassing monitoring and investigations into the safety of medicines. More and more, pharmacovigilance systems are facing challenges related to product quality; substandard, spurious, falsely labelled, falsified, and counterfeit medical products; and medication errors.

3.Icorporation of informatics

Good information is the backbone on which pharmacovigilance functions. New advances in availability of data and analytic methods are changing landscape of pharmacovigilance and can expand scope and reach of the field. For example, advances in informatics can be used to perform data mining in large spontaneous-reporting database, review huge numbers of reports with advanced techniques such as natural language processing, develop active surveillance systems, allow new sources of data for use in identifying drug safety signals, and to simplify reporting of suspected adverse drug reactions. A hypercritical challenge for pharmacovigilance is the development and validation of methods that maximize the utility of the vast number of electronic data which are accessible from a variety of sources, while at the same time minimizing false positive findings, which carry the cost of the evaluation of each signal and potential for diversion of patients from an appropriate therapy). It

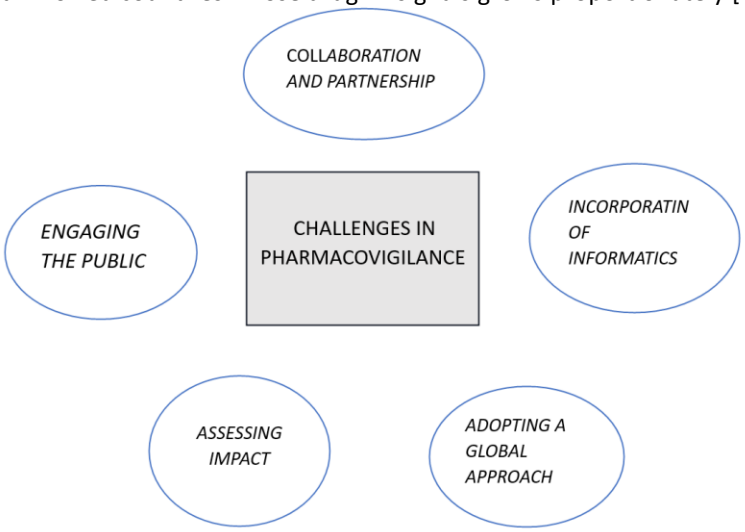
will be crucial to combine informatic approaches with other sources of information and integrating with clinical judgment.

4.Adoption of global approach

Pharmacovigilance is a worldwide effort. With the growing use and movement of medicines across the globe, the need for a global approach to the safe use of drugs can never be more relevant. A questionnaire-based survey of 55 low- and middle-income countries identified many gaps in infrastructure and resources for pharmacovigilance. An analysis of reporting over a 10-year period to VigiBase™ found that high-income countries had higher rates of reporting than did low-income countries. One component of global approach is harmonization, the process of establishing common technical standards across countries and regions that have diverse legal and regulatory bases for drug regulation. Efforts of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) began in 1990 and were directed towards achieving harmonization of interactions between pharmaceutical companies and drug regulatory authorities in three regions: the USA, Europe and Japan. Since efforts at harmonization transcend the three ICH regions and involved countries whose drug regulatory and pharmacovigilance Since systems are at different levels of maturity, it would become important that the harmonization processes be aware of the differences. Moreover, as laws come into existence across the globe, which detail extensive pharmacovigilance expectations from pharmaceutical companies in particular countries, it would become increasingly difficult to attain harmonization. For post approval drug safety activities that require interaction of the manufacturer with the healthcare system, such as specific risk management initiatives, full harmonization may be impossible because of differences in healthcare delivery across countries.

5.Assessing impact

Pharmacovigilance requires resources and is expected to protect and improve public health. While there have been substantial advances in pharmacovigilance activities around the world in the past decade, relatively little attention has been paid to the impact and burden of these efforts. As national, regional and international databases of suspected adverse drug reactions grow and, in some cases, in scope—the demand for data analyses (both by humans and by computers) to quickly identify important ADRS and to disapprove unconfirmed signals grows proportionately [4].



