WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 5, 305-315. Review Article ISSN 2277– 7105

EFFECT OF COVID-19 ON PHARMACOVIGILANCE & HOW GLOBAL LIFE SCIENCE COMPANIES CAN BE BETTER PREPARED FOR THE FUTURE PANDEMICS

Mohd Arif Uddin*[1] and Sameeksha Poldasari[2]

Clinosol Research Pvt Ltd.

Article Received on
22 January 2023,

Revised on 12 Feb. 2023,
Accepted on 02 March 2023,

DOI: 10.20959/wjpr20235-27468

***Corresponding Author**
Mohd Arif Uddin
Clinosol Research Pvt Ltd.

ABSTRACT

It is more than 2 years since the COVID-19 outbreak reported its first suspected cases in China. At the start of the pandemic, many countries including India seemed 'safe' and insulated as they watched many high-income countries across the world grapple with the devastating effects of the coronavirus. Sadly, this 'safe' state only lasted until January 27, 2020, in India when a 20 yr old female presented to the Emergency Department in General Hospital, Thrissur, Kerala, with a one-day history of dry cough and sore throat and was confirmed as having covid suspect on 30 January 2020. India faced multiple major challenges on the COVID-19 front. Thus the importance of monitoring the safety of drugs, vaccines, and medical devices has been stressed in the backdrop of a world health crisis. While the healthcare industries in every country are bent down upon coming up with effective vaccines, the stakeholders of Pharmacovigilance / Drug safety have been proactively working towards monitoring their safety. The main challenges faced by pharmacovigilance during the pandemic include the collection of data, analysis of data, and safety reporting, and the key problems faced by life science were in drug manufacturing, demand for an existing drug, and launch of a new drug, research, and development. However, the Pharmacovigilance industry has been facing persistent challenges in its functioning, owing to operational disruptions due to the pandemic. The volatility of the situation demands clinical remedies and therefore, pharmaceutical giants have been under duress, making every effort to bring about time-sensitive and effective solutions in the form of Covid-19 drugs and vaccines.

KEYWORDS: Pharmacovigilance, Drug Safety, Materovigilance, Clinical Remedies, Good Pharmacovigilance Practices (GPP).

INTRODUCTION

Pharmacovigilance (PV) deals with drug-related problems: detecting, understanding, and preventing adverse effects. Patient safety is the key goal of PV. Many approved medicines carry a risk of adverse effects. Although the benefits to the patient outweigh these risks, physicians and researchers need to remain cautious about any serious side effects. World Health Organization established the Pharmacovigilance program for International Drug Monitoring in response to the thalidomide disaster detected in 1961 because many children in the 1960s were born with Phocomelia as a side effect of the drug thalidomide, which resulted in the absence or shortening of limbs. In the year 2010, 134 countries were part of the World Health Organization Pharmacovigilance Program with the aim to enhance patient care and patient safety in relation to the use of medicines; and supporting public health by providing reliable, balanced information for the effective assessment of the risk-benefit profile of the drugs.

A successful PV system collects, analyses, and shares drug safety data while aiming to reduce risk to patients in the shortest time possible. PV applies to both; approved drugs and those under clinical trials.

During the COVID-19 pandemic, PV is more important than ever. Clinical trials, of both vaccinations and potential treatments for COVID, are taking place around the world. For example, the new anti-viral drug 'remdesivir' is being trialed, while several old drugs are being repurposed. Understandably, this research is receiving far more media attention than a "normal" clinical trial would. At the same time, many rumors – some based in fact, most not – about possible treatments are circulating on social media.

Doctors, public health specialists, and other healthcare providers urgently need accurate and up-to-date safety information on COVID-linked drugs and trials. Pharmacovigilance also has an important role to play in helping to fight misinformation.[1]

Effect of pharmacovigilance

Health agencies around the world is assessing the impact of the pandemic and issuing new guidance on the management of clinical trials by sponsors and pharmacovigilance systems by MAHs at this time. This rapidly changing situation has meant that sponsors need to be more vigilant and proactive in determining the effects of the pandemic and changes in authority expectations in order to minimize the impact on safety reporting and to maintain patient

safety. It is now more important than ever to request revised instructions and adopt regulatory changes swiftly to minimize disruptions to clinical trials. To effectively deal with this unprecedented situation, it is important to have an established and robust safety reporting solution.[2]

