Chapter

Introductory Chapter: Pharmacovigilance and Public Health Safety

Maria Teresa Herdeiro, Tânia Magalhães Silva, Inês Ribeiro-Vaz, Eva Rebelo Gomes, Adolfo Figueiras and Fátima Roque

1. Introduction to pharmacovigilance

Worldwide, pharmacovigilance is one of the most important scientific disciplines within public health [1]. According to the World Health Organization (WHO), pharmacovigilance is described as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [2]. The implementation of pharmacovigilance activities was essential to globally promote and protect public health, particularly by reducing the significant burden of morbidity, mortality and associated increased healthcare costs, triggered by the occurrence of adverse reactions to medicines [3]. The Memo/08/782, released in 2008 by the European Commission, highlights the importance of pharmacovigilance, namely for saving lives, by revealing estimates of about 197 thousand deaths per year and total costs to society of 79 billion euros in the European Union (EU), due to adverse reactions [4].

The fundamental goals of pharmacovigilance are [5–7]:

- To early identify drug-related problems, such as the occurrence of adverse reactions and other interactions previously unrecognized, reporting the resulting outcomes in a timely manner;
- To detect changes in the incidence of known adverse reactions;
- To carefully monitor and assess the benefit, harm, side-effects, efficacy and risks, together with the risk–benefit profile, of commercialized medicines, aiming to reduce their risks and increase their benefits during the drug's lifecycle;
- To boost the prudent, rational and more effective (including cost-effective) use of several drugs;
- To strengthen patient's care and safety, and consequently safeguard public health, concerning the use of medicines, including paramedical interventions;
- To promote education, knowledge, accurate information and clinical training in the field of drug safety and ensure its effective communication and accessibility to the public.

In sum, the golden objective of pharmacovigilance process is to enhance patient's safety and quality of life, and strictly preserve public health by identifying, preventing or decreasing the harmful effects and risks related to the use of health products in humans. Therefore, the science that assesses drug's safety and efficacy profiles stands as highly important throughout the entire drug development lifecycle, from preclinical development until post-market surveillance, as it promotes the continuous vigilance of the drug effects. It plays a crucial role within pharmaceuticals, not only for the prevention of drug-related risks in humans, as well as for the reduction of the financial expenses linked to the occurrence of unexpected adverse effects [5–8].

2. Pharmacovigilance history

Pharmacovigilance has a long history. Although the first findings were dated from 172 years ago, when a patient died after being anesthetized with chloroform, followed by 107 deaths in the United States of America in 1937, due to the high toxicity caused by diethyleneglycol, a sulfanilamide elixir-containing solvent, its official inception to address drug safety problems was only heralded after the thalidomide tragedy, in 1961 [1, 8]. This drug was commonly used in Europe by pregnant women as a nonaddictive, nonbarbiturate sedative for nausea treatment, and resulted into a devasting 10 thousand birth abnormalities, namely phocomelia, and increased miscarriage rates [9]. At that time, Dr. McBride highlighted the link between the consumption of thalidomide in pregnancy and the prevalence of fetal congenital malformations, by writing a letter to The Lancet journal editor and reporting an increase of 20% in these cases. In response to the thalidomide disaster, it became evident the urgency in requiring the rigorous safety and efficacy testing of drugs before their market authorization, as well as a global awareness concerning the need for creating pharmacovigilance systems [8].

The pharmacovigilance system suffered many alterations since then and, due to a collaborative effort of many stakeholders, such as physicians, pharmacists, other healthcare professionals, patients, regulatory health authorities, academia and industry, in 1968 the WHO Pilot Research Programme for International Drug Monitoring was instituted. This program intended to establish an active, systematic, organized and regulated network at an international level, mainly for uncovering formerly unknown or poorly recognized drug's adverse effects, leading to the formal adoption of the pharmacovigilance term in the 1970s [7, 8]. In early 1980s, the Council for International Organizations of Medical Sciences (CIOMS) introduced its programme on drug development and usage, together with WHO. In the 1990s, a remarkable impact on international drug regulatory activity was observed, specifically after the implementation of various of the recommendations provided by CIOMS by the formerly International Conference on Harmonization (ICH), currently known as International Council for Harmonization [1, 7, 8]. The ICH helped to harmonize the regulatory infrastructures of the regulatory agencies and pharmaceutical companies from Europe, Japan and the United States [1]. Thereafter, a positive development was observed in several countries, concerning the organization and associated regulations of drug safety, ultimately resulting in the creation of the European Society of Pharmacovigilance (ESOP) in 1992, posteriorly renamed to International Society of Pharmacovigilance (ISoP). Finally, in 1995 the European Medicines Agency (EMA) was founded, followed by the Eudravigilance launch in 2001 [7, 8].