Pharmacovigilance in special populations: opportunities and why implement PV in special populations?

Challenges Due to the specificity of physiological functions, the special population children, pregnant women, and the elderly-are more prone to ADRs and have a greater number of drug safety issues. The implementation of PV is helpful for the detection of safety risks throughout the drugs, so that HCPs can take early measures to reduce the drug use risks of patients. What are the problems to implement PV for special populations?

: Many countries have implemented a PV system. However, PV policies and systems for the special population are not complete in various countries, or no independent PV system for the special population has been set up.

What does this article add to our knowledge?

This paper reviewed PV systems in the European Union, the United States, and China with particular emphasis on the fundamental physiological aspects, drug use, and deployment of PV for children, pregnant women, and the elderly. Awareness of these issues is of great importance in the formation

of a more comprehensive drug management plan in the special population and can Provide reference for development of follow-up policies and Improvement of existing policies [5].

FUTURE CHALLENGES

- Comparison and Monitoring of Original/ Reference Products and Generic Products Biosimilars Unlike developing countries, most developed countries already have the fundamental institutions and processes of a pharmacovigilance framework in place, with strong systems of pharmacovigilance, but, they are facing difficulties in the monitoring of ADRs due to generic drugs or biosimilars. A high percentage of generic pharmaceuticals flood the market as soon as the patents of its innovator product expires. The cost effectiveness of these generic products has helped in matters of affordability and access to these medicines. Generic drugs are identical to the reference product in every respect except for the excipients used by the different manufacturers. Excipients are inactive agents and do not affect the drug's action but have also been blamed for causing instability and side effects, However, because biosimilars are structurally similar, though not identical to the originator biological product, there is a concern regarding immunogenicity safety issues. Even after the patient has switched over from a branded drug to a generic version, the adverse effect attributed to the generic version is linked to the branded drug. This requires careful vigilance under pharmacovigilance. The nomenclature of the generic/biosimilar drugs also plays a very important role in the Monitoring of marketed products. Thus, to have an effective and strict pharmacovigilance of biosimilars, the guidelines provided by Council for International Organizations of Medical Sciences (CIOMS), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and other guidelines need to be harmonized.
- **Monitoring of Disease-Specific Adverse Drug Reactions Cardiovascular Drugs:** Hypertension and cardiovascular disease is among the top causes of mortality and morbidity worldwide. India, with an approximate population of 1.27 billion, accounts for about 30 million CAD patients, out of which 14 million reside in urban and 16 million live in rural areas, and by 2020, the burden of CVD because of CVD will surge to 4.2 million by 2030. Mortality and morbidity due to CVD are on the rise alarmingly. Since the patients are on polypharmacy for a more extended period, the risk of ADRs is always present. Some studies have reported an ADR prevalence of 18–24% in CVD patients.

Antidiabetic Drugs

Diabetes is another disease with a large population of grip globally. Globally, 415 million have diabetes, and the number of people afflicted with the disease is expected to rise to more than 642 million by 2040. In India, more than 65.1 million people have been diagnosed with the disease, and the estimates suggest 89 million patients by 2030, and about 56% of patients. will be from urban regions.

Antipsychotic Drugs

An increased incidence and prevalence of psychiatric dis orders has led to increased use of antipsychotic drugs in India. Since antipsychotic drugs affect the multiple dopaminergic pathways, several ADRs have been observed in hospital-based, retrospective, prospective and community-based studies in India and abroad, such as gastrointestinal reproductive and neurological disorders impairing the quality of life of patients. The researchers of the studies Advise precautions in the prescription of antipsychotic drugs. However, the actual prevalence and the extent of the problem in India is very less sought-after information Awareness Among Medical and Paramedical Staff A large number of paramedical staff and even the HCPs are unaware of the national pharmacovigilance system. The medical interns and post-graduates were more aware than the medical graduate students due to the clinical association. It is recommended that pharmacovigilance courses should be included in the undergraduate curriculum, and education should be provided to paramedical and medical personnel to eliminate the barrier resistances to reporting.

