Pharmacovigilance

2

In this chapter, the fundamentals of pharmacovigilance are outlined with a particular emphasis on the role of healthcare professionals in reporting adverse drug reactions (ADRs). It also explains why pharmacovigilance is specifically important regarding biological medicinal products (biologicals).

2.1 Fundamentals of Pharmacovigilance

Before medicinal products are marketed, they undergo extensive risk assessment, including clinical trials. After marketing authorisation, drugs are prescribed to larger populations in medical environments that are less controlled than clinical trials. Hence, medicines might produce ADRs during normal therapeutic use, despite risk assessment during marketing authorisation (Belton and the European Pharmacovigilance Research Group 1997).

It is estimated that ADRs account for five percent of all hospital admissions and cause around 200,000 deaths per year in the European Union (EU) (European Commission 2008). Based on the estimation by the European Commission (Commission), the total cost of ADRs amounts to roughly €80 billion.

Hence, product safety is a substantive public concern and essential for public health. Patients might be harmed not only by a drug itself, but also due to the combined interaction of more than one prescribed drug. In order to prevent harm, the surveillance of medicinal products is vital and pharmacovigilance has become an important aspect of public health legislation (Johnson and Hutchinson 2015).

The World Health Organisation (WHO) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem" (WHO 2004).

Pharmacovigilance pursues the following four general objectives (WHO 2004):

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- "To improve patient care and safety in relation to the use of medicines, and all medical and paramedical interventions;
- to improve public health and safety in relation to the use of medicines;
- to contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use;
- to promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public".

In order to detect and assess ADRs, pharmacovigilance is based on the collection of information about the therapeutic use of medicines after marketing authorisation; most pharmacovigilance systems rely on the spontaneous reporting of adverse effects (Pal et al. 2013). The most important source of ADR information is collected through individual case safety reports (ICSRs).

The importance of pharmacovigilance for public health legislation is illustrated by the expansion of the Programme for International Drug Monitoring by the WHO. This programme began in 1968 with 10 partner countries and has continued to expand; more than 100 countries have joined the programme as of 2016. The WHO maintains a global database including information about which countries have submitted over 10 million ICSRs chronicling adverse reactions.

The Role of Healthcare Professionals

So that pharmacovigilance can be effective, all suspected ADRs must be reported in an accurate and timely manner (Alvarez-Requejo et al. 1998). In general, pharmacovigilance requires the close collaboration of various actors, such as politicians, policy officials, health administrators, the pharmaceutical industry, healthcare professionals and increasingly the general public. However, healthcare professionals have a key role in pharmacovigilance and ADR reporting in particular.

According to the WHO, healthcare professionals "maintain health in humans through the application of the principles and procedures of evidence-based medicine and caring" (WHO Education Guidelines 2016). In line with the WHO's definition, we are including the following groups under the general heading of healthcare professionals:

- Medical doctors (including general and specialised practitioners)
- Nursing professionals
- Midwifery professionals
- Dentists
- Pharmacists

However, these groups include further sub-groups and some variation also exists in the national terminology, which is reflected in the respective country chapters (see Chapter 5); healthcare professionals can be referred to as doctors, physicians, clinicians and practitioners. These terms are often country-specific and reflect the national variety of healthcare systems.

Causality Assessment and Signal Detection

With the increase of ADR reporting, establishing a causal relationship between the administration of a drug and adverse effects has become more challenging (Naidu 2013). Whereas causality assessments used to rely solely on expert judgment, automatic data processing through algorithms has become more important for determining the likelihood of a causal link. Thus, establishing a causal link between the prescription of a drug and observed effects is far from straightforward.

Causality assessment describes the systematic appraisal of reported adverse reactions in an attempt to establish a causal link between a prescribed drug and the adverse reaction.

