Chapter 2

Frameworks for Evaluating Qualitative and Quantitative Information on Adverse Drug Events throughout Development through to Marketing

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Additional information is available at the end of the chapter

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Abstract

Significant public health issues caused by adverse drug reactions in the post-marketing phase, such as birth defects by thalidomide, have been well described. Unfortunately, subjects in clinical trials cannot completely avoid severe harm during drug development. TGN1412 in 2006 and BIA 10-2474 in 2016 were withdrawn from development due to severe adverse reactions in first-into-man studies. Thus, monitoring drug safety is important throughout all phases of development. In twenty-first century, minimizing drug development cost and time is a challenge for pharmaceutical companies. When a drug is approved with a smaller size and fewer number of clinical trials, pharmacovigilance and benefit-risk evaluation after marketing need to be sufficiently performed. Underpinned by understanding of the traditional methods of evaluating adverse drug reactions, new developments in IT and computing might well help us to detect drug safety signals earlier, enabling prompt intervention for protecting the rights of subjects and public health.

Keywords: risk management, pharmacovigilance, DSUR, PSUR, ADR, causality

1. Introduction

A new drug application dossier, accompanied with the Common Technical Document (CTD), needs to provide a risk management plan, and a marketing authorization holder needs to set up both the policy framework and a quality system for pharmacovigilance. This approach has become more important and valuable in regulating drugs, because the novelty, rarity, or technical specificity of drugs produces complexities to evaluating efficacy and safety.

Furthermore, in this decade, the risk-based approach for application has been proposed to address and evaluate potential risks associated with the clinical use of medicines, with regard to quality, safety, and efficacy. While the risk-based approach is to be differentiated from the risk management system or the benefit-risk assessment for evaluating marketing authorization, the idea is very close to it. This chapter introduces pharmacovigilance in the clinical development phase, especially with the aim of stimulating discussion about identification of risks associated with the clinical use of drugs qualitatively and quantitatively.

1.1. What to do when any clinical safety problem happen in the development phase?

Throughout the history, humans have used a variety of different therapies to treat injuries and diseases. During the nineteenth century, medicines were developed by separating, isolating, and extracting certain active ingredients from medicinal plants, e.g., morphine, quinine, and ephedrine. Then, in twentieth century, chemists discovered new chemicals, e.g., penicillin and streptomycin, from bacteria and synthesized better chemical substances of sulfonamides. In the first decades of twenty-first century, the development of drugs had been dramatically changed. Pharmaceuticals benefit from advances in all fields relating to medicine, e.g. pharmacology, physiology, and biochemistry, and were derived from synthetic compounds to target a certain site of action. For example, the progresses in medical science helped to reveal many of the mechanisms of the pathophysiological and pharmacological effects at the molecular level; for example, cimetidine and histamine-2 receptor blocker, which was a break through pharmacotherapy at that time for gastric ulcer. Molecular-targeted drugs now have been developed to treat various diseases, especially targeting specifically expressed molecules of cancer cells, e.g., imatinib.

Common to all pharmaceuticals is that they can bring both benefits and risks to humans. Thalidomide, which is now administered with dexamethasone to multiple myeloma patients, used to be first sold in West Germany as a sedative or hypnotic drug in 1950s, and then it was withdrawn from the market in 1961, because it was found to be responsible for teratogenic deformities in children based on reports of children of those mothers who took thalidomide during pregnancy. This tragedy was both a pre- and post-marketing landmark; countries recognized the need of adequate testing of medicines prior to marketing, the regulation of medicines, and the systems to identify the adverse effects of medicines as well as the potential relationship between marketing claims and safety [1, 2]. Because of the need for effective therapies in myeloma, thalidomide demonstrated sufficient benefit to achieve authorization and turned around the balance of benefit-risk from negative evaluation. This depended on effective risk minimization to prevent pregnancies in those who receive thalidomide.

International activities actively promoted regulations and empirical knowledge on clinical development in 1990s. However, in twenty-first century, one programme of an investigational medicinal product was withdrawn due to serious adverse reactions in the first-in-human clinical trial in 2006. This was known as TGN1412, a CD28 superagonist monoclonal antibody. Six volunteers were seriously afflicted by a cytokine-release syndrome requiring intensive care just after they received a bolus injection of TGN1412.