- Combination Products in India, adverse event reporting regarding the use of combination products such as Fixed-Dose Combinations (FDCs) has been an issue because FDC formulations may contain up to five (or even more) drugs, so it is extremely challenging to establish a temporal relationship between any one drug and an event. However, in the current situation, the causality of adverse events related with FDCs is based on the clinical experience and expertise of the HCPs. Adverse Events Reporting with the Use of Diagnostics Adverse event reporting with the use of diagnostics is another emerging challenge. Because the medical device adverse event reporting through the Mv PI is still at the initial stage, it may take a few years down the line until

facts will be documented for root-cause analysis [6].

OPPOTTUNITIES

Students looking to pursue education in pharmacovigilance have opportunities for pharmaceutical education and training partnership programs The culture within traditional curricula in medical, public health, and pharmacy schools does not focus on drug safety and PV. This lack of understanding of reporting obligations lessens the potential pipeline of talent and diminishes the value of patient safety, in addition to efficacy, as a critical component of drug development. Although formal PV training programs are available, most PV specialists acquire their experience through at least a foundation level understanding of statistical methods and analytical problem solving combined with a broad education in pharmacology and clinical medicine. Often this is supplemented by a progression of training experiences that include increased levels of exposure and responsibilities in an apprenticeship environment. The pharmaceutical already invested in attractive and develop future potential talents through different pathways by investing in future generations of PV professionals and offering Introduction to PV and PE studies, PV regulations and PV practices, ADR reporting, clinical study and safety reporting activities, post marketing compliance for safety monitoring, GCP and GVP inspections and audits Courses on drug safety, safety regulations, safety reporting, safety Systems and Processes, signal detection and risk assessment, fieldwork. The purpose of these fellowships is mainly to analyse the safety profile of products throughout the development, approval, and post marketing process that will enable the health professional and patient to make an informed decision.

PharmDs will play a role in developing and evaluating risk management strategies and in post-marketing safety surveillance.

Internships may be available to undergraduate college students as an avenue of exposing them to PV. In an internship over the summer, a student could be given a short-term, for example, 12-week assignment that will allow them to work in a PV department and be exposed to PV specialists and key stakeholders. The student intern obtains mentorship and adds value, including the selection of a project of interest and presentation of his/her views at the end of the program. Applications and opportunities for PV internship programs can be found on relevant pharmaceutical company websites as relevant and through searching by the phrase "pharmacovigilance internships" using any internet search engine. Rotation programs have been between schools of pharmacy and the pharmaceutical industry providing for the pharmacy student to be fully integrated into a PV department as part of his/her academic curriculum.

Fellowship Programs

Fellowship programs are a longer term (e.g., 2 years) commitment, i.e., usually a post-doctoral program targeted toward recent Doctor of Pharmacy graduates and coordinated by both the pharmaceutical company and a sponsoring university. Through offering real-world, hands-on, and in-depth specialized training, the PV fellowship provides physicians with a chance at a corporation to develop their skills, expertise, and experience in order to eventually, at an advanced level, seek out this potential future career of a PV specialist. Over the past few years, the pharmaceutical industry has offered fellowships to graduate students. Such fellowships have been established between the pharmaceutical industry and academia, including but not limited to graduate degree recipients from a school of pharmacy have completed a fellowship program at a pharmaceutical company Pharmacy or school of public health may apply for fellowship positions in the pharmaceutical industry. Curriculum in fellowship will vary slightly; however, generally, the major objectives in these positions are to train the fellow on how to assess the safety profile of products in the life cycle of development, approval, and post-marketing setting, providing in some examples to add both in the development and assessment of risk management strategies, and to lead post-authorization safety studies. Once fellows complete their training, they can apply for open PV subject matter expert positions.

