Chapter 2

Pharmacovigilance

2.1 INTRODUCTION

Pharmacovigilance refers to the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects and other drug-related safety problems. Related to this general definition, the underlying objectives of pharmacovigilance are to prevent harm from adverse reactions in humans that arise from the use of health products within or outside the terms of marketing authorization and in relation to the life cycle of these health products.

The main goal of pharmacovigilance is thus to promote the safe and effective use of health products, in particular by providing timely information about the safety of health products to patients, health-care professionals, and the public. Pharmacovigilance is therefore an activity contributing to the protection of patients and maintaining public health.

Many other issues are also of relevance to pharmacovigilance-related activities and include medication errors, lack of efficacy reports, off-label use, acute and chronic poisoning, assessment of drug-related mortality, abuse and misuse of health products, and adverse interactions of medicines with chemicals and other drugs (see Annex 1).

The pharmacovigilance approach can be clinical, epidemiological, experimental (e.g., to reproduce an adverse effect in animals to better understand the mechanism involved for human protection), or diagnostic (e.g., imputable methods).

The ultimate goal of pharmacovigilance is to accurately characterize and optimize the benefit/risk ratio of a health product throughout its life cycle.

2.2 OBJECTIVES OF PHARMACOVIGILANCE

Once available on the market, a drug leaves the scientific and restrictive environment of clinical trials and becomes legally available for consumption by the general public.

At the stage of clinical trials, however, most of the drugs have been assessed for both efficacy and safety for only a relatively short period of time and only on a relatively limited number of carefully selected patients (see also

Pharmacoepidemiology and Pharmacovigilance. https://doi.org/10.1016/B978-0-12-816183-8.00002-0

the short glossary in Annex 2 Annex that discusses the phases of development of a new drug and the selection of participants for each of these phases).

After being exposed to the monitoring recommended in clinical trials, it is therefore essential that new drugs are subject to a control of efficacy and safety in real conditions of use, i.e., after their authorization for marketing. Historical tragedies such as those mentioned earlier in the introductory chapter of this book remind us of the importance of these pharmacovigilance activities.

According to the World Health Organization (WHO) (2004), Eurasanté (2006), the Framework of Vigilance of Health Products (2012), and Dugair (2009), the main objectives of pharmacovigilance programs are (1) to improve the care and safety of patients and the general public; (2) to contribute to the assessment of the effectiveness and risks presented by health products and to encourage a safe, rational, and more effective use of these products (including on the economic point of view); and (3) to promote better education and training in this field to improve the effectiveness of communication between health-care professionals, patients, and the general public.[1–4]

2.3 PRODUCT LIFE CYCLE

According to what is presented in Fig. 1.1 of Chapter 1, a product's life cycle refers to a set of regulatory, administrative, and monitoring activities, which, at first view, may appear cumbersome and bureaucratic, but the concept is of major importance in the prevention of adverse drug reactions and in the maintenance of a positive benefit/risk ratio of a health product during its entire life.

Because this life cycle refers to all stages preceding and following the marketing of a health product, it includes the following steps:

(i) the discovery of the product;
(ii) the preclinical studies;
(iii) the clinical trials;
(iv) the presentation of product information by the manufacturer to the regulatory agency for its evaluation and approval;
(v) the decision whether to allow the sale of the product;
(vi) the distribution and sale of the product;
(vii) the monitoring, inspection, and postmarketing investigations.

The ultimate goal is to ensure that patients have access to efficient and safe health products not only as participants during clinical trials but also in real life following the marketing authorization of these health products (see Fig. 1.1 of Chapter 1).[5,6] Fig. 1.1 of Chapter 1 shows the regulatory agencies monitoring activities as a variety of regulatory activities divided into a continuum. Thus, these activities can integrate and use information that continues

to develop throughout the life cycle of a health product. The most relevant regulations surrounding the product life cycle are presented in one of the appendices at the end of this book.

To have a concrete picture of the product life cycle please also consult the case reports presented in Chapter 4.

