IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW "NEW ERA OF PHARMACOVIGILANCE FUTURE CHALLENGES AND OPPORTUNITIES"

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ABSTRACT:

Medicines and vaccines have transform the prevention and treatment of disease. In addition of the benefits, medicinal product may also have side effects, some of which may be undesirable or unexpected. Pharmacovigilance is the science and activity relating to the detection, assessment, understanding and prevention of adverse effect of any medicine/vaccine related problem. All medicines and vaccines undergo rigors testing for safety and efficacy through clinical trials before they are authorized for use. However, the clinical trial process involves studying these products in a relatively small number of selected individuals for a short period of time.

Pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems." The objective is to extend safety monitoring and detect ADRs that have previously been unrecognized despite evaluation in clinical trials. Although these methods were developed for monitoring of pharmaceutical medicines, they are also used for additional evaluation of safety of other medicinal products, including herbals, blood products, vaccines, and even medical devices.[3,4] Some of the challenges and future opportunities in this field are briefly discussed below.

Keywords: - Pharmacovigilance, Adverse effect, Artificial intelligence, Post-surveillance marketing, Emergency Healthcare.

Introduction:-

Medicines safety monitoring is a continuous and dynamic process throughout all the phases of the life cycle of a drug. During the drug development, safety is investigated in different phases. In preclinical studies, the primary goal of safety evaluation is the identification of a safe dose in humans and of safety parameters for clinical monitoring. In clinical phase, phase I studies are designed to estimate the tolerability of the dose range expected to be needed for later clinical studies in healthy volunteers; phase II studies are

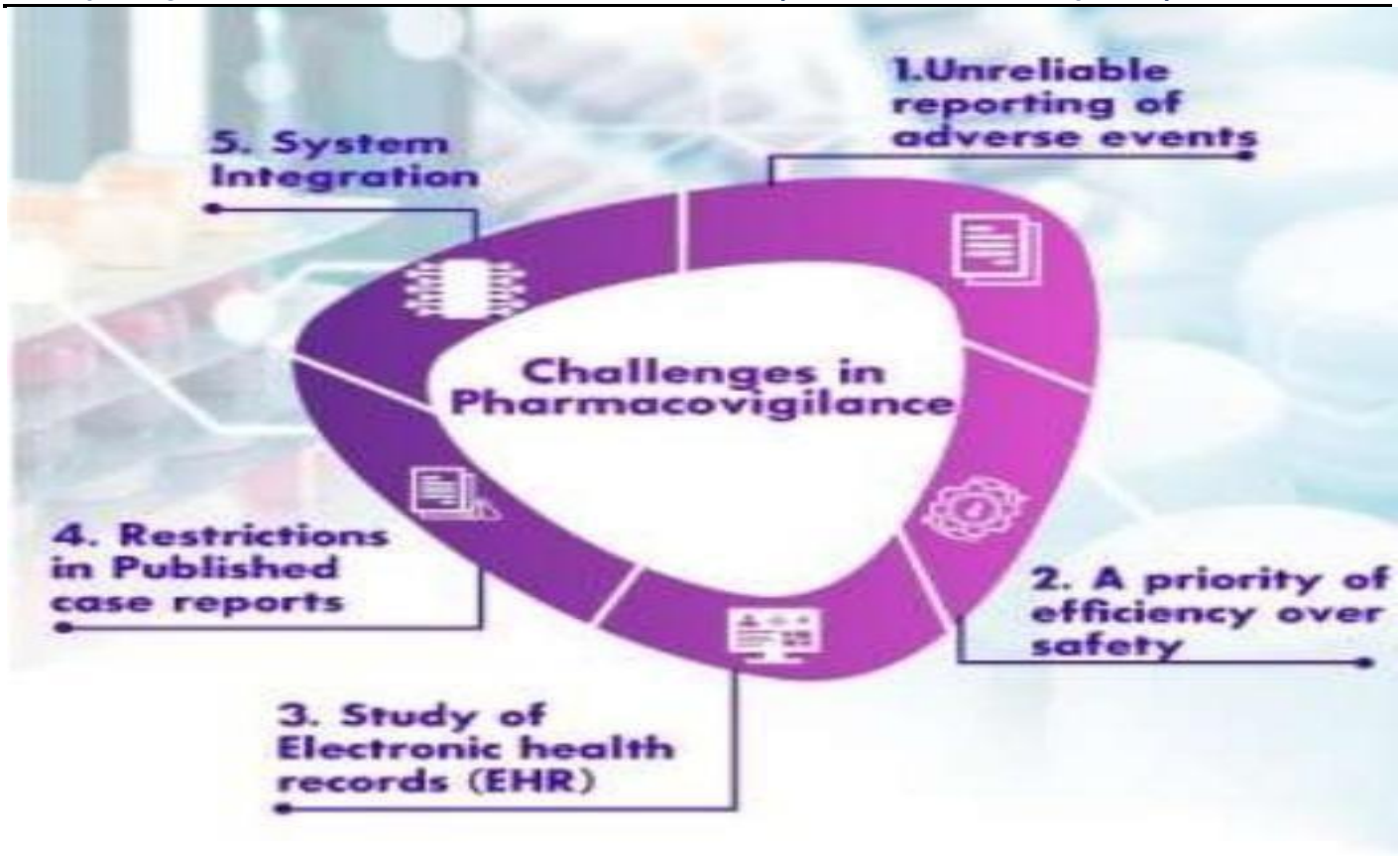
focused on determining appropriate range of drug doses in patients with a disease or condition of interest, while phase III clinical trials are the most important studies to refine understanding of benefit- risk profile of the drug and to identify less common adverse drug reactions.