Artificial Intelligence in Pharmacovigilance

Healthcare data has been rising at an impressive rate in the past few years and will continue to climb in the near future because of the rise of immense Marketing of digital tools for collecting patient-derived data. Huge amounts of electronic data present the possibility of the implementation of AI technologies in order to improve the quality of drug safety evaluation. Information extraction, using the capabilities of natural language processing techniques and text mining that that extract relevant insights from available largely sources in unstructured forms, is gaining increased emphasis in the clinical research domain. In pharmacovigilance, in text mining and NLP methods can be quite useful to gather information on a range of topics, including ADRs and drug-drug interactions through textual sources, in support of researchers and clinicians for monitoring drug safety (Wong et al., 2018). Indeed,

public and private entities are currently trying to develop AI tools that can allow to automatically process ADRs (Basile etal.,2019). Artificial intelligence and machine learning may also help in pharmacovigilance in 1) automation of the tasks assigned with case report entry and processing, 2) identification of clusters of adverse events indicative of symptoms of syndromes, 3) conducting pharma epidemiological studies, 4) data linkage, by conducting probabilistic matching within datasets and 5) prevention and prediction of adverse drug reactions by specific models based on real world data [7].

APPLICATION OF ARTIFICIAL INTELLIGENCE TECHNOLOGIES IN PHARMACOVIGILANCE

Opportunities and Advantages

The AI tool has been considered useful for the clerical, time consuming and mechanical process of data entry, AE, drug–drug interactions, very faint data patterns and individual case review. In addition, AI can transform unstructured, free-text format of drug safety data and hand-written documents to machine readable format.

What is more, the tool will enable the Medical Dictionary for Regulatory Activities coding, check duplicate reports, classify reports into physician or consumer reports, identify serious reports and rule out nonserious reports. Ironically, the AI platform may also scan unstructured data, pull the text, and retrieve relevant details in generating clinically informed auto-narratives and it can recognize patterns within structured and unstructured narratives, obviating the necessity of routine scrutiny of individual cases and manual identification and validation. Signalling. Moreover, it can extract ICSR information from several published documents such as medical literature, case reports, medication reviews of social media, free-text clinical notes in electronic health records, and discharge summaries. A recent survey claimed that AI tools process data very fast, accelerate computations that were impossible before, and save the scientists' time and money. As the vast amount of drug safety data is stored in an electronic form, the use of AI tools will save efforts, time, and cost of case processing, enhance data quality, and may prove to be a game-changer for PV activities.

AI/ML: Artificial intelligence

(AI) and machine learning (ML) can revolutionise pharmacovigilance by improving signal detection, data analysis, and predictive analytics. AI-driven algorithms can rapidly process huge volumes of data, potential safety signals, and alert healthcare providers for action. ML can offer more accurate adverse event reporting and analysis, with fewer false positives and negative results. In addition, AI chatbots may offer more convenient channels of patients' reporting and interactions in advancing pharmacovigilance towards being more patient-centred [8,9].

RWE: Real-world evidence

(RWE) can supply pharmacovigilance decisions with insights into the way drugs perform real-world settings. RWE could be obtained from electronic health records, claims data, and patient registries. Such information can help identify safety signals, monitor the effectiveness of medication, or inform regulatory decisions. RWE can also help facilitate personalized medicine through data on how medications perform in specific patient populations [10].

Digital Health

Through better patient engagement, data collection, and monitoring, pharmacovigilance will be improved using digital health technologies. Using mobile apps, wearables, and electronic health records, patients will be granted the right to report adverse events and medication adherence. Furthermore, remote monitoring will be done by using digital platforms; hence, in-person visits will be reduced while also enhancing data quality. Digital health technologies can further improve communication among healthcare professionals, patients, and regulatory agencies [11].

Personalized Medicine

Personalized medicine: The pharmacovigilance plans tailor to specific patients' requirements and characteristics. It encompasses the genetic difference, medicinal histories, and lifestyle factors to ensure medications' effective use and safety. Personalized medicine can also lead to focused interventions, decreased adverse effects, and improved patient outcome.