2.4 PREVENTION TOOLS FOR PASSIVE AND ACTIVE SURVEILLANCE

The purpose of this section is to give a brief overview of some of the main pharmacovigilance tools for passive and active surveillance of adverse effects associated with drugs (see Chapter 4 for concrete examples on active and passive surveillance of adverse drug reactions).

Passive surveillance (pharmacovigilance) is mainly composed of spontaneous reports of adverse drug reactions, case series, and annual safety reports, whereas active surveillance (pharmacovigilance) is mainly composed of patient registries and pharmacoepidemiologic studies (pharmacoepidemiologic studies will be explained in greater detail in Chapter 3). Of note, we should not neglect passive surveillance as it is an excellent way to generate hypotheses for pharmacoepidemiologic studies.

2.5 PASSIVE SURVEILLANCE (PHARMACOVIGILANCE)

2.5.1 Spontaneous Reporting of Adverse Drug Reactions

A spontaneous report is an unsolicited communication from health-care professionals or consumers to a manufacturer, or a regulatory authority such as Health Canada, or other organizations such as the WHO, the Food and Drug Administration (FDA), the European Medical Agency (EMA), the regional centers, the poison centers, and others that describe one or more adverse reactions in a patient who was given one or more health products but is not part of a clinical study or any organized data collection system.

These spontaneous reports play a major role in the identification of postmarketing safety signals.[7] In many cases, a manufacturer or a regulatory agency can be alerted of rare adverse drug effects that were not detected during clinical trials or other studies in preauthorization phase. They may also contain important information on risk groups, risk factors, and the clinical characteristics of known serious adverse reactions. See Chapter 4 for other information on the role and use of spontaneous reporting (pharmacovigilance) in the identification of new safety signals. For more information on those terms, please also consult the glossary of pharmacovigilance terms in Annex 1.

According to Wise et al.,[8] reports of adverse reactions that occur when a health product is used in clinical practice form the basis of most drug-prevention systems and regulators use these databases to store and analyze

reports of adverse events with the purpose of eventually doing a causality assessment of specific adverse drug reactions. For a definition of causality assessment, please consult the glossary of terms in Annex 2.

For example, the Medicines and Healthcare Products Regulatory Agency (MHRA) in United Kingdom operates a system of yellow cards for health-care professionals and patients to report adverse drug reactions and these reports are collected in the database of the MHRA.

The FDA runs a similar system in which reports of adverse events associated with drugs are stored in the AERS or the VAERS databases for reports of adverse events associated with vaccines.

Health Canada runs the Canada Vigilance database in which reports of adverse events associated with health products are stored. For your information, these systems are essentially considered passive systems. For more information and concrete examples on the usefulness of these databases, please see Chapter 4.

In other words, patients are not selected to participate in a specific database and reports are not actively solicited. These systems have the benefits of being able to be used throughout the health product life cycle.

They can be used to generate safety signals or to identify rare adverse effects associated with health products. Unfortunately, these databases cannot eliminate the risk of selection bias, correct low rates of reports, or reduce the high number of incomplete reports, thus limiting its ability to establish a causal relationship between a health product and an adverse effect.[8,9] This will be further discussed below.

That being said, we should certainly not neglect their potential in generating hypotheses of an association between exposure to a health product and a specific adverse effect that can then be confirmed with pharmacoepidemiologic studies. In short, these spontaneous case reports are the starting point of the adverse drug reaction pharmacovigilance activities: they are often the initial signal in prompting pharmacoepidemiologic studies.

To add efficiency in the spontaneous reporting of adverse drug reactions, it is essential to have the manufacturers, patients, and health-care professional collaboration in writing and sending detailed and good-quality reports to regulatory authorities including Health Canada (see below).

2.5.1.1 Identification of Safety Signals From Spontaneous Reporting

To compensate, at least up to a certain point, for the weaknesses inherent in the spontaneous reporting of adverse drug reactions, different epidemiologic techniques can be used for the identification of safety signals (see Chapter 3). These methods include the calculation of the disproportionality ratio, the use of Bayesian data exploration (data mining), and other techniques. However, these latest techniques should always be used in conjunction with the analysis of the individual case reports (for more concrete examples on the use of these

pharmacoepidemiologic methods please consult the relevant case reports provided in Chapter 4).