Key health authorities, including the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and the UK Medicines and Health Regulatory Authority (MHRA) have released guidance for stakeholders, providing information and guidance on the conduct of clinical trials and post-marketing surveillance during the COVID-19 pandemic. Although these agencies acknowledge the challenges involved, it is expected that safety reporting activities should continue as usual because patient safety is the priority. However, some traditional methods of safety reporting may be more challenging during the pandemic.[2]

Challenges faced by Pharmacovigilance due to the COVID-19 pandemic

Hidden Effects of Irrational Use Of Medicines And Medical Products

- Whereas access to treatment is a major priority in any emergency health situation such as the COVID-19 pandemic, patient safety must not be compromised by the need for access. Access to the wrong, poor quality or unsafe product might have worse consequences than lack of access.[3] The past weeks of the global pandemic have seen reports of increased sales and perhaps hoarding of some medical products, such as chloroquine, hydroxychloroquine, and lopinavir/ritonavir, in some countries,[4] as well as increased sales of fake medical products and medicines related to COVID-19, such as face masks, hand sanitizers, and antiviral medications.[5] Reasons for this may include
- Stockpiling and hoarding of medicines by doctors for themselves and their family members.[6]
- Individual consumers stockpile and hoard medicines such as chloroquine, antibiotics, vitamin C, and vitamin E in unregulated markets for home use in the event they or their family members become ill with COVID-19.
- Profiteering by some wholesalers through parallel exports.
- (Mis) guidance from social-media influencers, other celebrities, and a growing number of armchair ‘health experts’ offering advice and the sale of medical devices and technologies, including masks, gloves, and alcohol bases intended for ‘home manufacture of hand sanitizers for commercial sale.

- Although some of the medicines involved have well-established safety profiles, their irrational use without professional guidance and in an environment of fear carries the potential for abuse and misuse with consequences that might be worse for the users than a lack of access, including.[6]
- Alcohol poisoning through inhalation of substandard hand sanitizers.
- Alcohol burns from inappropriate use of industrial alcohol for homemade hand sanitizers.
- Cardiac arrest, arrhythmia, and apnea associated with acute chloroquine poisoning from overdosing.[6]
- Overdosing on multivitamins in an effort to boost immunity.
- High levels of suspected transmission of an infectious agent via a medicinal product (STIAMP) through unsanitary use of gloves and masks by non-healthcare professionals.

At this time of widespread apprehension and panic due to the public health situation, PV practitioners need to heighten the awareness of frontline healthcare providers (HCPs) on the hidden effects of the COVID-19 pandemic and constantly remind them to look out for these signs among persons seeking care as suspected or confirmed COVID-19 cases or uninfected persons, and document such reactions through their spontaneous reporting systems.[6]

Increased Poor Reporting of Adverse Effects

Even during normal times, PV and materiovigilance (the study and follow-up of incidents that might result from using medical devices).[6] are considered by many HCPs in low- and middle-income countries (LMICs) as a luxury and an additional responsibility to their overburdened and underpaid work. In the face of the growing number of confirmed cases of COVID-19 across Africa, the redirection of most national efforts, resources, and manpower, including the recall of retired HCPs, it is evident that the detecting and reporting of adverse effects of medicines and medical devices [including personal protective equipment (PPE)] will be further pushed to the back burner. This will worsen the already poor reporting of adverse effects, with the consequence that adverse effects experienced by patients and/or users of medical devices and PPE at this time are unlikely to be documented. As already noted, this is the time for more vigilance and documentation of the effects of products used to treat patients, including, as previously mentioned, the hidden effects of COVID-19.[7]

Furthermore, with pharmaceutical companies and marketing authorization holders bracing themselves for harsher economic times due to the pandemic, redundancies and layoffs are occurring to mitigate the impact.[7] During the last few years, efforts have been made to

improve drug regulation and safety in Africa, with some countries requiring pharma companies to employ a local 'Qualified Person for Pharmacovigilance' (QPPV). Unfortunately, during this period of economic downturn and uncertainties, newly established local QPPV positions may be some of the first casualties in the fight between COVID-19 and the economic survival of pharma companies. Some of the reasons for this include:

- A lack of appreciation of the value the QPPV brings to the companies that have largely focused on profits rather than patient safety.
- A lack or poor implementation of 'Good Pharmacovigilance Practice' (GVP) standards.
- Imposition of national labor/human resource policies that dictate 'last employed-first out' when companies are considering restructuring processes.