Besides thalidomide disaster, another significant landmark in the history of pharmacovigilance was the market authorization of rofecoxib, a cyclooxigenase-2

inhibitor. In the end of 2000, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study revealed an association between rofecoxib consumption and myocardial infections in patients with chronic pain [10–12]. By this time, this risk became a critical public health issue as rofecoxib was prescribed to tens of millions of people in more than 80 countries. This was one of the most highly publicized drug withdrawals ever reported and, together with other subsequent related episodes, raised some concerns regarding public trust on the role of pre- and post-marketing surveillance [10–13]. Due to the public's lack of confidence on pharmacovigilance, more robust regulations had to be adopted [12, 14]. These include, for instance, the EU risk management plan, implemented in 2005, which became a mandatory document for marketing authorization applications to evaluate the information on drug toxicology, the request for a pharmacovigilance plan as well as for epidemiological information on the population receiving the drug therapy, and the submission of protocols to the regulatory authorities prior to the study start for a proper safety assessment [12]. Other important measures implemented were the education of physicians and medical students, active participation of other health professionals (pharmacists, nurses) in adverse drug reaction (ADR) reporting, feedback transmission and improvements on ADR reporting [14]. The introduction of all these approaches were essential to safeguard public health, with the particularity of primarily assessing the effects on the population, especially on the patient, rather than over the drug under study [6, 12].

3. Pharmacovigilance systems

Given the high importance of pharmacovigilance, currently, countless countries around the world already have well-established, active and robust national pharmacovigilance systems to safeguard patient's wellbeing.

Pharmacovigilance activities of these systems can also involve the [1]:

1. establishment of the safety profile through data collection and management on the drug's safety;

2. analysis of individual case reports to identify early signals of potential drug-related security problems;

3. dynamic risk management to prevent the emergence of potential associated harmful risks following drug's use; and.

4. information transmission to stakeholders and patients.

Therefore, it is not surprising that the WHO programme, responsible to aid in the design, development and assistance of the pharmacovigilance systems, has already 170 countries as partnership members [15].

3.1 WHO collaborating Center for International Drug Monitoring: the Uppsala monitoring Center

As previously referred, the WHO Programme for International Drug Monitoring started, in 1968, to systematically collect all available information on drug's adverse effects, as a worldwide response to the thalidomide disaster. Ten years later, in 1978, with the intuit to support this programme, the Uppsala Monitoring Center (UMC) was set up. The UMC is an international, independent and non-profit center in

Uppsala, Sweden, devoted to investigating the harms and benefits of medicines, to ensure a safe and efficient consumption of these drugs by patients [5, 7].

The key mission of UCM, on behalf of the WHO, is to protect patients through an effective and global pharmacovigilance practice, namely the management of the international database of ADR reports received from each country national center, within the WHO's global pharmacovigilance network [5, 7]. This distinctive WHO data repository, known as VigiBase, is the world's single largest database system of individual case safety reports (ICSR), which are solely submitted by members of the WHO programme [16]. The ICSR, also commonly recognized as "spontaneous" or voluntary ADR report, is a safety document that includes the information needed to support the reporting of adverse events, as well as of products-related problems and consumer complaints generated during the drug post-marketing phase. An ICSR can be filled either in paper or electronically and, to be considered as valid, has to include at least the following four elements: an identifiable patient, one identifiable reporter, one suspected medicinal product and one suspected adverse event [17, 18].

In sum, firstly the national pharmacovigilance system of each country receives the spontaneous ADR reports from health professionals, consumers and pharmaceutical companies. Afterwards, the ICSR are locally validated and evaluated, and a regulatory action can be potentially initiated, if needed. Finally, all the member countries are committed to disclose the on-time reports comprising complete post-marketing data into VigiBase, therefore enabling the uncovering of ADR-associated signs between different countries.

Until May 2019, VigiBase has held over 20 million of ICSR associated with medicines [16]. VigiBase collects the reports sent by the member countries of the WHO program, including 140 full member countries and 30 associate members [19]. The majority of the national joining centers have a straightforward electronic access to these standardized and structured reports, which contain a specific hierarchical code for the particular ADR registered, aiming to help in the fast identification of signals by any country member [5, 7]. The terminologies established for coding adverse reaction terms within the WHO programme, such as the WHO – Adverse Reaction Terminology (WHO-ART), afterwards replaced by the Medical Dictionary for Regulatory Activities (MedDRA), have been broadly embraced by national centers, manufacturers and medicinal product regulators [5, 7].