Data-mining techniques facilitate the evaluation of spontaneous reports using statistical methods to detect potential signals to conduct a more in-depth safety assessment. These tools do not quantify the magnitude of the risk, and one must be careful when comparing health products.

The results obtained with these techniques should be interpreted considering also the weaknesses of the spontaneous reporting system and specifically, the major differences between the different health products. One should also consider the many biases and potential confounding factors that can also be associated to the spontaneous reporting of an adverse drug reaction.

All signals must be evaluated recognizing the possibility of false positives. In addition, the absence of a signal does not necessarily mean that there is no problem that needs to be followed.

2.5.2 Case Series Reports

Case series reports may also provide evidence of a link between a drug and an adverse effect, but they are also generally more useful to generate hypotheses of an association between exposure to a health product and an adverse effect, which can then be verified using one of the pharmacoepidemiologic designs described below.

There are some specific adverse events[7] that are known to be most frequently associated with, for instance biological drugs, such as autoimmune reactions, pure red blood cells aplasia (see case report # 7 in Chapter 4), Stevens–Johnson syndrome, progressive multifocal leukoencephalopathy (PML), and others.

Therefore, when these events are spontaneously reported, manufacturers should put more emphasis on these reports to promote fast and detailed follow-ups. They can also put in place an appropriate pharmacoepidemiologic design to further demonstrate whether a real causality link exists between the exposure to the health product and this specific adverse drug reaction.

2.5.3 Causality Assessment

A causality assessment is a method for assigning probability of causation to a suspected adverse drug reaction and the use of a health product. Analysis of causality consists of answering the question: *Is the factor A (health product A) the cause of the event B (e.g., anemia)*? In all cases, for causality to be true, it is pertinent that the exposure (to health product A) preceded the occurrence of the adverse event (anemia). Here anemia is just an example but any other adverse event could have been used for illustrative purposes.

Causality may be analyzed at the individual level by answering the following question: *Did the health product use in this study produce the event of anemia observed in this patient*? Or, at the population level by answering the following question: *Does the use of this health product increase the risk of developing anemia*?

A factor is called a "*specific relation*" if the occurrence of the event requires its presence (i.e., the factor will be found in all the subjects having presented the anemia, but its presence does not inevitably result in the occurrence of anemia).

On the other hand, a factor is called a "*sufficient relation*" if its presence inevitably causes anemia to happen (in which case all those exposed to this factor will present the anemia, although this does not necessarily mean that the factor will be found in all the subjects having presented the anemia).

Much more common (especially in pharmacoepidemiology) is the multifactorial causality in which several factors are identified as, independently or not, increasing the risk of the occurrence of the anemia, without any of them being specific or sufficient relations on their own.

In the strictest sense, only a controlled clinical trial with random allocation of treatment or exposure, and where a statistically significant association between exposure and the occurrence of an event is observed, can allow us to conclude to a causal relationship.

In observational epidemiology or pharmacoepidemiology studies (discuss in Chapter 3), the absence of a strong experimental design limits the validity of causal inference, notably because of the possible existence of bias and confounding factors.

As demonstrated in Chapter 4, case # 3, to assess the probability of an adverse drug reaction being related to a specific health product we use specific forms. Naranjo et al. created the Naranjo probability scale, which is made up of a series of 10 yes/no/do not know questions; each response is assigned a different value, and certain questions are assigned more points than others if the criteria are considered more important.

This produces a weighted score that the clinician can assign to the causality of each case as follows: unlikely (0), possible (1−4), probable (5−8), or certain (>9).[10]

2.5.4 Summary Reports

With the globalization of the drug industry and the withdrawal of some drugs from the market for safety reasons, regulatory authorities such as Health Canada, the FDA, the EMA, and others have recognized the need to better plan and implement earlier pharmacovigilance activities for adverse drug reactions, ideally before the authorization for marketing, and throughout the life cycle of health products.

