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WHITE PAPER

The Need for Evolution in Pharmacovigilance to Face the Pandemics

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Contents

Abbreviations

ADR	Adverse Drug Reaction
AEFI	Adverse event following immunization
AI	Artificial Intelligence
CHMP	The Committee for Medicinal Products for Human Use
COVID-19	Corona Virus Disease-2019
EHR	Electronic Health Record
EMA	The European Medicines Agency
E2B	International standard for transmitting medicine adverse event reports
H1N1	Influenza A virus subtype Hemagglutinin Type 1 and Neuraminidase Type 1
ICSR	Individual Case Safety Reports
ICH	International Conference on Harmonization
MAH	Marketing Authorisation Holder
NIPs	National immunization programs
NRAs	National regulatory authorities
PHAC	Public Health Agency of Canada
PSUR	Periodic Safety Update Reports
PV	Pharmacovigilance
RMPs	Risk Management plans
USFDA	United States Food and Drug Administration
UMC	Uppsala Monitoring Centre
WHO	World Health Organization
WEB-RADR	WEB-Recognizing Adverse Drug Reactions

1. Introduction

With the evolution in science and technology many thought that a global pandemic outbreak would be limited to history or movies. But humanity is confronted by a conspicuous pandemic in 2020. WHO saw it coming in 2019, but did not know when and how severe it would be. As a precaution, WHO had collaborated with all the key minds of the global health care domain to ensure active and reasonable access to health care needs all over the world. [1]

EMA on the other side, considering the lessons learned during the 2009 (H1N1) flu pandemic had been working on improving its pandemic preparedness plan. [2]

Some initial work on coronavirus vaccines had been completed before the COVID-19 pandemic, and challenges to the development of effective and safe vaccines against coronaviruses have been studied. [3]

Currently, World Health Organization (WHO)-led global solidarity trial, uses new drug, such as remdesivir, and 'repurposed' drugs, such as hydroxychloroquine and lopinavir/ritonavir, for effectiveness against COVID-19. [4]

2. Role of pharmacovigilance during a pandemic

Pharmacovigilance is no longer a mere regulatory compliant body with timely reporting of what has happened. It is now a proactive body with the inclusion of risk management and risk minimalization strategies giving it a more scientific sense. But with numerous guidelines in drug safety, overlap in the analysis, increased workload, and non-harmonized regulations we are at times striving to meet the regulatory compliance, which overshadows the scientific dimension.

A true opportunity to bring pharmacovigilance closer to healthcare systems arises during challenging times. Clinicians, faced with treatment challenges in the absence of data from randomized controlled trials, will use available real-life observational data on both treatment benefits and harms. Integration of pharmacovigilance with clinical practice is a key area of interest to many leaders around the world. Attention will also be required to detect false information, and corrections to prevent harm. There is a lack of experience worldwide in managing responses from a public health perspective with apparent differences in approaches between countries to containment/mitigation strategies and regulatory recommendations for treatment options. [5]

For instance, during the early stages, pandemic "infodemic" created a situation, where drugs approved for other indications (chloroquine, hydroxychloroquine, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, favipiravir, and umifenovir) were being used by communities inappropriately or stopped using some drug considering them to promote infection. [6]

3. What role did we play in the past?

Pre-pandemic activities by EMA to face 2009 (H1N1) outlines certain pharmacovigilance activities described in the core risk management plan. Those activities included strengthening the spontaneous reporting systems, for instance alternative channels for reporting (web-based) and close monitoring of events of special interest; simplified but more frequent PSURs, providing a monthly review of safety data received by the MAH; post-authorization safety and effectiveness studies, including a compulsory safety study in 9,000 subjects for each vaccine along with establishing teams dedicated to the pandemic areas in some member states.