Although drug safety evaluation is very rigorous and thorough, pre-marketingclinical trials have however intrinsic limitations that do not allow to exhaustively evaluate drug safety profile. These studies are conducted on limited numbers of patients that are selected based on strict eligibility criteria and not fully representingreal-world populations and have limited duration, thus preventing detection of rare and long-term adverse reactions.

Therefore, the post-marketing assessment of medicines plays a key role for better defining drugs safety profile in real-world setting and filling the evidence gap of pre-marketing studies. In the field of drug safety and regulation, a number of challenges have to be faced in the near future. First of all, COVID-19 pandemic highlighted how relevant Pharmacovigilance and proper risk communication during public health emergency are. Second, the development of advanced methodologies including machine learning techniques and the availability of large amount of electronic healthcare data offer opportunity for optimizing drug benefit-risk profile evaluation in real world setting. Finally, innovative therapeutics,such as advanced therapy medicinal products, digital therapeutics, vaccines developed based on advanced technologies, requiring special pharmacovigilance monitoring have been increasingly marketed in recent years, often upon accelerated pathway approval.

Definition of Pharmacovigilance:-

Pharmacovigilance is defined as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems.” The objective is to extend safety monitoring and detect ADRs that have previously been unrecognized despite evaluation in clinical trials. Although these methods were developed for monitoring of pharmaceutical medicines, they are also used for additional evaluation of safety of other medicinal products, including herbals, blood products, vaccines, and even medical devices.[3,4] Some of the challenges and future opportunities in this field are briefly discussed below



Mission

The Mission of Pv PI is to safeguard the health of the Indian population by ensuring that the benefit of use of medicine outweighs the risks associated with its use. Since there exist considerable social and economic consequences of adverse drug reactions and the positive benefit/cost ratio of implementing appropriate risk management - there is a need to engage healthcare professionals and the public at large, in a well structured program to build synergies for monitoring adverse drugreactions in the country.

Purpose

The purpose of the PvPI is to collate data, analyze it and use the inferences to recommend informed regulatory interventions, besides communicating risks to healthcare professionals and the public. The broadened patient safety scope of Pharmacovigilance includes the detection of medicines of substandard quality as well as prescribing, dispensing and administration errors. Counterfeiting, antimicrobial resistance, and the need for real time surveillance in mass vaccinations are other Pharmacovigilance challenges which need to be addressed.

Vision

The vision of Pv PI is to improve patient safety and welfare in Indian population by monitoring drug safety and there by reducing the risk associated with use of medicines. The ultimate safety decisions on medicines may need considerations of comparative benefit/risk evaluations between products for similar indications.