To facilitate the work of the manufacturers, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has developed various Guides and Guidelines that can be used by the manufacturers for the pharmacovigilance activities of adverse drug reactions in accordance with the Food and Drug Act and Regulations. For more information about these ICH Guidelines please follow this link: http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html.

In accordance with article C.01.018 of the Food and Drug and Regulations (1) the manufacturer is to prepare a report that synthesizes information received regarding adverse drug reactions on an annual basis. The 12-month period covered by the annual report must be specified by the manufacturer (see the annex at the end of this book for a better discussion of the regulations surrounding the life cycle of health products including the summary reports).

In addition, according to article C.01.019 of the Food and Drug and Regulations, the Minister may, for the purposes of assessment of the safety and efficacy of the drug, request in writing that the manufacturer submits a summary report on a specific issue of concern, if one exists. In both cases, the summary report must be kept on site by the manufacturer or be easy to access and must, on request, be submitted to Health Canada (and other regulatory agencies) within a period of 30 calendar days following the request.

When Health Canada (and other regulatory agencies) requests the annual safety report from manufacturers, it can be requested in different forms depending on the needs of Health Canada (and other regulatory agencies), and it is best to present the report according to the format and standards set out in the ICH Guidelines for each of the following documents: Periodic Safety Update Reports (PSURs), Periodic Benefit-Risk Evaluation Reports (PBRER), Risk Management Plans (RMPs), and Development Safety Update Reports (DSURs). Each of these reports will be described in the sections that follow.

2.5.4.1 Periodic Safety Update Reports

The PSUR is a stand-alone document allowing for a periodic but complete assessment of data on the safety of a marketed health product. The format and content permit providing an evaluation of the benefit/risk ratio of a health product for submission by the marketing authorization holder at defined time points during the postauthorization phase.

The PSUR is also a safety summary on international data on a health product used to facilitate the postapproval marketing communication between the manufacturers and regulatory agencies such as Health Canada.

It reports adverse effects associated with taking a health product, observed over a period of 12 months, usually based on the health product's international birth date, in accordance with article C.01.018 of the Food and Drug Regulations (See Annex 3).

In addition, according to article C.01.019 of the Food and Drug Regulations, the PSUR may be requested by Health Canada (and other regulatory agencies) for a shorter period of time or as needed if a safety concern warrants the request. Also notice that these articles are not only limited to the PSUR but also apply to other summary reports (See Annex 1).

According to Klepper (2004), the PSUR is also an important source for the identification of new safety signals, a way to determine a change in the benefit/risk ratio, an effective way to communicate risks to regulators, and an indicator that signals the need to set up risk management measures. It is also a mechanism for the follow-up and assessment on the effectiveness of these measures.

For these reasons, the PSUR can be a very important tool in the pharmacovigilance of adverse drug reactions. However, this document is largely dependent on the quality of the available data. Despite the fact that it is gradually replaced by the Periodic Benefit-Risk Evaluation Report (PBRER), it is still used by many manufacturers and Health Canada (and other regulatory agencies) continues to review it.

2.5.4.1.1 Usefulness of the Periodic Safety Update Reports

The usefulness of this tool for the identification and prevention of adverse drug reactions has been recently verified by Ebbers et al.,[11] with a pharmacoepidemiologic study in the form of a cross-sectional analysis. The details on how to perform a cross-sectional study are presented below.

This cross-sectional analysis was performed on 70 PSURs submitted to the EMA between July 1, 2008 and June 30, 2010. Possible safety concerns have been observed in 57 (83%) of all surveyed PSUR. Of these, 26 (37%) led to changes at the level of the warnings section of the European Summary of Product Characteristics (SPC). In comparison with the new products, the products authorized for more than 10 years contained far fewer safety concerns (60% against 92%; $P < .01$) and required fewer changes to the SPC (15 against 46%; $P = .03$).

These authors also concluded from the pharmacoepidemiologic cross-sectional analysis that PSURs facilitate communication between regulators and manufacturers, regarding possible safety issues that arise during the course of a product's life cycle. Nevertheless, for long-term established products and evaluations from the PSUR rarely lead to regulatory action.