International Cooperation

Global collaboration is vital in the practice of pharmacovigilance effectively because it is used as a platform for sharing safety data, best practices, and regulatory information. International cooperation can facilitate the harmonization of pharmacovigilance practices that, in turn, will decrease redundant efforts, thus improving patient safety worldwide. Also, through global collaboration, standardized safety protocols and guidelines may be formulated [12].

Data Visualization

Elaborate data visualization techniques might improve the communication of pharmacovigilance data so that healthcare professionals, patients, and Agencies can easily understand complex safety

information. Data visualization can be applied in the identification of safety signals, monitoring of the effectiveness of medications, and informed decision making.

Patient Engagement

Patient engagement is crucial for successful pharmacovigilance. This enables patients to become part of what can be referred to as reporting adverse events and medication adherence. Patient engagement offers the opportunity to identify safety signals early, improved medication safety, and patient outcomes. Patient Engagement can also foster trust among patients, health care professionals, and regulatory agencies [13].

Cloud-Based Solutions

Cloud-based solutions advance the management, storage, and sharing of data in pharmacovigilance, particularly in accessing real-time safety data and sharing with other stakeholders. Cloud-based solutions would reduce costs, increase scalability, and improve data security [14].

Regulatory Innovation

Regulatory innovation will be critical to push the adoption of new pharmacovigilance technologies and approaches, which in return will allow for the development of novel safety protocols and guidelines. Innovation in regulation can foster teamwork among agencies, industry players, and healthcare practitioners toward better pharmacovigilance [15]. Analytics Advances Analytics advances can provide new insights with sophisticated statistical models and machine learning approaches for enhancing pharmacovigilance performance. algorithms to safety data. Advanced analytics may be able to aid in the identification of safety signals, evaluation of drug efficacy, and informed decision-making [16].

FUTURE DIRECTIONS

Visioning the Future and Guiding Principles for Pharmacovigilance in an Evolving World

Ongoing Effort In 2019, the EMA published its outlook for the ongoing decade: smarter collection and management of individual case safety reports with digital technology and international standards; increased use of real-world data for Monitoring the performance of medicines in healthcare in terms of both safety and effectiveness; and enhanced engagement of patients and healthcare professionals leading to good health outcomes for the patients. Added to that, in 2020, in its regulatory science strategy, the EMA referred to real World evidence (RWE) and stakeholder engagement as strategic priorities for pharmacovigilance. Since then, major initiatives have been supporting the realisation of these predictions, in particular:

- The PRAC Signal Management Review Technical (SMART) Working Group fosters innovative methods for more sensitive and precise signal detection and management, including for special populations and risks with medicines' abuse, misuse, overdose, medication errors and occupational exposure.
- The Data Analysis and Real World Interrogation Network (DARWIN EU) fosters timely and reliable RWE from healthcare databases across Europe and creates an infrastructure for post-authorisation studies that investigate the use, safety or effectiveness of medicines, background incidences of medical events, data on diseases for contextualising benefit-risk considerations, effectiveness of risk minimisation measures (RMM), impact of regulatory actions or patient preferences in European populations. To generate EU RWE independently post-authorisation specifically for vaccines, EMA and the European Centre for Disease Prevention and Control (ECDC) have established the Vaccine Monitoring Platform (VMP).
- The PRAC Risk Minimisation Alliance (PRISMA) pilots enhanced stakeholder engagement by PRAC to gain more and earlier input from patient and healthcare professional networks on the feasibility of Implementation of RMM options, questions to be discussed at larger stakeholder events, and outreach strategies for implementing RMM in healthcare by collaborating with key stakeholders. Vision for the Future EU Regulatory Pharmacovigilance System From these, we will tackle the areas for further development and progress towards a future-proof pharmacovigilance system in changing medical, technological, and social circumstances with the following 10 elements:

