Commentary

Matthew Halma*

Towards robust pharmacovigilance surveillance systems

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Abstract: Public health officials are currently tasked with the role of regulating medicines, both during the approval process and post-market surveillance. While several successes of pharmacovigilance systems exist, pharmacovigilance systems in place are inadequate for protecting the public, as they are slow to show causation. We argue that while pharmacovigilance system were instrumental in the recall of AstraZeneca and Moderna mRNA Covid vaccines for young people during the Covid-19 pandemic, they were inadequate in identifying several clear safety signals which should have led to their withdrawal from the market. Pharmacovigilance systems have much room for improvement, both in terms of data management, accessibility, and use. We propose several guidelines for pharmacovigilance systems to take to improve their efficacy and their ability to protect the public.

Keywords: pharmacovigilance, data accessibility, public health, post-marketing surveillance

1 Introduction

Several famous cases exist of approved drugs being withdrawn from the market due to adverse effects being found in post-market surveillance [1]. A 2001 review examining the period from 1960 to 1999 found 121 drugs that were withdrawn due to safety reasons worldwide [2]. A similar study focusing on drugs marketed in the USA between 1980 and 2009 identified 118 drugs discontinued, approximately one in seven of the 740 new molecular entities (NMEs) approved during the study period [3].

The most oft cited example of drug withdrawal from the market is thalidomide, which was prescribed for pregnant women to reduce morning sickness [4]. Though effective as an anti-emetic for this indication [5], reports emerged of babies with birth defects, including malformed limbs [4]. An Australian doctor, Dr McBride, raised grave concerns in a letter to the editor of the Lancet in 1961, showing a 20% higher rate of congenital malformations in babies [6,7]. As mounting evidence of birth defects become impossible to ignore, Frances Oldham Kelsey, an FDA reviewer at the time, blocked the drug's market application in 1961 [8]. Currently, thalidomide is rarely used in the treatment of leprosy [9], though its use is not recommended by the World Health Organization (WHO) due to its contribution to birth defects [10]. However, thalidomide's most promising repurposing is in treating cancer via its anti-angiogenic mechanisms [11].

In these cases of market withdrawal, pharmacovigilance has arguably functioned, though debates may ensue over whether or not the drug could have been withdrawn sooner, or if the safety concerns identified were grave enough to mandate withdrawal, as opposed to just warning patients about potential side effects. In the famous case of Vioxx, it was estimated that, even though the manufacturer Merck was aware of the cardiac complications that people taking Vioxx were experiencing, yet the drug continued to be marketed, resulting in up to 50,000 [12] extra deaths from the time of knowing to the final regulatory decision on Vioxx.

Here, delays in knowledge translation are costly, as people continue to use dangerous drugs. In the similar case, delays in knowledge translation from laboratory to NME approval can also be costly by those lacking an efficacious way to treat a disease. Shortening these delays is an important priority, but less important fundamentally than getting these decisions correct.

We examine the development of safety knowledge from initial conception to further validation, ultimately to regulatory action being taken. In this model, there are several interventions that can drastically improve the speed and responsiveness of pharmacovigilance systems. Journal publishing can be slow and while developments such as preprint servers can speed up knowledge dissemination [13], the common criticism remains that these forms of evidence are unvalidated and more error prone.

Agility in knowledge translation is important for the responsiveness of a medical system. A similar case emerges with large companies, who become less manoeuvrable as they grow, and many create initiatives meant to speed up

* **Corresponding author: Matthew Halma**, EbMC Squared CIC, Bath, BA2 4BL, United Kingdom, e-mail: matt@worldcouncilforhealth.org

their responsiveness and nimbleness [14]. The best organizations combine a well-defined strategic mission with practices enabling fast cycle times and rapid iteration. Similarly, regulators need to be agile and adaptive to incoming information.

Drug	Year of approval	Year of withdrawal	Initial indication	Side effects leading to withdrawal
Thalidomide [4]	1957	1961	Sedative, morning sickness	Severe birth defects in infants
Fen-Phen [15]	—	1997	Weight loss	Linked to serious heart and lung problems
Rofecoxib (Vioxx) [16]	1999	2004	Pain relief	Increased risk of heart attacks and strokes
Terfenadine (Seldane)[17]	1985	1998	Allergies	Risk of serious cardiac arrhythmias, especially when taken with certain medications
Cisapride (Propulsid) [18]	1993	2000	Gastrointestinal issues	Associated with serious cardiac arrhythmias
Dexfenfluramine (Redux) [19]	1996	1997	Weight loss	Increased risk of heart valve disorders
Rituximab (Raptiva) [20]	2003	2009	Psoriasis	Increased risk of progressive multifocal leukoencephalopathy, a rare brain infection

The history of pharmaceutical regulation goes back to the early 1900s, where several remedies entered the market. This was near to the time of the discovery of the role of vitamins and minerals in human health. Given this new awareness of factors in health, several novel "concoctions" emerged with mixtures of ingredients. After incidents in which market concoctions caused injury and death, the Theodore Roosevelt administration responded to this challenge through the establishment of the US Food and Drug Administration in 1906 [21]. Other nations also have histories of the development of their own regulatory agencies. The remit of the FDA was expanded by the Food, Drug and Cosmetic Act of 1938, which brought more product classes under their aegis, including cosmetics and medical devices and established a process for approving new drugs.