Bouvy et al.[12] recently analyzed the cost-effectiveness of all PSURs submitted for biological products in Europe between 1995 and 2009 by comparing two regulatory scenarios: the monitoring of the complete regulation (submit PSUR and other documents on the pharmacovigilance of adverse effects, including adverse drug reaction spontaneous reporting, postapproval safety studies, and the risk management plan).

The cost-effectiveness of the complete regulation monitoring (including the submission of PSUR) versus limited regulation (no submission of PSUR)

was 342,110 euros per quality-adjusted life per year. This suggests that the use of this tool in the prevention of adverse drug reactions is cost-effective.[12]

2.5.4.2 Periodic Benefit-Risk Evaluation Report

As mentioned above, the main objective of the PSUR is to provide a periodic and complete safety profile based on what is currently known regarding the authorized health product. However, the information on the efficacy, the restrictions of use, the alternative treatments, and many other aspects of the health product therapy must also be considered in the assessment of the risks and benefits of health products. That is what the PBRER proposes. Given the fact that the assessment of the risk of a health product has its real significance when the product is also assessed in the light of its benefits; it can be added that the PBRER gives greater attention to the benefits (efficacy) than the PSUR.

2.5.4.2.1 The Periodic Benefit-Risk Evaluation Report Utility

Furlan[13] has considered the main safety features included in the various ICH Guidelines such as the PSUR, RMP, and DSUR (see below). He finds that the main elements and sources of information contained in these various guidelines overlap greatly with one another. What is to be considered in a context of limited resources?

The author proposes to reduce these overlaps as all these "regulatory" periodic reports should be in the form of a single document. This report should include all available information from all possible sources in regard to the identified and potential risks of a health product.

This single document should be updated on a regular (annual) basis or on request by Health Canada (and other regulatory agencies) to be in compliance with articles C.01.018 and C.01.019 of the Food and Drug Regulations (See Annex 1). One of the factors that led to the revision of the ICH E2C (R1) Guidelines is a desire to improve efficacy by reducing duplication of effort required for the preparation of the various regulatory documents.

Therefore, the guideline was drafted so that related sections of the PBRER, the DSUR, and the safety specifications of the RMP can be identical in terms of content. That being said, PBRER is still a very useful tool to generate hypotheses of an association between exposure to the health product and an adverse effect that are verifiable with one of the pharmacoepidemiologic study designs described in Chapter 3.

2.5.4.3 The Risk Management Plan

The RMP is a plan to perform activities relating to the detection, assessment, understanding, reporting, and prevention of adverse effects of health product during clinical trials. This plan should be initiated early and modified as necessary throughout the development process for a new health product in development for new indications.

The overall objective of the RMP is to ensure that the benefits of a particular health product (or a series of health products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. This can be done either by increasing the benefits or by reducing the risks. The risk management has three stages that are interrelated and reiterative: (1) characterization of the safety profile of the health product including what is known and not known; (2) planning of pharmacovigilance activities to characterize risks and identify new risks and increase the knowledge in general about the safety profile of the health product; (3) planning and implementation of risk minimization and mitigation and assessment of the effectiveness of these activities.

Carefully planned, the adverse drug reactions throughout the pharmacovigilance activities can reduce the health product risk of toxicity and increase the benefits to patients. For more information on the content and format requirements of the RMP and to consult the ICH E2E Guidelines, visit the following link: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf.

This guideline is also implemented for the planning of adverse drug reaction prevention activities during the postapproval marketing period. It also sets out the principles of good clinical practices for the design and implementation of postmarketing pharmacoepidemiologic studies including phase IV studies. The guideline is composed of three main components: (1) the pharmacovigilance specifications; (2) the pharmacovigilance plan; (3) the start-up of the postauthorization safety pharmacoepidemiologic studies.

In brief, the RMP is a very important tool in the assessment of the benefit/risk ratio and in the prevention of adverse drug reactions throughout the life cycle of health products. Even if presented differently, these main components are the elements that should be included in the other summary reports mentioned here.