Aim of Pharmacovigilance:-

- Improve patient care and safety in relation to the use of medicines
- Research the efficacy of drug and by monitoring the adverse effects of drugs right from the lab to the pharmacy and then on for many years
- Pharmacovigilance keeps track of any drastic effects of drugs.
- Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use.
- Promote understanding, education and clinical training in Pharmacovigilance and its effective communication to the public.
- Maintain a robust monitoring system for new safety issues.
- Implement effective approaches to minimize risk.
- Install procedures for rapid decision making and triggering actions in case of (immediate) safety concerns.
- Improve patient care and safety in relation to the use of medicines and allmedical and paramedical (services that support medical work, such as nursing, first aid, radiography) interventions.
- Improve public health and safety in relation to the use of medicines.
- Contribute to the assessment of benefit, risk, and effectiveness (including cost-effectiveness) of medicines.
- Secure the accessibility of information about the safety of medicinal products to patients, healthcare professionals and the public.
- Promote understanding, education and training in Pharmacovigilance and its effective communication to the public.
- Monitor impact of measures and activities and ensure continuous improvement of Pharmacovigilance system.

Objectives of the Pharmacovigilance:-

- Improvement of patient care and safety in relation to the use of medicines with medical and paramedical interventions remains to be an important parameter exhibiting the efficacy of drugs by monitoring their adverse effect profile for many years from the lab to the pharmacy

- To track any drastic effects of drugs.

- To improving public health and safety in relation to the use of medicines.

- To promote understanding, education and clinical training in Pharmacovigilance; and effective to the generic public.

- In addition, providing information to consumers, practitioners and regulators on the effective use ofdrugs along with designing programs and procedures for collecting and analyzing reports from patientsand clinicians conclude to the objectives of Pharmacovigilance studies.

Need of Pharmacovigilance:-

- Reason 1: Humanitarian concern - Insufficient evidence of safety from clinical trials Animal experiments Phase 1-3 studies prior to marketing authorization

- Reason2: Medicines are supposed to save lives Dying from a disease is sometimes unavoidable; dying from a medicine is unacceptable.

- Reason 3: ADR-related cost to the country exceeds the cost of the medicationsthemselves.

- Reason 4: Promoting rational use of medicines and adherence.

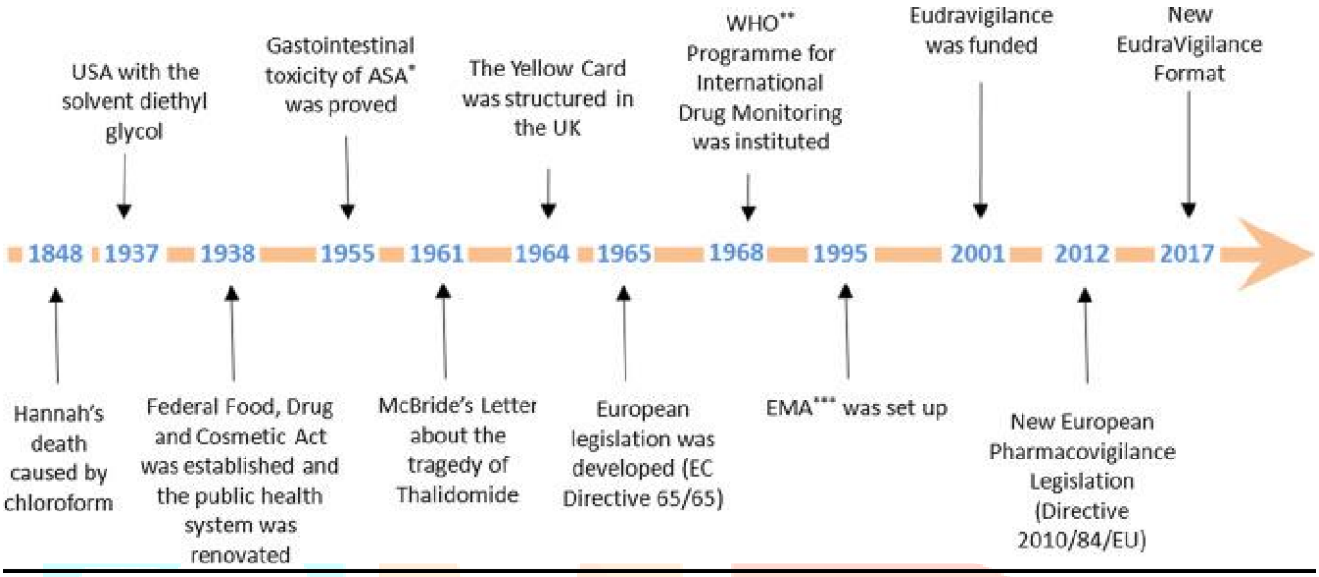
- Reason 5: Ensuring public confidence.