A signal is defined as reported information about a possible causal link between a drug and the adverse effect, and signal detection is an essential element of pharmacovigilance with the goal of identifying unexpected ADRs and to inform authorities about possible regulatory actions that should be taken (Inácio et al. 2015; Kumar and Khan 2015). In order to create signals, however, more than one ICSR is needed, and the strength of the signal depends on the quantity and quality of the information. In order to detect signals, pharmacovigilance relies on databases and statistical methods to collect information with a view to establish causality between a drug and adverse reactions.

2.2 Importance of Pharmacovigilance for Biologicals

Due to the use of living cells, biologicals pose a specific challenge to pharmacovigilance. Accurate reporting of ADRs regarding the use of biologicals is especially challenging because of the restrictions in clinical trials, sensitivity to changes in the manufacturing process, the reporting of batch numbers and the establishment of valid causality assessments.

First, biologicals have distinctive features that can cause ADRs and might not be detectable in conventional clinical trials (Calvo and Zuňiga 2014). For biologicals, data from clinical trials are quite limited due to various factors, including their sample size and duration. Conditions during clinical trials differ significantly from

conditions encountered under normal clinical practices. Moreover, biologicals are often prescribed only for rare diseases. In these cases, it is difficult to include a sufficient number of patients or special patient groups (such as children, the elderly or pregnant women) and to examine drug interaction in the clinical trials preceding authorisation (Giezen and Straus 2012).

Hence, it is unlikely that every risk can be identified before the drug receives market authorisation and can be administered to a large group of patients. Accordingly, it is crucial that regulatory action does not end after market approval but that the benefit-risk assessment remains an ongoing activity, ideally spanning a drug's full life cycle (Eichler et al. 2008). However, this is only possible when any adverse reaction or event of a biological is accurately reported to the competent authorities and can be traced back to the respective manufacturer.

Second, biologicals differ from small-molecule medicines in their highly complex structures and sensitivity to changes (Klein et al. 2016). Biologicals are developed in long and complex production processes involving different manufacturers and even minor changes in any step of the manufacturing process can affect the product quality and safety, e.g. through alterations of the molecular structure or non-adherence to quality standards. Potential changes in product quality and the safety profile can affect not only different products containing the same active substance, but also batches within the same medicinal product (batch-to-batch). Thus, changes, intended or unintended, could result in previously unobserved, severe ADRs, with unpredictable consequences for the consumer (Klein et al. 2016).

Third, because ADRs of biologicals can be batch-specific, it is crucial that not only the brand name, but also the batch number is accurately reported to ensure the correct and timely identification and facilitate the traceability up to the batch level (Vermeer et al. 2013). Recent studies have shown that brand-name identification is well established but that batch numbers are (still) under-reported (Klein et al. 2016).

Fourth, a drug can only be withdrawn from the market for safety reasons when a valid causality assessment is established. Yet to define this period – or the at-risk window – is especially challenging when it comes to biologicals (Giezen and Straus 2012; Arnaiz et al. 2001). Thus, calculating the risk-benefit balance and therefore deciding to withdraw a certain drug from the market is only possible with sufficiently valid data through accurate ADR reporting.

In order to ensure the correct and timely attribution of adverse events to the correct product and batch, the availability of information, such as the international non-proprietary name, the brand name, the company's name and the batch number, is necessary (Calvo and Zuňiga 2013:18).

For these reasons, timely and accurate reporting of ADRs is particularly important when it comes to the use of biologicals. Under-reporting reduces sensitivity because

it underestimates the frequency and thus the impact of the problem and makes the system more vulnerable to selective reporting which may introduce a serious bias (Alvarez-Requejo et al. 1998). Adequate availability of exposure information is necessary to timely link an emerging product safety issue to the correct product and batch (Klein et al. 2016). Even though the level of evidence of case reports is often poor, spontaneous reports contribute to the majority of safety withdrawals. And when there are no doubts about the causal relationship between an adverse event and a drug, spontaneous reports may be the sole source for regulatory action (Ebbers et al. 2011).

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