2 The current state of pharmacovigilance surveillance

In order for pharmaceutical products to be allowed to market within the USA, they must first be approved by the FDA. This is typically accomplished through a new drug application (NDA). While details of the process differ between drugs and small molecules, the broad process is similar. Two applications must be filed, an investigational new drug application and a NDA after clinical evidence has accumulated (Figure 1).

As clinical trials are expensive, with the average phase I trial costing $2.1 million (USD), the average phase II trial costing $7.6 million, and the average phase III trial costing $11.4 million [23], NDAs increasingly rely on surrogate markers, which can have less clinical relevance than direct clinical endpoints [24].

Following approval, there is often a period of post-market surveillance; "phase 4 trials" refers to ongoing surveillance of pharmaceuticals in a population after marketing [25]. Currently, some pharmaceuticals are mandated to monitor for adverse events after approval. Of the high risk medical devices approved in between 2005 and 2012, 48% were mandated to provide post-approval surveillance [26]. It is possible that adverse effects can manifest on a population level, as clinical trials are often underpowered to find low-prevalence events. Roughly 4% of drugs are eventually withdrawn due to safety reasons [1,3] after a median duration of 3.4 years [27].

Spontaneous reporting systems allow the primary care providers of the patients to submit reports of adverse events [28]. The USA has established several spontaneous reporting systems, including the FDA Adverse Events Reporting System (FAERS) and the Vaccine Adverse Events Reporting System (VAERS). However, there are significant issues with these passive surveillance systems which hamper their ability to detect safety signals.

1) They are often not known of by physicians.
2) They are often not used.
   a. Difficulty of use
   b. Possible penalties for misuse
3) Reporting depends on physicians' assessment of adverse event causality.

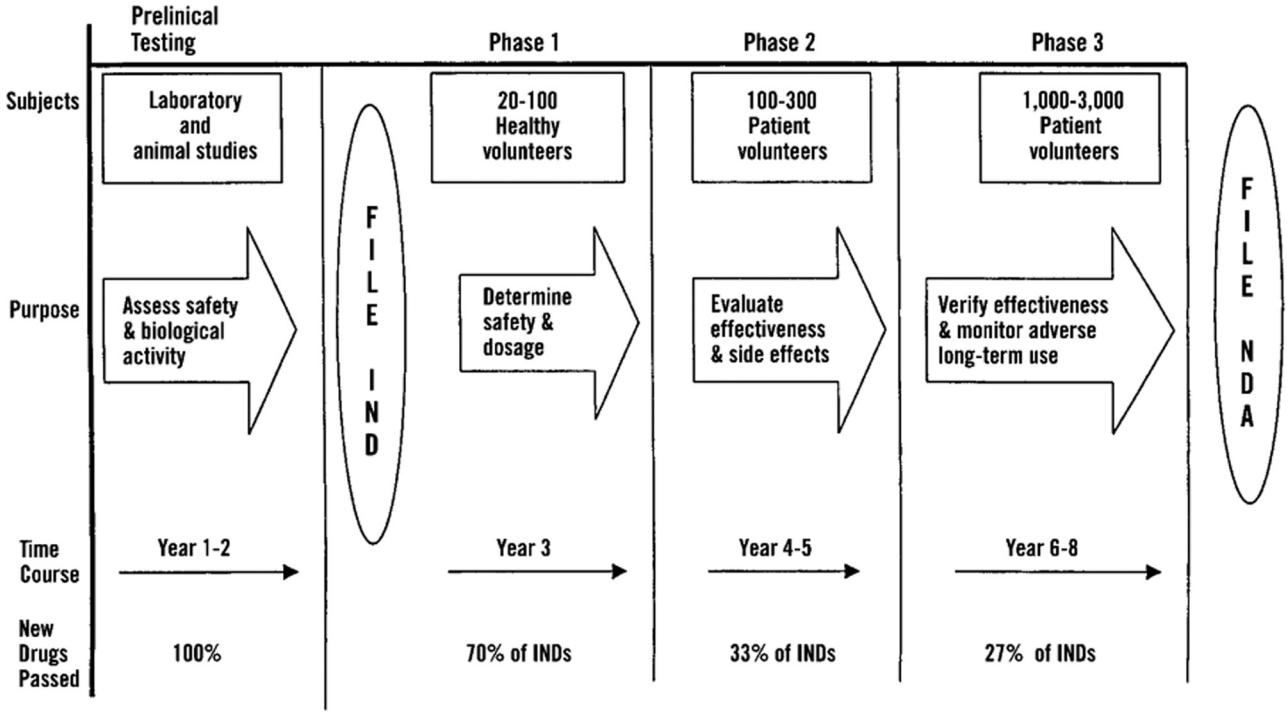

Figure 1: Drug approval process in the US Food and Drug Administration. Image Credit [22].