- Reason6: Ethics, to know of something that is harmful to another person who does not know, andnot telling, is unethical.

Historical Perspective Of WHO – Drug Safety Monitoring :-

In 2002, more than 65 countries have their own pharmacovigilance centers. Membership of the WHO for International Drug Monitoring is coordinated by the WHO Collaborating Centre for International Drug Monitoring, known as the Uppsala Monitoring Centre (UMC).Pharmacovigilance is now firmly based on sound scientific principles and is integral to effective clinical practice. The discipline needs to develop

further to meet public expectations and the demands of modern public health. The Sixteenth World Health Assembly adopted are solution [5] that reaffirmed the need for early action in regard to rapid dissemination of information on adverse drug reactions and led later to creation of the WHO. Pilot Research Project for International Drug Monitoring. The purpose of this was to develop a system, applicable internationally, for detecting previously unknown or poorly understood adverse effects of medicines



Ecopharmacovigilance:-

Ecopharmacovigilance is "the science and activities concerning detection, assessment, understanding and prevention of adverse effects or other problems related to the presence of pharmaceuticals in the environment, which affect both human and the other animal species" ecopharmacovigilance is a very important issue nowadays and it plays a crucial role to reduce the environmental risk of pharmaceutical pollutants. Indeed, pharmaceuticals are widespread environmental pollutants that may be excreted into the environment through different routes, such as the excretion by the patient as parent compound or active metabolites via the sewer system and the release into thewaste waters by manufacturers or hospitals and the terrestrial depositions

Several studies documented the effects of pharmaceutical pollution on various animal species, such as vultures and fish The role of ecopharmacovigilance is becoming more and more important to control and minimize the sources of pharmaceutical pollution through the detection, assessment and prevention of adverse effects related to the presence of pharmaceuticals in the environment.

Although the detected concentrations of pharmaceuticals in the environment were mainly low (ng/L to µg/L) potential direct and indirect risks for humans exist and should be carefully monitored. Indeed, it is known that sex hormones exert their pharmacological activity at very low concentrations and that exposure to antibiotics may contribute to bacterial resistance. Further more, special populations like pregnant women, children and older patients may be more vulnerable also to low concentrations of medicines. Addressing issues related to pharmaceutical pollution is therefore one of the main current aims of Pharmacovigilance.

The Erice Declaration

The Erice Declaration represented significant progress in the light of these changes for Pharmacovigilance the Declaration challenges all the players like public health administration, health professionals, the pharmaceutical industry, government, drug regulators, the media, consumers to strive towards the highest ethical, professional and scientific standards in protecting and promoting safe use of medicines. The Declaration urges governments and others involved in determining policies relating to the benefit, harm, effectiveness and risk of medicines to account for what they communicate to the public and patients.

There are several challenges facing Pharmacovigilance programmers in achieving the aspirations of the Erice Declaration. Like The difficulties and risks in communicating conflicting or contentious messages to the public. For instance, during the course of immunization programmers, communication of new safety concerns associated with the vaccine or with programmatic errors mayresult in a dramatic fall in coverage. Nonetheless, an approach of secrecy in such circumstances is likely to erode public trust and confidence, and it fails to respect therights of the public to participate in decision-making. Not only do facts and figures need to be shared with the public, but also the process by which the data is assessed and how decisions are made should be shared openly. Another challenge is Communication between national drug regulatory authorities and national Pharmacovigilance centers needs to be improved so that regulatory decisions with possible international implications are rapidly communicated to regulators, to avoid widespread public concern or panic.