Between DEC-2009 and AUG-2010, pandemic pharmacovigilance update was published on its website (weekly and then bi-weekly) providing estimates of exposure, summary of PV data available in Eudravigilance and conclusions of signal reviews which were very effective tools for the agency to deal with concerns.[7]

On the other side, UMC developed PaniFlow - a tool specifically designed to capture AEFI of A/H1N1 2009 pandemic influenza vaccines and of the adverse events associated with treatment with oseltamivir (Tamiflu) and zanamivir (Relenza). WHO offered this tool free to countries, particularly emerging and developing countries that did not have a good AEFI reporting system in place. PaniFlow enabled countries to quickly detect potential safety problems in their own populations and take remedial action if causality was established. The global picture could be rapidly reviewed and the international community alerted when problems were suspected or confirmed. [8] The features of PaniFlow are being incorporated into VigiFlow and VigiBase during Covid-19 pandemic.

4. What lessons were carried to the present?

Rolling review – This is one of the regulatory tools that EMA uses to speed up the assessment of a promising medicine or vaccine during a public health emergency. EMA's human medicines committee - CHMP reviews data as they become available from ongoing studies, before a formal application is

submitted. So that the CHMP can reach its opinion sooner on whether or not the medicine or vaccine should be authorized.[7]

EMA's human medicines committee has started the first 'rolling review' of a COVID-19 vaccine, which is being developed by the company AstraZeneca in collaboration with the University of Oxford as on 01-OCT-2020.[9] and BNT162b2, which is being developed by BioNTech in collaboration with Pfizer as on 06-OCT-2020.[10]

5. What is the need for evolution?

With all the preparedness, EMA listed out challenges that required attention, like; better coordination on communication among the main EU stakeholders; the practice of common approaches, such as vaccination strategies and systems for data collection (number of vaccinated people, vaccine effectiveness, pregnancy registries and background incidence rates of diseases). Research activities were needed ahead of a novel pandemic into areas such as technologies and serology assays, and methodologies for efficient detection of safety signals during a pandemic.[2]

Big Data analytics empowers pharmacovigilance with analytical and prescriptive insights in addition to traditional monitoring and reports. An effective pharmacovigilance analysis requires capturing and harnessing data from a wide range of sources and systems (research studies, EHR data, health economic analysis, drug usage information, market research, clinical data, social media and search data) to be transformed into actionable insights.

Though the Sentinel system achieved it to a significant extent, one of the major limitations is its limited effectiveness in detecting uncommon diseases or diseases that occur outside its catchment areas of the sentinel sites. To resolve this and other challenges, USFDA has Sentinel System – Five-Year Strategy 2019-2023 that outlines the challenges and action plan which aims at enhancing and expanding the Sentinel System's foundation, including data, infrastructure, operations, and technology. All this to augment its safety analysis capabilities using advances in data science and signal detection and to accelerate access to and broaden the use of real-world data for real-world evidence. [11]

6. Where is the challenge?

Collecting medicinal data globally to study drug safety across the borders needs technology along with awareness. Timely review of incoming data and real-time signal detection can provide important safety information for healthcare providers.

7. Technology

Pharmaceutical companies need to follow a wide range of processes to ensure their pharmacovigilance is up to standards. When a system is built on unguided evaluation of big data, active signal detection is exposed to the inherent risks of false positive and false negative findings. [11]

The vast diversity in safety reporting across the globe is apparent with some countries using E2B gateway, portal entry and email, while some are using traditional methods of courier or hand delivery for paper reporting or electronic reporting by the compact disc. This pandemic highlight how electronic or paperless reporting is the most effective reporting method.

8. Collaboration

Sharing and collaboration both within and beyond our pharmacovigilance community especially supporting pharmacovigilance colleagues in lower-income countries, will be integral. Bringing many different stakeholders onboard building and coordination among members of the WHO program for international drug monitoring is vital.[4]

Collaboration with other scientific organizations emphasizes the importance of spontaneous as a source of real-world data. Combining data from spontaneous databases with real-time observational studies using technology and networking with other sources like EHR, insurance claims can allow more efficient evidence generation to explore any medicines safety issues that arise.[8]

Collaboration is important because when NIPs and NRAs fail to work with each other when developing national AEFI or ADR surveillance systems, it leads to duplication of effort and a failure to capture all relevant data in one central repository. In addition, potential crises may go undetected through such confusion and this becomes an additional barrier for reporting AEFIs and ADRs [12].