Spontaneous reporting systems are indispensable to post-marketing surveillance, and have shown to be effective in detecting various types of ADR, especially rare ones. Moreover, the ADR report method also evaluates the need to pursuit further investigations to check if exists an association with the medicine and can hence trigger alarm signals [20]. However, the search for complements to the existing pharmacovigilance systems has shown to be extremely important, mainly due to the significant delays encountered on the detection of more common types of ADR, in addition to the persisting high amount of unreported ADR [20].

3.2 European Medicines Agency

Globally, it is possible to find a selection of regulatory authorities whose main function is to regulate and support pharmacovigilance. For instance, while in the United States, the responsible structure is the Food and Drug Administration (FDA), in the EU is the EMA [21].

Briefly, EMA's gold mission relies on the promotion of scientific merit pertaining to medicine's evaluation and oversight, for the benefit of public and animal health in the EU. In compliance with the EU legislation requirements, EMA's main responsibilities are related to the:

1. supply and communication of independent science-based recommendations concerning the quality, safety and efficacy of medicinal products, especially when highly important to public health safeguard;

2. implementation of measures for continuous control of the quality, safety and efficacy of legalized drugs, namely by guaranteeing a positive benefit/risk ratio;

3. publication of unbiased and reliable information on medicinal products; and

4. development of good practices for drug assessment and regulation in Europe, together with the promotion of harmonized international regulatory standards [21, 22].

The legal pharmacovigilance framework for human medicines marketed within the EU/European Economic Area (EEA) is given in Regulation (EC) No 726/2004, with regard to the EU authorized medicinal products, and Directive 2001/83/EC, concerning the nationally authorized medicinal products, together with the Commission Implementing Regulation (EU) No 520/2012, which summarizes the practical aspects and obligations to be respected and followed by marketing authorization holders and regulatory authorities. Posteriorly, the Directive 2010/84/EC was introduced to substitute the previous directive, with minor amendments being performed in 2012. The EU law requires marketing authorization holders, national competent authorities and EMA to operate services and processes in line with EU legislation, aiming to support a quality assured EU regulatory pharmacovigilance system and to reduce the number of ADR in EU [21–23]. The EU pharmacovigilance system is one of the most sophisticated and comprehensive in the world and allows monitoring the safety of medicines on the European market through prevention, detection and assessment of adverse reactions to drugs, leading to an increased level of public health protection throughout the EU. This system operates through a robust and close collaboration between the competent regulatory authorities from the EU member states, EMA (system coordinator responsible for centrally authorized drugs) and the European Commission (competent authority for drugs centrally authorized in the EU), to rapidly manage and act against an emerging problem, unceasingly prioritizing a safer and more efficacious access of patients to medicinal products. The Pharmacovigilance Risk Assessment Committee (PRAC) was formed in response to this need in July 2012, thus being responsible to provide recommendations on all aspects related to human drugs risk management [21–23].

The European pharmacovigilance network not only successfully collaborates at the European level with high transparency, but also coordinates the necessary regulatory actions, hence producing efficient and accurate safety results able to be transmitted to the EU public in a timely manner. Some of the regulatory tools accessible after the implementation of the revised legislation involve risk management planning, signal detection and management at EU level, periodic safety update reports assessment, drug reviews through referrals post-authorization safety and efficacy studies, communication and training [23].

Within EU, the implementation of the different national pharmacovigilance systems occurred at distinct times. In 1963, The Netherlands became the first EU country to launch their own pharmacovigilance system for spontaneous ADR reporting, followed by the United Kingdom, in 1964, via the Yellow Card Scheme [24].

To achieve a consistent pharmacovigilance system, it is imperative that guidelines and standards are established as they clarify the practical details of the intended information flow, thus being very valuable, for instance, for health professionals training [5]. Thereby, the pharmacovigilance legislation in force in EU since

July 2012 led to the development of an important set of principles and measures on Good Pharmacovigilance Practices (GVP), to conduct the safety monitoring of medicines in EU [25]. One of the EMA's advisors on the development of these guidelines and standards on operational features of the EU pharmacovigilance is PRAC [22]. The GVP guidelines, covering medicinal products authorized in the EU either centrally via EMA or nationally, apply to EU marketing authorization holders, EMA and the competent authorities from each member state. The GVP can slightly differ between countries, thus being established by each country regulatory authorities. Moreover, the guidelines set is divided into two chapter types [25]:

I. major *Pharmacovigilance Processes* (with each module referring only to one distinct process); and

II. *Product- or Population-specific Considerations* (includes vaccines, biological medicinal products and the pediatric population).