The following statements set forth the basic requirements for this to happen, andwere agreed upon by all participants from 34 countries at Erice:

Drug safety information must serve the health of the public. Such information should be ethically and effectively communicated in terms of both content and method. Facts, hypotheses and conclusions should be distinguished, uncertainty acknowledged, and information provided in ways that meet both general and individual needs.

Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for patients and health-care providers. Such education requires special commitment and resources. Drug information directed to the public in whatever form should be balanced with respectto risks and benefits.

All the evidence needed to assess and understand risks and benefits must be openly available. Constraints on communication parties, which hinder their ability tomeet this goal must be recognized and overcome. Every country needs a system with independent expertise to ensure that safetyinformation on all available drugs is adequately collected, impartially evaluated, and made accessible to all. Adequate non-partisan financing

must be available to support the system. Exchange of data and evaluations among countries must be encouraged and supported.

A strong basis for drug safety monitoring has been laid over a long period, although sometimes in response to disasters. Innovation in this field now needs to ensure that emergent problems are promptly recognized and efficiently dealt with, and that information and solutions are effectively communicated

Artificial Intelligence in Pharmacovigilance:-

Artificial intelligence (AI) is being increasingly used in Pharmacovigilance (PV). On the basis of a MEDLINE search for the terms artificial intelligence and Pharmacovigilance, the field of artificial intelligence in Pharmacovigilance (AIPV) is rapidly growing .Although the recent increase shown in this figure is only a crude signal of the magnitude of increasing interest, it aligns with observations of scientific meeting agendas and initiatives in this area. For example, the newly formed Drug Safety Research Unit International Working Group on Signal Detection and Evaluation has a subgroup devoted to AI.

A dictionary definition of AI is different from a working definition of AI. An insufficient understanding of the scope of AIPV, for example, which terms, methods, tasks, and data sets are ordinarily considered to be included in the application of AIPV, will likely hamper efficient and consistent execution of various activities for which decisions about what is and is not AIPV must be made. Such activities potentially adversely affected would include, for example, conducting systematic reviews or planning scientific meetings or working groups. AIPV scoping is even more essential given the nested and overlapping fields of AI, machine learning (ML), deep learning (DL), data mining and cognitive computing. In addition, AIPV stakeholders are a diverse range of scientific and policymaking disciplines with variable baseline knowledge.

