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I Know What This Drug Did Last Summer: Pharmacovigilance as a Mechanism For Consumer Protection

Eu sei o que esse medicamento fez no verão passado: a farmacovigilância como um mecanismo de proteção ao consumidor

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ABSTRACT

Drugs are, by their own nature, especially risky products, in particular those that just reached the market and were developed in a short time, such as the COVID-19 vaccines. The potential hazards they can involve for patients/consumers require additional measures of consumer protection, in addition to the general legal framework of manufacturer's liability. This paper focused on one of these additional measures: pharmacovigilance, i.e., the post-commercialization monitoring of pharmaceutical products, from the perspective of European law. The aim of this paper was to demonstrate the role of pharmacovigilance in the prevention of harm caused by defective drugs and consequent consumer protection, highlighting its benefits and flaws. Pharmacovigilance is not a miraculous solution and has its flaws. However, it can be a useful tool for the management of benefit-risk to ensure appropriate drug use after marketing. Liability for defective products only addresses compensation for injuries that already occurred, while pharmacovigilance intervenes ex-ante to prevent the occurrence of some of those damages.

Keywords: Consumer Protection; Drugs; Pharmacovigilance; Prevention.

RESUMO

Os medicamentos são, por sua própria natureza, produtos especialmente arriscados, em especial aqueles que acabaram de chegar ao mercado e foram desenvolvidos em um curto espaço de tempo, como as vacinas contra a covid-19. Os possíveis riscos que esses produtos podem apresentar para os pacientes/consumidores exigem medidas adicionais de proteção ao consumidor, além da estrutura jurídica geral de responsabilidade do fabricante. Este artigo se concentrou em uma dessas medidas adicionais: a farmacovigilância, ou seja, o monitoramento pós-comercialização de produtos farmacêuticos, sob a perspectiva da legislação europeia. O objetivo deste estudo foi demonstrar o papel da farmacovigilância na prevenção de danos causados por medicamentos defeituosos e na consequente proteção do consumidor, destacando seus benefícios e falhas. A farmacovigilância não é uma solução milagrosa e tem suas falhas. Entretanto, pode ser uma ferramenta útil para o gerenciamento da relação risco-benefício a fim de garantir o uso adequado de medicamentos após a comercialização. A responsabilidade por produtos defeituosos trata apenas da indenização por danos já ocorridos, enquanto a farmacovigilância intervém *ex-ante* para evitar a ocorrência de alguns desses danos.

Palavras-chave: Proteção ao Consumidor; Medicamentos; Farmacovigilância; Prevenção.

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Introduction

This paper aims to demonstrate how pharmacovigilance - that is, the post-commercialization monitoring of pharmaceutical products – can operate as a mechanism of consumer protection against defective and potentially dangerous drugs. This demonstration will be conducted considering essentially European law (the law issued by the European Union (EU), with some references to the Brazilian legal regime. Note, however, that this paper does not intend to describe the mechanism of pharmacovigilance in place in Europe, but to demonstrate how pharmacovigilance can work as a mechanism of consumer protection.

The paper will start by analyzing the specificity of pharmaceutical products when compared with other products, namely their intrinsic possibility of leading to serious harm and the risk/benefit analysis. Drugs are products that can be especially beneficial to consumers, able to substantially improve their quality of life and even prevent death; however, they are also especially dangerous.

Subsequently, this paper will address the various mechanisms in place to protect patients - that is, consumers – from those intrinsic hazards, including the legal norms on defective products. There are no reliable reports/studies regarding the number of incidents involving defective drugs. One powerful reason might be the fact that many lawsuits involving pharmaceutical companies are solved by extrajudicial settlements, and some of them don't even make it to the courts (moreover, there is no obligation to publicly disclose them), as pharmaceutical companies have the financial power to pay and a firm willingness to avoid scandals and reputation damages (FAUS *et al.*, 2020).

This paper will then focus on pharmacovigilance as a potential tool to prevent harm and protect consumers/patients. This paper will explain what pharmacovigilance is and its goals to demonstrate its potential as a mechanism for consumer protection.

Lastly, this paper will highlight the shortcoming of pharmacovigilance in the fulfillment of this role to show how it can be a very useful tool but cannot operate alone.