Although many new drugs implement a lifecycle risk management, another tragedy in clinical trial happened with a dose-finding study for BIA 10-2474, an experimental fatty acid amide hydrolase inhibitor for the treatment of anxiety disorder, Parkinson's disease, etc. An acute and rapid progressive neurologic syndrome developed on the fifth day of BIA 10-2474 administration (50 mg). The underlying mechanism of adverse drug reaction is still unknown regarding BIA 10-274, but it is supposed to be associated with drug accumulation as no clinical severe adverse events had been observed in single dose (0.25–100 mg) and 10-day administration (0.25–20 mg) [3].

The stories addressed above are extreme examples. However, a number of drug development programmes have been abandoned because of safety concerns or lack of efficacy. As mentioned in ICH Good Clinical Practice (GCP) [4], "A trial should be initiated and continued only if the anticipated benefit justifies the risks." Thus, sponsors need to make sure that benefit for patients should overweigh risk to patients. Information sharing and a system for risk management throughout the lifecycle of drugs from preclinical, clinical, and post-marketing are crucial, and this is reflected in the development safety update report (DSUR) which had been proposed [5] and then taken forward by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [6]. This emphasizes the importance of the principle of the benefit-risk balance, which is supported by pharmacovigilance concepts which originally emerged in the post-marketing phase.

1.2. The latest strategy to promote marketing a new medicine

Drugs are approved based on the evidence of efficacy and acceptable level of harm that have been observed during clinical trials. Now, to tackle remaining unmet needs of patients globally, the regulatory schemes for supporting early access have been adopted, such as compassionate use, accelerated assessment by regulatory agencies, and conditional marketing authorization. If it is expected to have new medicines with conditional use, an applicant is allowed to provide comprehensive data after approval. Once such a new medicine is approved, definitely, there is little evidence of efficacy and safety in real-world practice, so that effective pharmacovigilance should produce the important data to supplement the evidence as well as cost savings for an applicant in the drug development. As we receive more applications of early access program, the more careful that we should be to pay attention with not to confusing "absence of evidence" with "evidence of absence" at approval. It is critical to detect precisely and promptly the harms potentially caused by an investigated drug (monitoring), to assess individual cases (qualitative evaluation) and comparative groups as planned (quantitative evaluation), and to finalize benefit-risk assessment at defined points in time (**Figure 1**).

How we can define "risk" then? According to the International Organization for Standardization, risk is the "effect of uncertainty on objectives" [7] and in terms of drug development, the objectives are patients' and public health. Another definition can be "combination of the probability of occurrence of harm and the severity of that harm" for medical devices and manufacturing medicinal products [8, 9]. As such, risks related to use of a drug is defined "any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health