Clearly, the consequences of these actions will include a disproportionate impact on safety data in the near future. In the face of these challenges, PV practitioners and regulators have an opportunity to keep HCPs and the pharma industry informed of the critical role of safety data in improving drug and medical device use. Additionally, the current situation presents an opportunity for PV experts to collaborate with frontline HCPs to undertake drug utilization studies to inform clinical and regulatory decisions. Finally, regulators have a role in ensuring that the pharma industry and marketing authorization holders continue to implement good PV practices, including maintaining product safety and undertaking routine PV activities.

Further Weakening of Already Weak PV Systems

In the past, new products were approved and marketed in countries with strong surveillance systems for several years before they were marketed in developing countries, by which time a great deal was known about their safety profile. In recent years, however, new health products, such as malaria vaccines and new tuberculosis treatments, are launched either exclusively in LMICs or simultaneously in LMICs and high-income countries. With public health emergencies such as the Ebola epidemic in parts of Africa and the current COVID-19 global pandemic, new products for these emergencies are typically granted accelerated approval based on limited safety data.[9]

Functional PV systems are critical to identifying safety signals.[8] for new or older medicines. According to the WHO, 'Fewer than 30% of the world's medicines regulatory authorities are considered to have the capacity to perform the functions required to ensure medicines, vaccines, and other health products actually work and do not harm patients'.[9] In 2018, the

Tanzania Medicine & Medical Devices Authority became the first African medicine regulatory authority to achieve a functional regulatory status, including in its PV functions. It was recently followed by Ghana in May 2020. This means, in Africa, only Tanzania and Ghana have systems considered by the global benchmarking tool (GBT) standard to be stable and functional regulatory systems.[10] Clearly, considerable work remains to be done in strengthening regulatory systems, including PV, to deliver on their mandate to ensure access to safe, quality-assured, and efficacious medicines and health technologies. Some of the key areas for strengthening PV systems as prescribed by the GBT include establishing

- Legal provisions, regulations, policies, and guidelines to define the regulatory framework for PV.
- Adequate structures and human resources for PV.
- Procedures for PV activities, including the use of data for decision-making.
- Mechanisms to monitor performance and output.
- Mechanisms to promote transparency, accountability, and communication.

As the world searches for treatments and vaccines against the coronavirus and continues to face growing shortages of PPE and medical diagnostic devices, some countries have risen to the occasion by discovering and implementing innovative solutions. These include the local manufacture of PPE kits and COVID-19 medical devices and COVID-19 rapid testing kits. These innovations are commendable but add to the regulatory challenges faced by overwhelmed regulatory systems in many African countries, including the challenge of ensuring the safety of these products. This is even more relevant as the sale and use of this locally manufactured COVID-19 diagnostic and PPE kits increases, as do social media reports of the sale of poor quality ‘unregistered’ products by unlicensed and unqualified persons.[11]

Other challenges faced by Pharmacovigilance during the pandemic

1. Data Collection
2. Data Analysis
3. Safety Reporting

Table-1: Challenges faced by PV during the pandemic.

Data Collection	Data Analysis	Safety Reporting
People are unable to reach doctors because of the lockdown globally and some patients who report through couriers were facing issues in logistics which significantly affected the data collection process from people. However, some patients were reporting through telephone and E-Mails, but the health care professionals were busy serving the COVID-19 patients due to this, the other patients were less attended, creating a void in the data collection process.[12]	Data analysis has many steps involved such as Book-in data, Triage, Data Entry, Finalization, Quality review, etc. Involves many people. But many organizations around the globe were shut down due to the local government measures to handle the pandemic situation and travel restrictions. resulted in the scarcity of people involved in data analysis and as discussed above, there is a shortage in data collection all these factors became challenges for the analysis of the data.[12]	Many countries have adopted electronic reporting (portal entry, Email, and E2B gateway to the Authorities). Many other countries still use the traditional methods of courier or hand delivery to the Authorities or reporting through the e-compact disc (data devices). Electronic reporting is not directly impacted due to the COVID-19 pandemic, the coordination becomes difficult among the pharmacovigilance teams, local legal representatives, and teams distributed across different parts of the globe. As some portion the safety reports are still submitted using a hand delivery/ courier to national Competent Authorities, these reports include expedited like Serious Adverse Drug Reactions (SADR), Suspected unsuspected serious adverse reactions (SUSAR), and Serious adverse reactions (SAE) and periodic Periodic safety update report (PUSR), Drug safety update report (DSUR), etc. In the early stage of the COVID-19 pandemic, there was disruption to courier delivery services from the sender/ receiver due to travel restrictions and logistic obstacles. Therefore, there were delayed or failed deliveries.[12]