I Specificities of pharmaceutical products

Drugs have several distinguishing features that differentiate them from other products. They are products closely linked to the satisfaction of a fundamental right, the right to health. However, and as a consequence of the previous distinguishing note, consumers (patients) do not have complete freedom of choice over what medicines to use or when to consume them, unlike with other products (RÄGO; SANTOSO, 2008). Furthermore, although drugs are primarily intended to treat and/or relieve pain, and even to save lives, they may be extremely dangerous for their users and ultimately lead to death (GREEN, 1999, p. 211). One of the main features of drugs is the paradox of risk versus value. No drug is absolutely innocuous, and any person can have an adverse drug reaction (ADR).

Due to their specific characteristics, drugs are strictly regulated products. No drug can be marketed without prior assessment and authorization by a competent authority, the so-called marketing authorization (MA). The entire existence of drugs is strictly regulated by law, starting with their creation and improvement (including clinical trials), manufacturing, marketing, payment and reimbursement, distribution, and advertising. This has turned the pharmaceutical industry into one of the most heavily regulated sectors. The only area in which legislative intervention has retreated is prescriptions. These have been left to the doctors by virtue of the principle referred to as the freedom of therapeutic prescription (GORDON, 2013; RICH, 1982).

To protect patient-consumers from the risks involved with pharmaceutical products, there is a very strict procedure for drug approval and a demanding regime regulating manufacturers' liability. Despite this, the approval procedure cannot be too complex, and the liability regime cannot be too severe. Otherwise, pharmaceutical companies may be discouraged from launching new products, and patients will not have access to new and innovative medicines. Either of these scenarios - patients/consumers lacking new medicines and patients/consumers unprotected from injuries caused by drugs - would threaten patient/consumer rights and seriously jeopardize public health.

II Protection from pharmaceutical products

As with any other injured consumer, patients harmed by pharmaceutical products can request compensation from the manufacturer (in this case, the pharmaceutical company) by filing a civil liability lawsuit. However, it is not always easy to build a successful case under the rules of liability for wrongful acts because culpability is difficult to prove in court.

To remedy this difficulty and recover damages caused to consumers, several jurisdictions have implemented a cause of action for strict liability. The EU has created a strict liability regime to improve consumer protection (RAPOSO; MORBEY, 2015), including for injuries caused by drugs. This regime is included in Council Directive 85/374/EEC of July 25, 1985 (EU, 1985). This regime of strict liability has led to mixed results: on the one hand, as with any other strict liability regime, it provides incentives for the manufacture and sale of safer products (GONZÁLEZ CASTILLO, 2012, p. 291); but on the other hand, "liability [the authors are referring to the regime of strict liability set forth in the Directive] has a negative effect on firm's willingness to develop new technologies" (KOVAC *et al*., 2021, p. 3). Moreover, the actual effects of this Directive on consumer protection are open to debate. It is argued that the demanding regime of strict liability encourages producers to adopt safer practices (GONZÁLEZ CASTILLO, 2012, p. 291), but it is also stated that "the EU directive not only failed to enforce the fundamental right of victims to get compensation, but it also decreased their chances to obtain damages in court as it replaced more favourable pre-existing liability regimes in most EU countries" (WHY..., 2019).

The Directive has remained in force all these years, but in September 2022, a draft proposal for its revision was presented by the European Commission (EU, 2022). The revised version (as released in September 2022) has several norms that might affect individuals harmed by defective medicinal products, such as the elimination of the thresholds for compensation and the manufacturers' duty to disclose relevant information for the claimants to prepare their claims.

Moreover, some member states have specific laws regarding defective drugs. Notably, this is the case in Germany under the Medicinal Products Act (Arzneimittelgesetz – AMG), whose division 16 deals with liability for damages caused by defective pharmaceutical products (ARZNEIMITTELGESETZ). In addition, the fault-based regimes for all types of defective products classically provided for in national laws still apply.

Consumers of pharmaceutical products are also patients. Thus, their protection can be accomplished through medical liability procedures whenever the injury is caused by an erroneous medical judgment of the drug to be prescribed or its dosage. Liability for medical procedures follows the ordinary regime of negligence (i.e., not strict liability). Thus, all elements of liability must be proven in court, even though some presumption of culpability may apply.

However, the manufacturer's liability and medical liability, and the compensation for injuries derived therefrom, are post-damage remedies. They only operate after an injury

has occurred, and as with any other form of liability, their main purpose is to compensate for that injury. Whether liability has a preventive effect can be debated (i.e., whether finding someone liable can lead to deterrence and prevent future injuries). I contend that deterrence is a side effect of tort liability (OWEN, 1985), and not its main effect. It is a collateral outcome not always achieved. Accordingly, its ability to avoid future harm is limited.