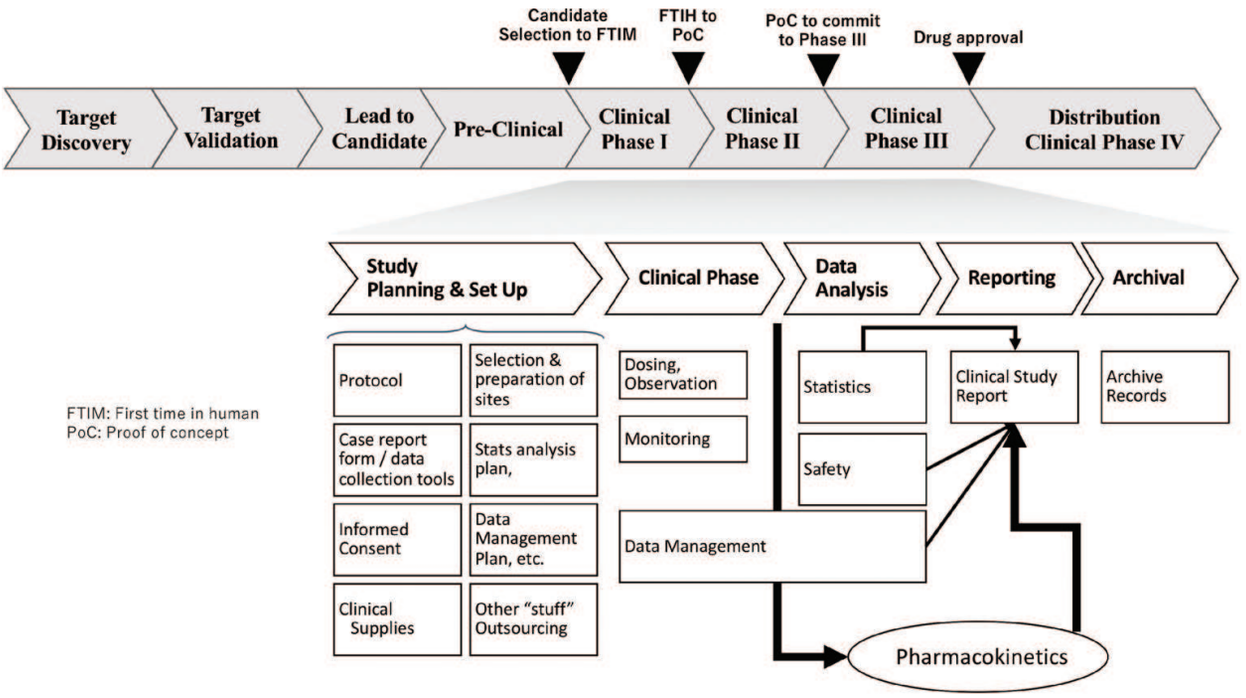

Figure 1. Drug development process and clinical data review. The figure is arranged and restructured from some of slides provided with the kind permission of the Product Safety Culture Initiative in the Alliance for Clinical Research Excellence and Safety.

or public health and any risk of undesirable effects on the environment" [10]. In traditional pharmacovigilance, the concept of risk concerns adverse drug reactions [11], as described later, however EU regulations now emphasize that it is as been expanded to include ineffective use outside the label, misuse and abuse. In reality for pharmacovigilance, we propose to bear in mind other systematic factors impacting risks of medicines as well (such as facilities, procedures, computerized systems) that may cause medication errors. Those risks cannot be evaluated enough in drug development, therefore the plan is necessary to continue vigilance once marketed and take action once a potential harm is identified. Thus pharmacovigilance has become even more important to manage various safety problems with these new rapid access regulatory approvals.

Risk management encompasses "risk assessment" and "risk minimization" with the management cycle to assess, implement, evaluate, and modify safety measures; the former is to identify and characterize the nature, frequency, and severity of the risks associated with the use of a product, as focused in this chapter; the latter is to minimize or mitigate a product's risks through communication, education, and restriction of use while preserving its benefit.

2. Pharmacovigilance in clinical trials

Data obtained from clinical trials vary depending on the situation of an investigational substance and those are different from post-marketing data; the patient being administered can be perfectly observed, the number of patients is small, and the information on subjects can be

biased under restrictions of subjects' health background. As with post-marketing data collection, the data collection method is an essential element of the pharmacovigilance process during clinical trial with proper data collection to enable analysis of medical interpretation of the case narrative and the aggregated data. Evaluation of case information obtained in clinical trials is possible by use of the approaches cultivated in pharmacovigilance over years of experience.

2.1. Characteristics of pharmacovigilance in clinical trials

It is commonly known that not all hazards can be found before a drug is marketed. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems [12]. It is now also more involved in pre-approval drug assessment as well-designated clinical trials in phase IV, referred to "the clinical safety activities throughout the lifecycle of a medicinal product" [13]. Drugs at approval have limited clinical information from clinical trials. For example, 16,000 subjects are needed to receive a drug to detect one adverse drug event out of 10,000 people with 80% probability, while clinical trials for most new drugs are conducted with 2000–3000 patients prior to approval. Therefore, rare adverse drug reactions are hardly detected, although relatively common adverse drug reactions (ADRs) are identified. Patients with complex conditions are excluded in order to eliminate factors that may affect efficacy of a tested drug. Most, but not all, ADRs occur in rather short time after administration. The short duration of observation, for example, 1 year or less in clinical trials is another limitation that will not observe late-onset ADRs. CIOMS VI [13] would help readers understand systematic approach for safety management during clinical development. Missing information at approval concerning clinical safety often refers to use in children, elderly, kidney disorders, drugs for oncology, HIV, vaccines, biologicals, and other advanced drugs as they will all mostly have a comparatively small number of subjects. All those limitations are to be addressed in pharmacovigilance plan for post-marketing. Clinical trials need to be monitored by the Data and Safety Monitoring Boards (DSMBs), also known as Data Monitoring Committees (DMC), who periodically review and evaluate the accumulated data from one or multiple clinical trials for safety of trial subjects. After DSMB evaluation, apparently obvious favorable or unfavorable results in the treatment group will lead to recommendations to discontinue a trial for the reason of negative benefit-risk in the treatment of the control group. However, the benefit-risk assessment continues throughout the drug development lifecycle.