1. In the interest of all patient population groups and health equity, the EU regulatory pharmacovigilance system should simplify timely implementation of consistent safety-related actions for all medicines across Member States, irrespective of their route of marketing authorisation, and with implementation adapted to national healthcare systems.
2. The contextual understanding of diseases, exposure to medicines, healthcare systems and the performance of medicines in terms of risk minimisation as well as effectiveness in everyday healthcare in the EU should be deepened for more comprehensive benefit-risk assessments and important updates to the product information.
3. Multiple data sources and multidisciplinary methods should be used and improved for real-

time monitoring and assessment of risks, RMM (including their enablers and barriers to achieve intended outcomes) and effectiveness of medicines in consistent formats, based on study feasibility assessments, and in a complementary manner with cross-validation of results.

4. Strategic, real-life data research conducted neither sponsored nor undertaken by regulatory authorities, should complement the influential body of evidence obtained through law from pharmaceutical companies, which also would become expanded and enhanced.
5. Areas of technology, such as artificial intelligence, should be exploited in order to handle significant quantities of data in a way to support timely evaluation.
6. Active engagement and research with patient and healthcare professional communities to inform decisions and design of RMM must be accessed through frameworks for their independent inputs and must focus on risk minimization behaviours and how these can be appropriately put in place in local healthcare practices.
7. Communication on risks and RMM must be framed in ways that assist patients and healthcare professionals in making individual therapeutic choices and using medicines Accordingly.
8. Regulators should consult patient and healthcare professional communities and public health agencies in order to foster appropriate use of medicines and social trust in medicines regulation and safety monitoring.
9. All pharmacovigilance activities like spontaneous reporting of suspected adverse reactions, post authorization safety studies, and RMM development and implementation shall be aligned in patient-centred Health care, and thus require robust health system engagement. The EU regulatory pharmacovigilance system needs to respond with adequate promptness to various crisis situations. The STAR Compass to Guide Action to Further Progress Pharmacovigilance.
10. To achieve this vision, action to progress the EU regulatory pharmacovigilance system within the quality cycle may:
    - Develop further capacity, technology, and methods.
    - Drive enhancement of existing regulatory processes; and
    - Extend policies, frameworks and research agendas must be guided by the following four principles:
    - Synergistic interactions with health care systems.
    - Trustworthy evidence for regulatory decisions.
    - Adaptive process efficiency.
    - Readiness for emergency situations. By their first letter those guiding principles could be memorized by the acronym 'STAR'. They are designed, as a compass is, to orient improvement actions toward increasing the output of pharmacovigilance activities in terms of safe, effective and trusted use of medicines and positive health outcomes within patient-centred healthcare. Actions for progress in accordance with these principles should not only address the ongoing changes but make use of the opportunities arising from the changing world. The STAR principles therefore top up the established pharmacovigilance quality principles and add the following foci:
    - Synergistic interactions with healthcare systems: While Regulatory bodies regulate medicinal products but not healthcare delivery. The regulatory engagement with stakeholders has changed significantly over the last decades: from mere interaction to taking advantage of the possibilities that increasingly networked societies and digitally connected systems offer, and to generate synergies between activities led by different stakeholders. We believe that synergistic interactions that respect the mandates of each will help to lead health systems toward desired outcomes. stakeholder party, may support stakeholders in converging on pharmacovigilance objectives and engage healthcare leaders more in the safe use of medicines within patient-centred care.
    - Trustworthy evidence for regulatory decision: medicines regulatory bodies have been legally required to assess all available evidence and therefore established standards and guidance for the robustness of data and increasingly multidisciplinary analytical methods. However, the additional focus now is that stakeholders and the Overall, the public can appreciate the appropriateness of regulatory decisions as robust and unbiased evidence even though there is often a limitation in the available

evidence. It is expected that contextual understanding of disease, healthcare systems, medicine use, and its outcomes shall enrich the evidence base for regulation decisions and provide common ground among stakeholders. engagement, whereby regulators using sophisticated knowledge of the clinical conditions patients and healthcare providers face.