Effective collaboration was noted in Canada with PHAC and public health authorities during the 2009 influenza pandemic in identifying a higher than normal rate of anaphylaxis linked to one lot (Lot 7A) of a newly released adjuvanted H1N1 flu vaccine. [13]

9. Prioritization

Every time there is a mass administration of a drug or vaccine, you need to monitor in real-time, which helps to report any problems as quickly as possible. Prioritizing ICSR processing as per the need of the hour with clinical trial (serious and non-serious) cases for products developed/tested for pandemic takes the highest priority. Prioritize products with significant risk minimization programs like Pregnancy prevention programs vs. provision of educational materials. Deprioritize RMPs for established products without additional pharmacovigilance or risk minimization measures. Delay determination of any corrective actions until the pandemic is declared over by WHO or capacity is back to normal and stable. During pandemics having a dedicated safety intelligence team enables an established communication channel with authorities, to have proactive communication with regulatory agencies to arrange alternative measures and actions instantly.

10. Harmonization

Do all countries have systems for monitoring vaccine safety in place? International sharing of data from post-marketing surveillance will be vital in guiding risk-benefit assessments and determining whether changes in vaccination policies are needed. To improve collaboration, it is suggested that creating an electronic platform to quickly share trusted information with healthcare professionals. Also, consortiums could be useful to allow more rapid and comprehensive sharing of information, particularly with industry. [14]

11. Education, training, and communication

During pandemics having a dedicated safety intelligence team enables an established communication channel with authorities in order to arrange alternative measures and actions instantly.

Effective communication, which needs to be timely, accurate, truthful should be free and available to everyone. Unless the system is well understood and used by health workers at lower levels, there will be a gross underestimation of reports. Hence governments and partners should allocate enough resources to establish a dedicated system and train health workers on the importance of reporting. Training of local staff on signal detection, including procedures for passive and active surveillance and communicating the importance and use of reporting tools is essential as there is not enough training done at the clinic level.

There has been a desire for clear, up-to-date, and utilized pharmacovigilance regulations on international forums as well. Specifically, crisis communication plans, active surveillance and causality assessment should be prioritized in terms of the global vaccine safety initiative's technical support, training, resources and sharing of information. [15]

To boost pandemic-related signal detection activities focus should be on certain key locations where large amounts of data can be gathered, analysed, and extrapolated for a broader investigation. An Increase in the availability of training (like e-learning modules) could help to improve the quality of both inputs and analysis, according to experts.

Patient safety can improve only when a culture of pharmacovigilance is encouraged. The European Union's innovative medicines initiative WEB-RADR project has brought two digital tools for pharmacovigilance: mobile applications (apps) for reporting the adverse effects of drugs and social media data for its contribution to safety signalling. The Med Safety App is designed for healthcare professionals and also the patients to report suspected ADRs directly to the national centre. The app is built on ICH E2B(R2) messaging standard and the ICSRs can be transferred directly to a national database. [16]

The competence in a country for data analytics and interpretation is important because when there is data but no idea what to do with it, then the data is of no use. Hence the promotion of understanding, education and clinical training in pharmacovigilance and effective communication of its surveillance role to the public is important. To improve patient safety worldwide, pharmacovigilance cannot exist in a vacuum.

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Author's Profile

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With the awareness of GVP modules and understanding of the relevant guidelines, Sowmya is engaged in activities involved in ICSR processing. She had been involved in receipt of ICSR, triage, case creation (including MedDRA coding) and peer review. To ensure meeting of regulatory compliance and service level agreements, she is also involved activities related to awareness of company procedures and guidelines.

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