2.2. Hazard data collection: planning and practical realization

Although there are regulatory systems for both pre- and post-marketing individual case safety reports (ICSRs), the concept of cases to be reported is somewhat different between pre and post. After marketing, it is rather appropriate to pay more attention to unknown serious adverse reactions than known or non-serious ADRs, although the latter can provide useful supporting information about risk factors and nature of known ADRs. Clinical trials explore unknown properties and use of a medicine, and so taking ethics into account, all adverse events (AEs) must be collected and in addition, serious and unexpected adverse events are subject to expedited reporting.

All serious adverse events must be assessed regardless of causality by the applicant at the time of application submission. Furthermore, what kind of AE data can be collected in the development phase depends on the clinical evaluation stage in the development process in which the investigational drug is as described in the protocol. The judgment as to whether a case is expected (known) or unexpected (unknown) is based on the labeling of the marketed drug, while in clinical trials, the reference safety information in the investigator's brochure is used. It is necessary for clinical trial sponsors to update the investigator's brochure at any time as needed, and the latest reference safety information receives close regulatory attention to ensure it is up to date for the judgment of known/unknown (or listed/unlisted) cases.

In addition, since many of post-marketing ICSRs are spontaneous reports, there is a vast range in the quality of the information from rich cases to poor cases (e.g., age/gender, drug, and adverse event are minimum requirements for regulatory reporting), mostly without laboratory results and the exact size of the exposed population is unknown. Since laboratory test values of participants in a clinical trial are regularly collected, assessment of individual case safe report, described later in this chapter, should effectively utilize theses results for each subject as well as the corresponding case narratives. Clinical trials have detailed information on cases such as the AE development date and dose (details of which are often missing in post-marketing ICSRs) and the size of population is known, so it is possible to calculate the frequency of occurrence and the incidence of AE. Of course, efficacy is statistically evaluated in a prospective statistical analysis plan. Various designs of clinical investigation are available, not only clinical trials for the development of new drugs but also that for the extension of indication of existing drugs, development of new routes of administration, and changes in dosage regimen.

As regard to data collection of safety information in clinical trials, the Good Clinical Practice guideline [6] does not address details of standards for the types of data to be collected for safety monitoring although traditionally reliance has been placed mainly on AE case reporting to the regulatory agencies. While another guideline, ICH E2A [14], specify only the key data elements for inclusion in expedited reports of serious unexpected adverse drug reactions, it is prudent to collect more comprehensive safety data during development because poorly established safety profiles need to be clarified in greater detail with the collection of non-serious adverse events and essential laboratory data. Therefore, the study protocols should be well designed defining the data to be collected, which differs according to characteristics of a drug.

When collecting data, sponsors may prepare different procedures for targeted or untargeted AE detection. However, the methods are commonly used in the same manner such as questionnaires, patient diary cards, and medical records supplemented with serious adverse event (SAE) reporting forms. Safety outcomes can be presented using descriptive text or visual analogue scales for severity rating, based on subjective opinion, of adverse events during investigation, pre-, during-, and post-trial, since a participant was enrolled. Patients' opinions may not be scientifically presented, but an understanding of benefit and risk and impact of an AE on quality of life, thereby revitalizing patient-focused drug development, can be elaborated. Narratives are important information for in-depth investigation of suspected unexpected serious adverse drug reactions (SUSARs) and to understand the reasons why a participant has

dropped out from a trial. A protocol needs to specify testing intervals and thresholds for evaluating data later. Discordance of coding interpreted from collected data will cause both false positives and false negatives. Issues of coding, if left unresolved, will worsen with multicenter research which will provide aggregate data for quantitative analysis.

How data are presented influences the impression that an assessor would have. An appropriate approach should be selected among many options such as tables with strata according to, for example, dosage, duration of treatment with scatter plots for clinical chemical data, Kaplan-Meier plots for cumulative hazard clinical chemical data and outcome evaluation, and so on.