2.5.4.3.1 The Risk Minimization Activities (Measures)

An intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a health product, or to reduce its severity should it occur. These activities may consist of routine risk minimization (e.g., product information) or additional risk-minimization activities (e.g., health-care professional add letters or patient communications/educational materials).

2.5.4.3.2 Pharmacovigilance Specifications

This part of an RMP provides a synopsis of the safety profile of the health product(s) and should include what is known and not known about the health product(s). It should be a summary of the important identified risks of a health product, important potential risks, and missing information. It should

also address the populations potentially at risk (where the health product is likely to be used, i.e., both labeled and off-labeled use), and outstanding safety questions that warrant further investigation to refine understanding of the risk−benefit ratio during the postauthorization period.

The specification may include, but is not limited to (1) identify the preclinical phase safety concerns; (2) analyze the missing preclinical data; (3) assess adverse drug reactions observed during the clinical trials; (4) analyze human safety databases and the frequency of adverse drug reactions that have been detected during these clinical trials; (5) analyze potential adverse drug reactions that require a more thorough assessment throughout pharmacoepidemiologic studies to clarify the assumptions of risk; (6) assess populations that have not been studied in the preauthorization phase via pharmacoepidemiologic studies; (7) analyze documented drug interactions; (8) determine the potential for unidentified interactions that may occur during the postmarketing approval; (9) carry out epidemiological studies of diseases; (10) assess the effects of drug class.

As for the other safety summary reports, the RMP is a very useful tool to generate hypotheses of an association between exposure to a drug and an adverse effect that can be verified with various pharmacoepidemiologic study designs described in Chapter 3 with concrete examples in Chapter 4.

These specifications will help the manufacturers and the regulatory agencies to identify all specific data that need to be collected and analyzed during the postmarketing period. This also facilitates the preparation of the adverse drug reactions pharmacovigilance plan that incorporates the concept of life cycle of health products. For more information on the content and format requirements of the RMP and to consult the ICH E2E Guidelines, visit the following link: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf.

2.5.4.3.3 Usefulness of Risk Management Plan

To determine if the RMP is an effective tool to improve the safety of drugs, Frau et al. conducted a pharmacoepidemiologic study designed to describe the characteristics of these plans for 15 drugs approved by the EMA and their impact on the postapproval pharmacovigilance period. Among 90 new chemical entities approved during 2006 and 2007, 15 were selected and their security and their RMP components have been analyzed.

All safety pharmacovigilance communications related to these drugs in the postmarketing period were also considered. A total of 157 safety specifications have been implemented for these evaluated drugs. Postmarket safety concerns have emerged for 12 of them, leading to 39 changes to the Summary of Product Characteristics (SPC) of these European products. Nearly half of these changes, 19 (49%), covered security features not provided by the RMP. In addition, 9 safety communications have been published for 6 of the 15 drugs evaluated.

The pharmacoepidemiologic study revealed that the RMP is an effective tool to prevent adverse effects associated with drugs, but several activities offered by the RMPs do not seem to be sufficient to deal with all the potential risks associated with drugs.

The authors add that the lack of risk communication between clinicians and the public and especially the limited risk assessing transparency seems to transform the RMP into a tool to reassure the public when a drug has been insufficiently evaluated and received a marketing authorization prematurely.[14]

2.5.4.4 Development Safety Update Report

The DSUR is a periodic summary of safety information for regulators, including any changes in the benefit−risk relationship, for a drug, biologic, or vaccine under development, prepared by the sponsor for all its clinical trials.

During the clinical development, periodic safety analysis is crucial to the ongoing risk assessment of participants in clinical trials for all marketed or nonmarketed drugs at all dosage forms, for all indications and for all patient populations in study with the health product used. Whereas the majority of clinical trials are multinational and/or multicenter, it is necessary that these reporting requirements be harmonized for all regulatory authorities around the world including Health Canada, which adopted this report in June 2012.