4) Database surveillance is limited.
   a. Officials miss items frequently.
   b. Poor interfaces for public access

As such, any spontaneous reporting system benefits from being paired with an active surveillance system, which use electronic medical records to monitor for safety signals in data that would already be recorded. Spontaneous reporting systems require the patient's physician (and in some cases the patient) to file a report. This latter approach necessarily misses many events due to the above reasons.

3 Systems

Pharmacovigilance system	Regions surveyed	Date founded	Total reports	Reports per year
FAERS	United States	1968	27.6 million (through September 30, 2023 [29])	1.8 million in 2017 [30]
EudraVigilance	European Union	2001	25.3 million (through December 31, 2022 [31])	173,000 (2019) [32]
MedEffect Canada	Canada	2005 [33]	Unknown	96,559 in 2019 [34]
VigiBase-WHO Global Individual Case Safety reports Database	Worldwide	1968	23 million (through June 2020) [35]	~2 million (2019)
Japan Adverse Drug Event Report	Japan		607,361	Unknown
TGA Adverse Event Management System (AusVigilance)	Australia	1970	Unknown	57,771 (2020–2021) [36]
China Adverse Drug Reaction Monitoring System	China	1999	16.9 million (1999 through 2020) [37]	1.7 million (2020) [37]

VAERS	United States	1990	2.6 million (through November 3, 2023)	48,000 (2019) 753,000 (2021) [38]
Yellow Card Scheme	United Kingdom	1964	Unknown	27,000 (2018) [39]
Netherlands Pharmacovigilance Centre Lareb	Netherlands	2003	200,000 (2021) [40]	30,000 (pre-covid)
Centre for Adverse Reaction Monitoring	New Zealand	1965	110,000 (through 2023) [36]	Unknown

Several systems for pharmacovigilance are shown in the above table, many have publicly available datasets which provide summary statistics of reports.

4 Requirements for robust pharmacovigilance

1) A culture of reporting

   Initiatives like the UK Yellow card systems "Every Report counts" are positive initiatives to increase reporting of adverse events (AEs) [41]. This also requires expanded awareness of pharmacovigilance, their importance, and how to use them. This should become part of medical school teachings and notices should be visible in practitioner's offices, pharmacies, and hospitals. AERS should seek to reduce the level of underreporting and reporting needs to become part of professional standards by medical practitioners. It is important to communicate that reporting not only serves the patient, but possibly any future person who may use the drug in the future, or future people who may be treated with a safer alternative treatment owing to the information in the reports.
2) Accessible and visible dashboards

   Several databases provide simple user-friendly graphical user interfaces to access the data, ease of use and accessibility must be prioritized to ensure that the public can access these important (anonymized) data. These should have functionalities allowing one to search by condition and treatment, as well as segment searches by year, age, sex, or other characteristics.
3) Follow up on safety signals by an independent board

   Where safety signals are found, there must be a defined process for investigation which involves determining causality. If causality is found, notices should go out to those affected, or at least to the broader public. In some cases, the pharmaceutical may need to be removed from the market where adverse events are found. Boards without conflicts of interest, composed of a cross-section of professionals with relevant experience should be established on an *ad hoc* basis to follow up on safety signal thresholds being surpassed. The analysis of raw count numbers can be performed automatically and trigger the creation of a "ticket" to investigate the signal.
4) Harmonization and cross-compatibility with other pharmacovigilance systems

   Detection of rare events relies on having a sufficient sample population to draw from. Lack of data pooling between systems can lead to AEs being overlooked (false negatives) [42]. Leveraging the reporting capability of other pharmacovigilance systems enables rare AEs to be detected and investigated further. System harmonization also enables benchmarking of different systems against each other.

Lastly, it is important to stress that all approved drugs are only provisionally approved, and this can be removed should they demonstrate unsafety. If a safety signal is observed and found to be significant and causal, further research can be performed on mechanisms of action to alleviate AE-associated illnesses.

5 Conclusion

While the drug approval process successfully identifies many safety issues, still, some medicines enter the market with extant safety issues. Given this reality, robust pharmacovigilance and post-marketing surveillance is necessary to ensure public safety and to ensure that consumers and patients are making informed decisions. While current pharmacovigilance systems have identified and responded to several safety signals, cases remain of avoidable delay costing lives and injuries.

In order to combat this, it is necessary to create a pharmacovigilance culture, where events are reported. Physicians and patients prescribed medicines need to be aware of reporting databases, and anonymized data should be accessible for independent bodies to identify safety

signals. Furthermore, real-time display of information can help to reduce delays in investigating safety signals.

Together, these changes make for a safer consumer environment for pharmaceutical products, which is especially important, given the high rate of iatrogenic harm in the current medical system. Examples abound of unsafe drugs being marketed out of ignorance for their safety issues. Regulators can learn from these examples by adapting robust pharmacovigilance systems in their jurisdictions.

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