Beyond the injury caused to the plaintiff, litigation does not always address public health concerns. A drug can continue to harm other patients as long as it remains on the market, and it can remain there for many years because a condemnation (or several) does not necessarily lead to the drug being withdrawn. The removal of a drug from the market is a decision that must be made by the drug authority in charge or by the pharmaceutical company's voluntary withdrawal. However, the drug authority is not always aware of judicial proceedings, and the public may be even less aware. Pharmaceutical companies tend to conceal data revealed in court and keep legal procedures and the facts therein discussed secret, frequently hiding behind the excuse of industrial secrets or similar. Moreover, the manufacturer is unlikely to withdraw drugs when they are still earning huge profits unless the menace of future litigation becomes very real. For instance, Merck only opted to voluntarily take the drug Vioxx off the market when it was no longer possible to stifle the scandal surrounding its negative effects. By that time, 100 million prescriptions for Vioxx had been filled, leading to approximately 88,000 to 140,000 additional cases of serious coronary heart disease (ABBOTT, 2013, p. 243).

In the specific case of pharmaceutical products, there is a way to protect consumers beforehand: pharmacovigilance. This mechanism aims to prevent ADRs. It will not prevent all hazards, but it can certainly reduce their frequency and spare many patients from pain.

The COVID-19 pandemic caused by the new coronavirus SARS-CoV-2 exposed our generation to unthinkable risks. The world claimed for a vaccine, and soon after - too long for who was waiting but too soon in light of the regular process to develop and approve a new drug (RAPOSO, 2018) - several different vaccines were launched into the market (RAPOSO, 2021). The relationship between drug innovation and drug safety has always been turbulent (RAPOSO, 2020). Because these vaccines were developed in such a speedy manner and approved under particularly expedited approval procedures, the risks of adverse drug reactions might be higher than those in other drugs (EMA, 2020, p. 1). This conclusion is open to discussion, but even if not correct, it does undermine patient/consumer confidence. An effective pharmacovigilance mechanism may boost confidence and encourage vaccinations (RAPOSO, 2021).

III Pharmacovigilance

1 Definition of pharmacovigilance

Modern pharmacovigilance dates back to December 1961, when Dr William McBride published a letter in the prestigious medical journal *The Lancet*. In his letter, McBride revealed his suspicions about the connection between phocomelia and the drug thalidomide (MCBRIDE, 1961, p. 1358). This drug was prescribed to pregnant women to treat pregnancy sickness. However, when the babies began to be born with severe deformities, such as the absence of limbs (phocomelia), anxiety arose within the scientific community over the drug's safety.

Notwithstanding the thalidomide scandal, the term 'pharmacovigilance' only began to be used in the 1970s by a group of French pharmacologists (BÉGAUD; CHASLERIE; HARAMBURU, 1994). The first country in the world to have specific legislation in this

area was the US, under the Federal Food, Drug, and Cosmetic Act of 1938.[1] Nowadays, almost every jurisdiction imposes some type of pharmacovigilance.

Currently, the term pharmacovigilance refers to identifying, evaluating, understanding, and preventing ADRs. According to the WHO, pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem (WHO, 2015).

The EU has issued several norms in the domain of pharmacovigilance: Directive 2010/84/EU (EU, 2010a), Regulation (EU) n. 1235/2010 (EU, 2010b), Commission Implementing Regulation (EU) n. 520/2012 (EU, 2012a), Regulation (EU) n. 1027/2012 (EU, 2012c), and Directive 2012/26/EU (EU, 2012b). In Brazilian law, the most important documents are RDC n. 406/2020 on Good Pharmacovigilance Practices for Human Use Medicines Registration Holders (ANVISA, 2020b), and IN n. 63/2020 on the Periodic Benefit-Risk Assessment Report (RPBR) to be submitted to the Brazilian Health Regulatory Agency by Holders of Registration of Medicines for Human Use (ANVISA, 2020a).

2 The role of pharmacovigilance

Before any drug can be commercialized it is subjected to several years of research and development (R&D) and submitted to a long and demanding process of evaluation (APIFARMA, 2013). It all starts with the research phase, in which the drug is tested, first in cells and then in animals. Subsequently, during the development phase, the drug begins to be tested in humans in so-called clinical trials, composed of three phases (I, II and III). In the end, if the pharmaceutical company is satisfied with the results obtained in the various tests and clinical trials, it collects the results obtained during several years of R&D and presents them to the competent authority in charge of assessing new drugs. In Europe, the authority in charge is the European Medicines Agency (EMA). It evaluates whether the product is sufficiently safe and effective to be made available to consumers. If the assessment is positive, the drug obtains authorization to be commercialized the already referenced MA. Moreover, each member state has its own drug regulatory agency, all coordinated by EMA. In Brazil, the entity in charge is the Brazilian Health Regulatory Agency. Unlike EU member states, Brazil is not part of any international organization with supranational powers in the pharmaceutical domain (PEPE; HILLEGONDA, 2020).