The concept of DSUR was first introduced by the Council for International Organizations of Medical Sciences (CIOMS) VI working group (http://www.cioms.ch/) and pursued by the CIOMS VII Working Group. In 2010, the ICH published the E2F Guidelines on the DSUR, incorporating the context, objectives, and the scope of the DSUR by providing advice on its content.

For more information on the content and format requirements of the DSUR, the readers can consult the ICH E2F Guidelines and visit the following link: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2F/Step4/E2F_Step_4.pdf.

2.5.4.4.1 Usefulness of the Development Safety Update Report

The main objective of the DSUR is to present a comprehensive annual review of the safety information associated with a drug in development collected during the reporting period.

The DSUR's unique value is to identify the trends and characteristics of the safety issues related to a drug in development, which cannot be obtained by looking at the individual case reports in isolation. It is therefore a tool for the prevention of the adverse effects associated with the very important drugs, serving not only in the analysis of safety signals but also to update the product monograph (when the product is marketed) and to update the Investigator's Brochure (when the product is in the research phase).

The DSUR allows for an assessment of the health product within the life cycle concept including the safety of participants in clinical trials and, in many cases, the safety of patients in real-life (in postmarketing approval) condition.

2.6 ACTIVE SURVEILLANCE (PHARMACOVIGILANCE)

Active surveillance, unlike passive surveillance, seeks to determine potential safety concerns through a continuous preorganized assessment process as completely as possible. It involves regular systematic collection of clinical information on a population of patients who receive drugs that are on the market.

There are several ways by which this clinical information may be collected: sentinel sites, intensive monitoring protocols, follow-up of specific events, patients' registries, observational studies, clinical trials, and others. For more information on this collecting of information methods, please consult Chapter 4 and the glossary of terms in Annex 2.

In general, it is easier to get comprehensive evaluation of adverse drug reactions through an active surveillance system compared to a passive reporting system. In the following pages, we will discuss on patients registries emphasizing on the most important tools of the active pharmacovigilance system, which are the pharmacoepidemiologic studies.

2.6.1 Patient Registries

A patient registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a wide variety of information using standardized questionnaires in a prospective fashion. Exposure (drug) registries collect information over time on populations exposed to health products of interest and/or specific populations. Patients can be included in a cohort study to collect data on adverse events using standardized questionnaires. They can be useful for signal detection, particularly of rare outcomes.

In many countries, disease-based registers have been established for the specific reporting of clinical information and management of certain diseases and procedures. The potential for analyzing the effects and safety of drugs has further developed with the introduction of electronic health records containing not only prescription drug data but also other clinical parameters, such as diagnosis, vital signs, laboratory data, and more or less structured clinical notes. In some countries, biobanks have also been established enabling linking drug utilization to genetic data.

At the market-authorization phase, all the risks and all the adverse effects related to a health product are rarely entirely known.[15] This section is therefore intended to describe the essential role of patient registries in the active surveillance of specialized health products. Thus, patient registries have become more attractive in the active surveillance of adverse drug reactions. For more information on the use of patients registries in the active surveillance of health products, please consult Chapter 4 for concrete examples.

However, their exact role continues to evolve. These registries consist of a defined patient population with the same characteristics for which data are

collected in a systematic way over a defined period of time. Therefore, they are useful for providing reliable estimates of the adverse events incidence among a defined population and they are also very useful for pharmacoepidemiologic studies.[15]

The purpose of these registries is to improve our knowledge on the safety of a health product, especially on the long-term use of this product.[8]

However, as registries do not systematically include control groups of similar patients who did not receive the health product, they are not able to answer questions related to the efficacy or treatment effect and cannot serve as replacements for clinical trials. In addition, due to their high operational costs, registries are more important for monitoring highly specialized health products that are used in significant clinical settings.[15]

The disease registries, such as registries for blood dyscrasias, severe skin reactions, congenital, or other abnormalities can help collect pharmacoepidemiologic data on drug exposure and other factors associated with a particular clinical condition. A disease registry can also be used as data for a case-control study (see below) comparing exposure to the drug (cases) identified in the registry and a selected group of patients in the registry with another condition, or from patients outside the registry (controls).[15]