How global Life Science companies can be better prepared for the future

This is the moment to strengthen primary healthcare globally. The COVID-19 pandemic has shown what's at stake, upending the lives of families around the world. Millions of lives have been lost, while a generation of students faced a learning crisis. It's been a stark reminder of the need to build resilient health systems globally. Better primary healthcare will help us protect against future pandemics. These are some of the areas to focus on.[13]

1. Recruit, train, and prioritize healthcare workers

It goes without saying, healthcare workers are at the heart of any strong healthcare system. Throughout the COVID-19 pandemic, frontline workers, which includes community health workers, have selflessly risen to the challenge. Whether it's been caring for the sick, making

sure that vaccines reach the most vulnerable, testing and reporting cases, or keeping routine healthcare services going, their efforts have been immense. Jennifer Boateng, a pharmacist who works at the Greater Accra Regional Hospital in Ghana, epitomizes the efforts of so many other healthcare workers. "I live with my husband, three children, and my mother, who is 80 years old. I was still breastfeeding when I started work at the COVID-19 intensive care unit," she remembers. "I was truly terrified of contracting the virus and putting my family at risk. Painfully, I had to stop my children from hugging me." The physical and emotional strain of the pandemic on healthcare workers like Jennifer has been incalculable. To try and protect against future pandemics, healthcare workers must be prioritized more than ever. That means providing them with the necessary training, making sure they're first in line for vaccines so they're protected, and financially and emotionally supporting them. That includes building the confidence of healthcare workers, ensuring their thoughts and concerns are understood and working with them to address those issues.

2. Pharmacovigilance Initiatives for the Future

The Pharmacovigilance community has been quick to respond to the pandemic.

In anticipation of the many COVID-19 therapies expected to be available in near future, the UK's MHRA has launched a new online reporting system, called the Yellow Card. The Yellow Card service aims to track reports of adverse effects in any treatments, vaccines, diagnostic methods, or medical devices that might be used in the care of COVID-19 patients. This should create a robust knowledge base of safe treatments for the disease.

"While we aim to ensure that potentially lifesaving COVID-19 treatments and medical equipment reach patients as quickly as possible, patient safety is our highest priority," said Dr. June Raine, Chief Executive of the MHRA.

Some companies are using Big Data analytics in the fight against COVID-19. This refers to the in-depth analysis of data from multiple different sources. This technique should reveal patterns in the data that might not be possible to detect from any single database. Additionally, it may not only assist in finding solutions to current medical issues but also predict any prospective problems.

Finally, the WHO has five established Collaborating Centres, set up to advance PV in countries around the world. The five centers handle Drug Monitoring, Statistics and

Methodology, Advocacy and Training in PV, Strengthening PV Practices, and PV in Education and Patient Reporting, respectively.[12]

3. AI: adapting and innovating the process

"This pandemic has been a tremendous opportunity to change the way we operate fundamentally, and adapt and adopt new technologies," Williams says. "And we've done that in a multitude of ways." AE reporting is a highly time and resource-consuming activity for regulatory bodies, and the exponential increase in AE information relating to new Covid-19 drugs and vaccines has presented further challenges for the field. One means of alleviating the pandemic's burden on an already process-heavy area is the automation of AE data intake, through which reports are interpreted and presented more quickly and accurately than is possible for a human being. IQVIA has embraced this approach, Williams says; the company is using robotic technology and machine learning to process AE reports, as well as automatically standardizing and translating the safety data coming in "Obviously, Covid-19 is a global problem, so not everything comes to us in English," Williams explains. "We need to be able to react to that."Using advanced technology to optimize pharmacovigilance is not a new idea – a study in 2018 found that 62% of drug safety experts prefer using artificial intelligence (AI) for AE processing – but the sheer amount of AE reports received due to new Covid-19 drugs and vaccines means that traditional methods are simply no longer an option.

CONCLUSION

There is no place to hide from COVID-19, the healthcare industries have to be better prepared to face it and develop significant efforts to Diagnose, Treat and Prevent the pandemic which needs extensive collaboration between the Life sciences companies, Health care systems, and the government. The impact of COVID-19 would be limited to the short term, we must strive to perform better in long term, and healthcare systems are struggling to respond effectively. Developments that used to be taken in months and years are being accelerated. As a blessing in disguise, COVID-19 exposed all the loopholes in the industry. The demand for antibiotics, and gastrointestinal medicines is slowing down, with people staying indoors, eating home-cooked food, and taking care of their health.

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