Despite such strict regulations, not every risk can be prevented. The authority in charge of granting the MA performs a primary assessment and operates as a kind of gatekeeper, but still "[t]he gate is intrinsically porous, and safety cannot be achieved by fighting that fact but rather by responding to it" (EVANS, 2010).

The granting of the MA does not end clinical trials because phase IV of the clinical trials, also known as pharmacovigilance, takes place when the drug is already on the market. Even though clinical trials continue after commercialization (phase IV), usually the concept is used to designate pre-marketing clinical trials, whereas IV clinical trials are referred to as pharmacovigilance. Therefore, every time this paper uses the expression 'clinical trial' it should be understood to be a pre-marketing clinical trial.

Pharmacovigilance can take place at any moment in the drug life cycle, but usually the concept is restricted to post-marketing surveillance, i.e., post-marketing clinical trials. The purpose of this stage is to collect more information about the product, especially its application in regular clinical practice. At this stage, most ADRs are identified. This task obviously belongs to the producers, but it also belongs to other players in the health sector, particularly doctors and patients.

The purpose of pharmacovigilance is to collect information on the nature, severity, clinical characteristics, and outcomes of ADRs (MAZZITELLO *et al.*, 2013). These goals are achieved by examining and documenting all reported events and establishing a connection between those events and taking a given drug. Rather than working with structured data collected from controlled environments (clinical trials), pharmacovigilance uses data from real life.

Traditionally pharmacovigilance only dealt with serious and severe events, even though there was no consensus on the level of seriousness required. According to the guidelines provided by the US Food and Drug Administration, serious events are those that are fatal or at least life threatening, lead to hospitalisation (initial or prolonging), cause significant persistent disability, result in a congenital anomaly or birth defect, or are considered serious by the reporter (GUIDANCE..., 2002).

Pharmacovigilance also includes practical measures, such as implementing remedial actions to eliminate (or at least minimize) the hazards posed by ADRs and monitor the impact of those hazards. The outcomes of pharmacovigilance may lead to changes in a product's label or to modifying the original assessment of the risks/benefits that led to the granting of the MA. It may lead to the MA's modification, suspension, or even revocation, thereby forcing the product to withdraw from the market (MCNAUGHTON; HUET; SHAKIR, 2014).

Considering the current pandemic, the need for strict control of newly released vaccines is particularly pressing. The EU has created its own pharmacovigilance plan, the so-called ACCESS project ('vACCine COVID-19 monitoring readinESS, which "focuses on data sources and epidemiological methods to monitor the safety, effectiveness and coverage of COVID-19 vaccines" (EMA, 2020, p. 4; VAC4EU, 2020). Moreover, special task forces were created – first, the COVID-19 EMA Pandemic Task Force; and subsequently the Emergency Task Force (ETF) (EMA) – to assist EMA in its regulatory tasks (EMA's…, 2020; FERREIRA-DA-SILVA *et al.*, 2021). Transparency is essential. On the EMA website, information can be found regarding the number of COVID-19 vaccine doses administered and the number of suspected side effects reported.

3 Definition of an adverse drug reaction

The traditional definition of ADR (SCHATZ; WEBER, 2015, p. 7) is that provided by the World Health Organization: any harm caused by using one or more medicinal products for therapeutic purposes. This includes "a response to a drug that is noxious and unintended and occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function" (WHO, 1972). In other words, "[a]n appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazards from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (EDWARDS; ARONSON, 2000, p. 1255).

The definition of ADR currently relied on in European law - introduced by Directive 2010/84/EU (EU, 2010a) is very broad (KLIKA; KAEDING; SCHMÄLTER, 2017): "A response to a medicinal product which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function" (article 1(11) of Directive 2001/83/EC, as revised by Directive 2010/84/EU) (EU, 2010a). It refers to any harmful and unintended reaction to a medicinal product. Therefore, it covers both the negative consequences resulting from the use of authorized products in accordance with their label and the consequences resulting from unauthorized use (off-label drug use), overdoses and other medication errors (BALDO; FRANCESCON: FORNASIER, 2018, p. 750-752).