The drug or exposure registries are used in populations exposed to specific health products (for example, the rheumatoid arthritis registry in patients exposed to biological therapies) to determine if a drug has a specific effect in this group of patients.[15]

Certain exposure registries address exposures to drugs in specific populations, such as pregnant women. With this registry, patients can be monitored over time and included in a cohort study to collect data on adverse events using standardized questionnaires.[15]

These cohort studies (see below in Chapter 3) can be used to measure the impact, but, without a comparison group cannot provide proof of an association (causality) between the adverse events and the health product. However, they can be useful to increase signal detection in particular for rare adverse events. This type of registry can be very useful during the safety review of an orphan drug, indicated for a specific rare condition, for example. For more information, please consult Chapter 4 for concrete examples.

One of the most important and known examples of exposure registry involved natalizumab, which is a specific monoclonal antibody for the $\alpha 4$ integrin that is used for the treatment of multiple sclerosis.

Clinical trials and postmarketing data indicated that natalizumab is associated with an increased risk of PML, a potentially fatal disease affecting the central nervous system.

Natalizumab was voluntarily withdrawn from the market by the manufacturer in 2005, when the initial cases of PML associated with the use of natalizumab were identified.[8]

After a review of the safety and benefits of this biologic product, natalizumab was reintroduced on the market in 2006 under a risk-minimizing program for PML while patients receiving the drug are recorded and monitored for this specific adverse effect. The TYGRIS Registry aims to recruit 6000 patients worldwide; and follow-up of this registry will help to increase our knowledge about the security of this biologic product.[8]

There are other registries such as registries of specific conditions that include those put in place to monitor the treatment of rare diseases. The purpose of these registries is to identify the impact of different treatments in the long term. Clinical trials of drugs for these diseases are usually performed on just a few patients. Therefore, the safety information may be limited.

For example, the idursulphase is a health product used in the treatment of the Hunter syndrome, a rare genetic disease that occurs in approximately two people per million inhabitants. After the marketing authorization of the product, the manufacturer has implemented a registry called "Hunter Investigation" where all patients with the Hunter syndrome are invited to participate in the survey, regardless whether or not they are treated with idursulphase.

This registry will help provide information on the progress of the Hunter syndrome, as well as its associated medical consequences.[8] Even if often limited by the lack of a control group and the need to produce a comprehensive analysis of individual cases to maintain the data integrity, registries are useful for monitoring highly specialized drugs and rare health conditions.[15] They are also very useful to generate hypothesis for pharmacoepidemiologic studies.

2.7 CONCLUSIONS

The assessment and analysis of adverse drug reactions is critical for early detection of the potential security issues with health products. An effective assessment of these adverse effects either in pre- or in postapproval development market may point to the need to put in place additional security measures that can lead to a faster response by the regulatory agencies and the medical profession such as placing restrictions of use on some health products or in extreme cases, suspend the use of a health product.[16]

Historically, the premarket phase was the only phase for determination of effectiveness and safety of health products. The postapproval surveillance setting becomes more and more important in this environment; so we are now more talking to an assessment of the risks and benefits throughout the life cycle of a health product.

As it has been discussed in this chapter, there are important limitations to pharmacovigilance including the quality of the adverse drug reactions reporting, the absence of reporting, and others. However, the pharmacovigilance activities remain an essential discipline in the management of adverse effects of health products that are evolving.

Pharmacovigilance activities are essential to answer the safety questions posed by a number of more effective health products having inevitable and sometimes unpredictable potential to generate adverse effects.

Whether at the pre- or postapproval marketing level when adverse effects appear, it is essential that they are analyzed and reported through effective means to regulatory organizations to interpret their impacts (see Annex 1 for some regulations regarding the reporting of adverse drug reactions).

This chapter gives an overview of the main pharmacovigilance elements to be considered in the analysis and management of adverse drug reactions. Some of these elements will be explored in greater detail in the chapters that follow. The reader is invited to consult Annex 1 at the end of this book to help consolidate the information that has been provided so far.

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