- Adaptive process efficiency: Efficiency has been improved since 2010 legislation, but this is to facilitate the capacity of pharmacovigilance systems to adjust efficiency promptly and without difficulty to the challenges and opportunities of the medical, technological, and social changes. world-wide.
- Readiness for emergency situations: While pandemic preparedness as well as business continuity planning Goal: Safe, effective and trusted use of medicines and positive health outcomes within patient-centred healthcare have been established at EMA for decades, the focus now is on being ready both through proactivity as well as responsiveness to imminent or developing, foreseen or unforeseen emergencies of a wider range, arising from the ongoing changes or crises [17].

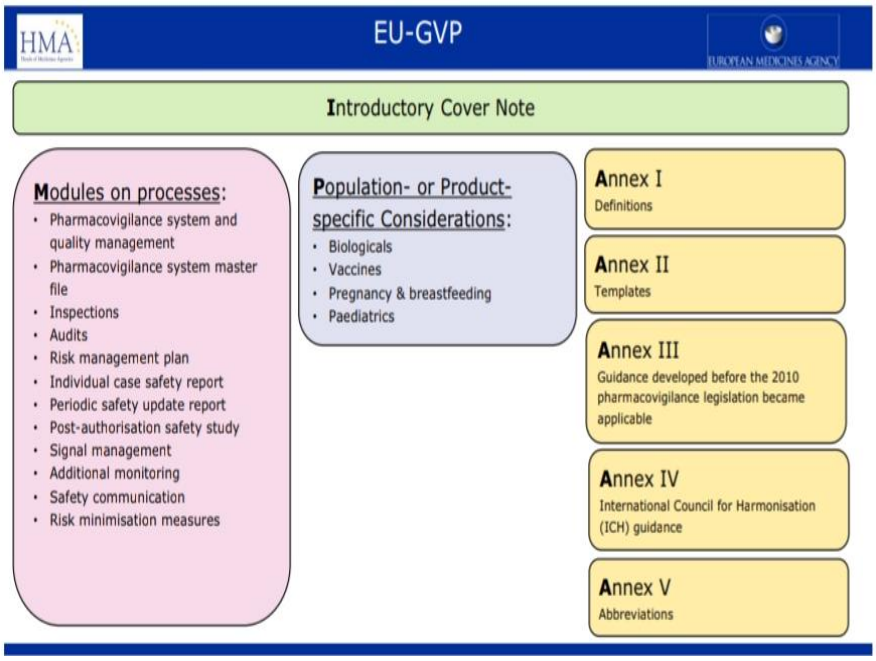


Fig 1: Overview of the guidelines on "Good Pharmacovigilance Practices" issued by the European Medicines Agency and the Heads of Medicines Agencies in the European Union (EU-GVP) (37).

Fig 2: Cycle of the pharmacovigilance quality management system defined in 'good pharmacovigilance practices' issued by European medicines agency and the heads of medicines agencies in the European union (EU-GVP)

CONCLUSION:

Pharmacovigilance becomes a core tool in promoting the safety of drugs, protecting public health despite its centrality, the field still encounters many challenges that need to be addressed to ensure high efficiency.

The ongoing pharmacokinetics, pharmacodynamics, and drug interactions in elderly people have been studying very critically for developing safe and effective therapies and drug toxicities and adverse drug Reactions. With age, there is an increase in the presence of chronic illness and anatomical changes that impact drug absorption, distribution, metabolism, and excretion. Regulatory compliance, resource constraint, and data complexity have made some things difficult for pharmacovigilance. However, with the advancement of technology, global harmonization, and personalized medicine, opportunities come along.

The challenges must be addressed along with taking on all the opportunities so that the pharmacovigilance community will be able to achieve

- Enhanced safety of the patient
- Improved regulatory compliance
- Enhanced pharmaceutical innovation.

However, pharmacovigilance is highly important in the defence of public health as well as providing the pharmaceutical industry with public confidence.

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