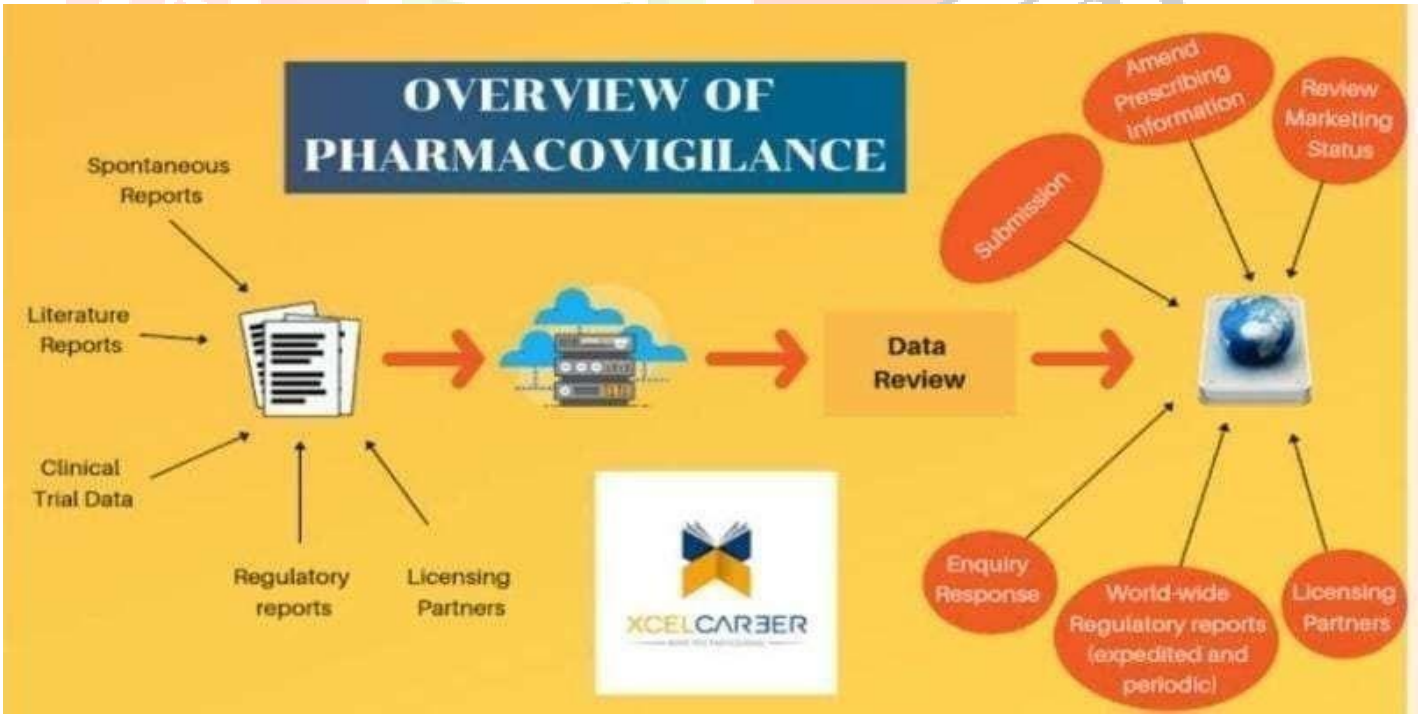
Another key use of a scoping exercise is to create a well-defined mapping of what is and is not known about a topic.2 Systematic literature reviews can often return many false-positive results, even with sensitive and specific search strategies,3 which then necessitates arduous and potentially inconsistent relevance adjudication via title, abstract, and possibly full-text review. A case in point is a recent systematic review of one circumscribed subset of AIPV, natural language processing for electronic health records–based PV, which returned 1422 citations of which all but 48 were excluded.4 An upfront sharper topic scope may ease the burden following such systematic literature reviews. A well-defined scope of AIPV can also provide orientation for new entrants into the field. In this article, we explore relevant points to consider (PTCs) regarding defining the scope of AIPV and offer a potential working definition of the scope of AIPV to, in conjunction with the PTCs, facilitate further deliberation on this topic.

The availability of healthcare data has been tremendously increasing over the last years and will further increase in the near future thanks to massive marketing of digitaltools collecting patient-derived data.

Huge amounts of electronic data present an opportunity to apply artificial intelligence (AI) techniques to improve drug safety assessment. Information extraction, using natural language processing (NLP) techniques and text mining to gather relevant insights from available, largely unstructured sources, has been gaining importance within the field of clinical research. As regards Pharmacovigilance, text mining and NLP methods can be very useful together information on adverse drug reactions (ADRs) and drug- drug interactions from various textual sources, supporting researchers and clinicians in monitoring drug safety. Indeed, both public and private entities are currently trying to develop AI tools that can allow to automatically process ADRs.[7]

Artificial intelligence and machine learning may also be useful in Pharmacovigilance for The automatic execution of tasks associated with case report entry and processing.

- The identification of clusters of adverse events representing symptoms of syndromes.
- The conduction of pharmacoepidemiological studies.
- Data linkage, through the conduction of probabilistic matching within datasets.
- The prediction and prevention of adverse events through specific modelsusing real-worlddata[2]



Pharmacovigilance In Health Emergency:

During the first waves of the pandemic, the absence of vaccines and drugs for treatment/ prevention of COVID-19 led to a rush to repurpose drugs already approvedfor other indications. As a consequence, a large number of drugs (e.g., hydroxychloroquine, ivermectin and azithromycin) has been off-label used for the treatment of COVID-19 patients, even if underlying scientific evidence on benefits was of low quality and mostly based on in vitro studies[7]