Although EMA is known to support several pharmacovigilance databases, the network system used for collecting, managing and analyzing suspected ADR related to authorized medicines within EEA is EudraVigilance. This electronic reporting database system allows the early detection of potential safety signals of post-marketed drugs by effectively analyzing the spontaneous reports previously submitted by marketing authorization holders and member states [26].

The **Figure 1** below synthesizes the key features of pharmacovigilance for the global protection of the public health.

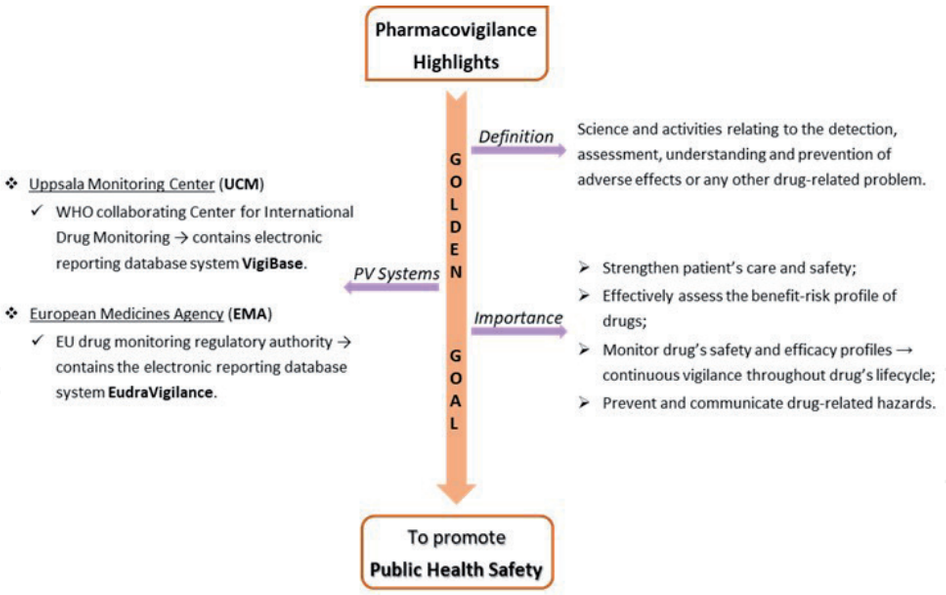

Figure 1.
Pharmacovigilance (PV) highlights in public health safety.

Appendices and nomenclature

ADR	Adverse Drug Reaction
CIOMS	Council for International Organizations of Medical Sciences
EEA	European Economic Area
EMA	European Medicines Agency
ESOP	European Society of Pharmacovigilance

EU	European Union
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practices
ICH	International Council for Harmonization
ICSR	Individual Case Safety Report
ISoP	International Society of Pharmacovigilance
MedDRA	Medical Dictionary for Regulatory Activities
PRAC	Pharmacovigilance Risk Assessment Committee
UCM	Uppsala Monitoring Center
VIGOR	Vioxx Gastrointestinal Outcomes Research
WHO	World Health Organization
WHO-ART	World Health Organization-Adverse Reaction Terminology

Author details

Maria Teresa Herdeiro[1*], Tânia Magalhães Silva[1], Inês Ribeiro-Vaz[2,3], Eva Rebelo Gomes[4], Adolfo Figueiras[5,6] and Fátima Roque[7,8]

1 iBiMED - Institute of Biomedicine, Department of Medical Sciences, University of Aveiro, Aveiro, Portugal

2 Porto Pharmacovigilance Center, Faculty of Medicine of University of Porto, Porto, Portugal

3 Center for Health Technology and Services Research (CINTESIS), Faculty of Medicine of University of Porto, Porto, Portugal

4 Allergy and Clinical Immunology Service, University Hospital Center of Porto, Porto, Portugal

5 Department of Preventive Medicine and Public Health, University of Santiago de Compostela, Consortium for Biomedical Research in Epidemiology and Public Health (CIBER en Epidemiología y Salud Pública - CIBERESP), Santiago de Compostela, Spain

6 Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain

7 Research Unit for Inland Development, Guarda Polytechnic Institute (UDI-IPG), Guarda, Portugal

8 Health Sciences Research Center, University of Beira Interior (CICS-UBI), Covilhã, Portugal

*Address all correspondence to: teresaherdeiro@ua.pt

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