ADRs are a major public health concern. They are estimated to account for 5% of hospitalizations within the EU, are the fifth-leading cause of death in hospitals (EPF, 2012), and it is predicted that between 10% and 20% of inpatients will have at least one ADR during their hospitalization (SCHATZ; WEBER, 2015, p. 5). These outcomes have resulted in 197,000 deaths per year (BENNETT *et al.*, 2007) in a cost of approximately 79 billion Euros (ARNARDOTTIR *et al.*, 2011).

IV Why do we need pharmacovigilance?

1 Clinical trial flaws

Pharmacovigilance serves two main purposes. First, it allows data to be collected on the safety and quality of pharmaceutical products. Thereafter, it serves as a base upon which to design risk management plans and provide data to physicians, other health care professionals, and pharmacists on ADRs caused by drugs (SAHU *et al.*, 2014). These goals cannot be achieved through clinical trials. Regardless of how thorough they are, controlled studies cannot identify all the risks associated with drugs. Often, these can only be detected after years on the market (LASSER *et al.*, 2002).

Several factors explain the inability of clinical trials and the entire R&D process to detect all ADRs (ARNARDOTTIR *et al.*, 2011; MAZZITELLO *et al.*, 2013; RAPOSO, 2018; RODWIN, 2013). First, animal test results, which are the first stage of clinical trials, are not fully transposable to humans. That is, what is valid for a rat is not necessarily valid for a person. Even in trials with humans, the results are always limited and insufficient because they cannot be assimilated into real-life clinical practice. Trial participants are carefully chosen and do not necessarily reflect the effective population to which the drug will be administered. For example, clinical trials are rarely conducted with at-risk populations, such as pregnant women, the elderly, or children. This means that there are virtually no authorized drugs for these vulnerable populations (MANN, 2015, p. 377). Nonetheless, most drugs are used on these types of patients (under the so-called off-label prescriptions) (LOUGHLIN; GENERALI, 2006; MCINTYRE *et al.*, 2000; RAPOSO, 2014) without being subjected to studies that scientifically support such use. Often, the consequences of such uses are unknown, and some may be potentially disastrous.

Another group excluded from clinical trials are polymedicated patients; therefore, there are not enough information available on the possible drug interactions that could occur.

Likewise excluded are those who present with severe medical conditions, meaning that the participants in clinical trials are not as sick as the patients who will effectively take the drug. Therefore, we do not know how the drug will react in extremely ill patients (EVANS, 2010, p. 448-449). If a pharmaceutical company knows in advance (from the results obtained in pre-clinical trials) that a certain group of patients (for instance, people with heart problems or obesity) will most likely suffer from an ADR, it can simply exclude those patients from the trials to prevent possible ADRs from being exposed (BARD, 2013, p. 514-515).

Even in clinical trials involving many participants, it is difficult to detect rare ADRs. For example, suppose a study has 5,000 participants; it will certainly be possible to detect ADRs likely to happen to 1 in 100 people, but it will be almost impossible to detect ADRs that happen to 1 in 5,000 people (STROM, 2006).

Clinical trials are also temporally limited and therefore do not detect ADRs that are identifiable only in long-term treatments. For instance, cancer is a severe adverse event caused by some drugs, but it can frequently be detected only after prolonged exposure to the drug. Accordingly, it is unlikely to manifest during clinical trials. Because the

pharmaceutical company establishes the length of the trial, it is not difficult to set a duration long enough to demonstrate the drug's efficacy, but not so long that ADRs might appear (BARD, 2013, p. 504-505). The question becomes even more complicated because some medical conditions (e.g., depression, diabetes and other chronic diseases) require a drug to be taken for many years or even for life. This is a time frame that favours the exposure of ADRs, but clinical trials are unable to replicate this. Consequently, ADRs are less likely to be found during clinical trials than after commercialization when the drugs are taken by real patients.

Further, clinical trials monitor drugs that are taken under optimal conditions, omitting cases of abuse, misuse, or forgetting to take them. However, these situations occur very frequently among patients in everyday life. Clinical trials are aimed more at controlling the efficacy of drugs rather than their safety. Thus, they rarely provide information on ADRs or the toxicity of medicinal products (CAMPOS; ORDIOZOLA, 2018).

Pharmacovigilance can identify drugs' safety issues that only become evident during commercialization not in clinical trials. These include contamination, abnormal odour or taste, product packaging problems (broken seals, leaking bottles), labeling flaws (missing labels, missing expiry dates), and even counterfeit products.