Pharmacovigilance monitoring in this context has been crucial for identifying therisks associated to drugs off-label used, thus reminding the "do not harm first" principle, especially if no or weak evidence on benefits is available. This is the case of azithromycin, a macrolideantibiotic that has been widely used, for the treatment of COVID-19 patients[8.] known proarrhythmogenic activity, which can be exacerbated when used in combination with other drugs proposed for COVID19 treatment (e.g., hydroxychloroquine), led regulatory agencies to issue warnings against the use of this drug, unless in case of bacterial super infection occurrence.[9]

Understanding Emergency Situations in Pharmacovigilance

Emergency situations in Pharmacovigilance encompass unforeseen and severe adverse events requiring prompt attention to mitigate patient risks. These events can range from unexpected adverse drug reactions to widespread safety concerns triggered by a specific product. While such events are rare, their potential impact on public health underscores the need for a well-orchestrated emergency response strategy.

The Need for Preparedness

Preparedness is the cornerstone of effectively managing emergency situations in Pharmacovigilance.

Regulatory agencies, pharmaceutical companies, healthcare professionals, and other stakeholders must anticipate potential scenarios and establish clear protocols for rapid response. A robust emergency plan allows for seamless coordination, communication, and decision-making in the face of a crisis

Swift Communication and Information Sharing

In emergency situations, timely communication is paramount. Regulatory agencies must promptly disseminate information to healthcare providers, patients, and the general public. Clear and accurate communication helps prevent panic, facilitates appropriate medical interventions, and informs patients about potential risks and mitigation strategies.

Pharmaceutical companies also play a crucial role in sharing relevant data with regulatory bodies and healthcare professionals. This collaboration ensures that the most up-to-date information is available for informationdecision-makinng.

Database Network For Post marketing Surveillance For Vaccine and Medicine:

The increased access to large scale distributed database networks provides new ways and opportunities to monitor the post marketing safety of vaccines and medicines and to generate real-world evidence to support decision-making. With this aim, in May 2008 the FDA launched the Sentinel Initiative, an

infrastructure analyzing electronic healthcare data to assess the safety of approved medical products. To date, Sentinel has developed one of the largest distributed database networks for the assessment of medical product safety, comprising the Sentinel System, which uses common data models and analytic tools to analyze pre-existing real-world data, and the FDA-Catalyst, which uses routine queries, interventions andinteractions with health plan members and/or providers.

One of the lessons learned from COVID-19 is that the potential of distributed networks of administrative databases to promptly generate robust real-world evidence is particularly high in conditions of public health emergency. This is the example of the ITA-COVID19 network, an Italian multiregional network established for the conduction of pharmacoepidemiological studies to evaluate the association between drugs, vaccines and COVID-19 through the linkage of claims databases to COVID- 19 registries [11]Other examples of distributed networks of real-world data sources being widely used to support COVID- 19 research are Open SAFELY, an English analytics platform for analysis of electronic health records data and the Observational Health Data Sciences and Informatics (OHDSI) program, an interdisciplinary collaborative aiming at generating real-world evidence through large-scale analytic.

Conclusion:-

Pharmacovigilance looks at all available information to assess the safety profile of a drug. Pharmacovigilance should also take the benefit of the drug in account. Pharmacovigilance required for systematically identifying and correlating drugs and side effects and taking corrective actions.

Pharmacovigilance play an important role in meeting the challenges offered by the increased range and potency of medicines. After the appearance of adverse effects and drug toxicities, it is essential that these are reported, analyzed and communicated to the general public having knowledge to interpret the information. Although, a significant amount of information regarding the effective use and adverse reactions has been collected, but more information is required in order to offer effective drug use in specific populations like children, pregnant women and the elderly. Moreover, providing the regulators with the necessary information to amend the recommendations on the use of the medicines improving communication betweenthe health professionals and the public; and educating the health professionals to understand the effectiveness and risk of medicines they prescribe, is the need of the moment.

Emergency situations in Pharmacovigilance underscore the dynamic nature of patient safety. Swift responses, coupled with effective communication, collaboration, and data-driven decision-making, constitute the pillars on which successful emergency management relies. As the pharmaceutical land scap econtinues to evolve, the vigilance and adaptability demonstrated in these emergency situations reinforce the commitment of regulatory agencies, pharmaceutical companies, healthcare professionals, and global organizations to the well-being of patients worldwide.

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