The ADR occurrence rate is not uniform among countries because each country is conditioned by several factors, including its predominant pathologies, genetics of the national human group, current diet, the medications available and how they are usually prescribed in clinical practice (dosage/posology), and the interconnection of drugs typical of Western medicine and traditional medicinal products, among others. Therefore, the results obtained in a clinical trial in one country may not be transposable to another (MAZZITELLO *et al.*, 2013, S20). Only pharmacovigilance, as a post-marketing control over products, allows the tracking of ADRs likely to occur in a specific geographical area or human group.

In conclusion, regardless of how comprehensive clinical trials are, serious ADRs have been detected in approximately 10% of the drugs commercialized in Europe and the US (MAZZITELLO *et al.*, 2013, p. 491). Some high-profile cases involving pharmaceutical products in the EU show the failure of clinical trials. Some examples: Agreal was withdrawn from European markets after the EMA recommended the revocation of the Marketing Authorization of all productions containing veralipride (EUROPEAN..., 2007); Vioxx, a nonsteroidal anti-inflammatory drug, was withdrawn from the market after the discovery that it quadrupled the risk of heart attack or stroke (MEYER, 2020, p. 20-22); the antiseptic Bohmclorh was also withdrawn because a dangerous bacterium (*Serratia Marcenscens*) was found in its composition (GONZÁLEZ SANCHIDRIÁN; MARÍN ÁLVAREZ; DEIRA LORENZO, 2018). Eventually, some cases reached the Court of Justice of the European Union, such as one involving a vaccine against hepatitis B produced by Sanofi Pasteur[2]. In conclusion, many of these products were involved in court cases, but ultimately it was pharmacovigilance that led to their withdrawal. These events demonstrated that many ADRs cannot be detected by clinical trials.

To address this problem, the answer is not to make the already complex and time-consuming process of obtaining the MA even more demanding, but to invest in post-marketing monitoring, that is, in pharmacovigilance. Therefore, the solution is not to aggravate pre-marketing procedures but to invest more in what happens once the product is in the marketplace (RAPOSO, 2018, p. 33).

2 Compliance with the duty to inform

An additional reason justifying the need for pharmacovigilance relates to the producer's duty to inform (RAPOSO, 2018; UEFFING, 2013, p. 373). A producer can be liable for failing to provide information to consumers on the aspects of drugs that are relevant

to their safety, such as the mode of taking the product, precautions, contraindications, and risks.

Regarding risks, it is now common knowledge that risks discovered after a product is launched on the market must also be communicated to the consumer. Sometimes this requires updating the product leaflet. For instance, in the US several drugs can receive a black box warning (that is, the sign that appears on the label of a prescription medication to alert consumers and healthcare providers about safety concerns) several years after being on the market (CHEN; YANG, 2013).

Not only are manufacturers required to inform about the risks they become aware of, but they are also required to actively look for them. This implies constant vigilance by the pharmaceutical company. Pharmacovigilance is the proper mechanism through which to exercise that vigilance.

3 Pharmacovigilance as a mechanism of consumer protection

Pharmacovigilance essentially aims to identify new ADRs, deepen the existing information on previously identified ADRs, compare the benefits of a medicinal product with other medicines, and disseminate the conclusions obtained to improve clinical practice. Therefore, it is an important consumer protection mechanism.

It is especially important to address safety issues as soon as possible so that effective preventive measures can be taken against them. For example, physicians could be notified and/or the risks could be displayed on the drug label. When doctors and patients are duly informed of risks, they can take necessary measures to prevent serious consequences. For instance, patients can seek medical assistance as soon as the first negative symptoms appear, and doctors can start their treatments earlier. In summary, pharmacovigilance identifies hazards that can eventually be prevented.

Pharmacovigilance also has the potential to force the withdrawal of dangerous products from the market. For a product to be allowed into the market, the risk/benefit analysis carried out by the competent authority must necessarily conclude that the benefits exceed the risks, and thus the drug shall be made available to consumers. However, that initial assessment can be subsequently modified based on data collected during pharmacovigilance, demonstrating that the risks have overcome the benefits. Having said that, drug withdrawal must be decided thoughtfully. The perils associated with drugs are not always sufficiently relevant to remove them from the market, and withdrawing the drug could deprive patients in need of its benefits. Accordingly, withdrawal must be a last resort (RAPOSO, 2018, p. 44).

V Problems faced by pharmacovigilance as a mechanism to protect consumers

The final aim of pharmacovigilance is to create a post-marketing surveillance system that allows as much data as possible to be analysed and subsequently sent to an entity capable of compiling and organizing them. Once this is done, the rough data can be transformed into useful knowledge to be considered in regulatory policies. However, this aim faces several doubts and difficulties.

1 The most suitable person/entity to report

The duty to report adverse events falls on several healthcare players.

First, it falls on the producer. To minimize the risks associated with their products, pharmaceutical companies begin to plan their pharmacovigilance activities long before

the products reach the market. For instance, under European law, together with the MA request, companies must present a so-called risk management plan (EMA, 2017), which requires some preparation regarding post-marketing vigilance (SANTORO *et al.*, 2017, p. 859). In Europe, mandatory risk minimization measures are routine and apply to all medicines. However, there can be additional risk minimization measures that are only applicable to certain medicines. These additional measures may include active communications with healthcare professionals (known as 'Dear Doctor' letters) or non-interventional post-authorisation safety studies (PASS) (WOODER; HUCKLE, 2016). Traditionally, the reporting of ADRs was purely voluntary (so-called passive surveillance). However, the low reporting rate became a concern and is now mandatory under some circumstances. As for November 2017, when the new EudraVigilance (EV) systems were launched (WHAT'S..., 2017), both the holders of a Marketing Authorization and the national competent drug authorities have the duty to report non-serious ADRs, including on behalf of patients unable to report directly (CANDORE *et al.*, 2022).

In a sense, pharmaceutical companies are in a privileged position to prepare good reports on ADRs. As manufacturers, they have profound knowledge of the drug and vast resources with which to perform surveillance activities. However, any investigation carried out by pharmaceutical companies faces several limitations because of their direct interest in the outcome of surveillance. Eager to maintain their profits, they must guarantee that sales do not decrease. Thus, they may be biased regarding the results reported

Some years ago, the pharmaceutical company GlaxoSmithKline agreed to plead guilty and pay US$3 billion to resolve criminal and civil complaints alleging that the company failed to provide relevant safety data. According to a note from the Deputy Attorney General, James M. Cole,

> Today, I am pleased to announce that the Justice Department and our law enforcement partners have reached an historic $3 billion resolution with the pharmaceutical manufacturer GlaxoSmithKline, LLC, to resolve multiple investigations into the company's sales, marketing, and pricing practices. This action constitutes the largest health care fraud settlement in United States history. It underscores our robust commitment to protecting the American people from the scourge of health care fraud, and it proves the effectiveness of the strong relationships we've forged with our partners to help ensure the health and safety of the American people, and to safeguard the integrity of our health care system (GLAXOSMITHKLINE..., 2012).

Patients and their families can also report (MATOS; HUNSEL; JOAQUIM, 2015, p. 883), even though their notification remains voluntary. Although useful, their reports can also be misleading and unclear because of their lack of pharmaceutical knowledge. Furthermore, they may describe the incident surrounding the ADR using imprecise concepts.

Those who use drugs in their profession, such as doctors, nurses, hospitals, and pharmacists, are also bound by the duty to report ADRs. Therefore, many hospitals have implemented their own internal reporting mechanisms.

Doctors tend to present the most accurate and complete reports (MANN, 2015, p. 384-386). After all, they are enlightened reporters. They have specific knowledge that the average patient (or the patient's relatives) does not have. Surely, the same kind of expertise is shared by pharmaceutical companies and pharmacists. However, doctors have another advantage over them: knowledge about the patient's history and current condition and knowledge about other drugs being taken by them. This privileged position enables knowledgeable doctors to distinguish a real ADR from normal reactions associated with a given product and from symptoms related to the patient's underlying

disease (MANN, 2015, p. 385). These considerations explain why the reporting of ADRs is viewed as the physician's role (AMA) and some advocate that, in their case, it should become mandatory (MANN, 2015, p. 389-390).

2 The low number of reports

Despite efforts to increase ADR reporting over the last couple of years, the number of reports has remained low. Obviously, pharmaceutical companies have little incentive to report. They spend billions on a drug's development and approval process, and it is only natural that they might omit data that could potentially jeopardize their investment return. The position of pharmaceutical companies could eventually change if they realized how pharmacovigilance could become an efficient measure to protect them from litigation and severe economic losses, including drastic crash sales, compensation paid in court, and economic penalties.

Pharmaceutical companies have been so focused on maintaining their image and profits that there have been reports of retaliation against employers, prescribing physicians, and other whistleblowers (BARD, 2013, p. 500), which could also account for the low number of reports.

Patients do not usually report. The situation might be different if they were informed whenever they use a new product (information they do not always have), because being aware that the drug is new would make them more likely to be alert. Therefore, it has been suggested that pharmaceutical companies should be required to inform patients of new drugs (BARD, 2013, p. 501), however, it has been unclear how the information would be provided.

Faced with a low level of ARD reporting, some measures have been suggested. One possible option could be a mandatory mechanism for post-marketing surveillance of all newly approved drugs (BARD, 2013, p. 500). The cost could be paid by the pharmaceutical companies because they earn huge profits from selling the drugs (BARD, 2013, p. 500). Another useful mechanism would be to collect more data using all the information gathered in electronic health records (EHR) (MANN, 2015, p. 390-391). By their very nature, EHRs allow for the collection of huge amounts of data. If properly designed, the system could permit the selection of data considered relevant to pharmacovigilance. This solution could lead to the creation of huge databases, allowing a fast and easy correlation between the data and prediction of ADRs (SHARRAR; DIECK, 2013).

3 Privacy issues

The idea of creating databases for pharmacological purposes is not totally new. There are four main databases worldwide: VigiBase™, from the World Health Organization for International Drug Monitoring; the Adverse Event Reporting System (AERS) and the Vaccine Adverse Event Reporting System (VAERS), both from the FDA; and EudraVigilance, from the EMA. EudraVigilance is the European database that electronically reports suspected side effects, both from the pre-authorization and post-authorization phases (EUDRAVIGILANCE). It receives spontaneous reports from healthcare providers, patients, and their families, noninterventional postauthorisation studies, and even scientific publications (SCIENCE PHARMA, 2022).

Databases collect data from several different sources: information gathered during clinical trials, reports from consumers, health care providers and manufacturers, and notices from the medical literature (SHARRAR; DIECK, 2013, p. 212)[3] (EHRs are still not widely used to create such databases).

These types of databases always raise privacy concerns (ABBOTT, 2013, p. 254) because the information gathered (health and genetic data) is especially private and very sensitive. However, even though these risks cannot be annulled, they can be minimized by data anonymisation.

4 Misleading adverse events and misleading data

Despite its many virtues, several flaws may render pharmacovigilance misleading (SHARRAR; DIECK, 2013, p. 212). Currently, it is not yet possible to calculate the ADR incidents with precision and reach trustful conclusions, much less predict future events. This deficiency is related to the high rate of under-reporting and lack of important data, such as the total number of patients taking a given drug.

One main problem has been the lack of a clear definition of ADR. The concept may be understood in different terms by the various players in charge of reporting, leading to a heterogeneous list of events. Furthermore, each reporter uses its own terminology when reporting, which means that the descriptions of the facts and the qualifications of the events vary considerably. Reports may be especially misleading when done by a layperson.

In addition, some of the incidents apparently caused by a drug may not be related to it, so it is necessary to investigate the real causes of each incident. This problem is particularly stringent when patients are using several drugs because it is difficult to accurately identify the product that caused the damage.

Concluding remarks

Pharmacovigilance is indispensable to fill the gaps left by pre-marketing assessments. In a perfect world, every drug would undergo extensive research prior to its approval, in such a way that pre-marketing studies and clinical trials would detect every single ADR. However, such a complete pre-marketing phase would be too expensive to carry out, and it would take too long before patients could access new products. Even if clinical trials were perfect, not all ADRs could be detected. Only post-marketing surveillance allows some of the perils of pharmaceutical products to be tracked. Although it is not perfect - the reporting rate remains too low, some of the reports are incomplete or unclear, and pharmaceutical companies still hide prejudicial data - pharmacovigilance can still detect several ADRs.

Compared with compensation mechanisms, pharmacovigilance has undeniable benefits because it is the most efficient tool for protecting consumers. It operates beforehand, avoiding injuries and not simply compensating for their consequences.

In a health crisis of this magnitude, many drugs (vaccines and other types of drugs) reach the market, sometimes because of the extremely compressed procedure of development of approval. This is not, de per se, an indicator that the product might be unsafe (RAPOSO, 2021); however, we must focus on the follow-up of their performance in the real world, with real patients. Drugs can save lives, and pharmacovigilance can help them pursue that aim.

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Notas

1 Pub. L. No. 75-717, 52 Stat. 1040 (1938).

2 Judgement of 21 June 2017, W and Others, C-621/15, ECLI:EU:C:2017:484.

3 Other possible sources of data can be social networks (MUJALLID; ALGHAMDI, 2018); forums and blogs, because quite often patients share there their experiences with drugs in internet (LENGSAVATH, 2017). However, right now we still lack reliability with those data. Furthermore, privacy in social media and similar venues has become a particularly pressing concern.