2.3. Safety profile and risk assessment

It is important to gain an understanding of the safety profile of a drug as early and as much as possible during development as possible as risks can be more easily controlled. Once the efficacy is proven at the end of clinical development, the benefit-risk profile of the drug is reviewed whether it is acceptable for approval. Both medical judgment (qualitative) and statistics including descriptive and inferential approach (quantitative) influence the evaluation of clinical safety during drug development. The same principles apply to post-marketing evaluation. It is more likely, however, that safety signal detection and assessment during clinical development depend as much on clinical judgment with case reports, especially for serious rare AEs. Such an approach is reasonable and necessary for small-size trials, since data accumulation is limited due to the small number of subjects. With accumulated data, statistical methods are possibly available for the evaluation of safety signals in clinical trials, especially for more commonly occurring adverse events, and it is certainly a practical option to use a database for the phase IV studies especially after conditional approval has been granted. Any approaches need to consider patient population characteristics including natural history of disease and current therapeutic standards for comparison, when evaluating safety. Safety evaluation is the basis of risk assessment as a whole, and it is required to report an unusual or worrying ICSR, especially for AE of special interest, routinely anytime and when a certain evaluation milestone is reached such as with DSUR submissions.

Risk assessment as a part of pharmacovigilance in drug development requires analyzing and interpreting the safety profile. After risk assessment, investigator's brochure may be updated and risk management measures may be taken to minimize the risks, if necessary and medically significant. From perspectives of public health, risk assessment and decision-making should be done at the right time rather to wait for punctual dataset for review.

Although the clinical efficacy is steadily and iteratively demonstrated through phase I, II, and III, and then confirmed at the end of development, serious harm can occur at any stage of drug development. Thus pharmacovigilance in drug development may be more of a risk-based approach relating to any other drug-related issues that could affect patient safety and safe use of drug, including concerns about quality and efficacy as well as safety. In this sense, pharmacovigilance is consistent with a "risk-based approach" which to some extent can be found in regulatory guidances recently [15–17].

3. What can be done for "evaluating benefit-risk balance"?

Many methods have been proposed and each of them gives us thoughts to some extent. So, do we need to apply all to our daily work? Those evaluation methods have been reviewed in terms of usefulness in benefit-risk assessment and reported by the European Medicines Agency, suggesting three quantitative methods for regulatory assessment use, Bayesian statistics, Decision trees and influence/relevance diagrams and Multi-criteria analyses, as well as qualitative approach [18]. They also pointed out some limitations, for example, Bayesian statistical model do not generally deal with multiple criteria, and some other approaches such as conjoint analysis may contribute to some specific cases. An assessment process, which includes many dimensions of public health to consider, will be enforced by the integration of methods/approaches. Authors make the point that quantitative methods/approaches are effectively adopted in practice only when a qualitative approach works.

3.1. Basic processes of adverse event evaluation

The identification of a potential safety issue for a drug requires processes to distinguish adverse reactions from unrelated adverse events. These cases can be found in reports submitted to regulatory authorities or published articles/posts through journals, media and even through social media and Internet. As a basic reference for risk assessment, the evaluation result of each individual case of suspected ADRs, as well as adverse events, is important because even one ADR case can be sufficient by evidence itself of a risk serious enough to stop a clinical trial. Therefore, the first step of the process is the assessment of individual case observations, and the difficulties of causality assessment are addressed further in the next Section 3.2. Case evaluation needs to consider clinical significance, seriousness, severity (continuous variables), and expectedness based on the latest investigator's brochure, causality, place and time of occurrence, dosage, and predisposing factors of trial subject. AEs based on laboratory data need to be interpreted as to whether they are of value as surrogate markers, whether testing intervals are adequate and whether such surrogate markers can be correlated with or help predict harmful endpoints.

Detection of specific ADRs as harmful properties of a medicine itself has an obvious purpose. These can be grouped or aggregate cases with features in common or a case series where the number of cases, individual causalities, inter-case consistency, and severity/seriousness can all be assessed. Plausibility of causal relationship between a drug and event can be discussed on the ground of causal assessment of each case or of a group of cases as an aggregate.

The next stage for attributing causality is to review the statistical quantification of safety data from individual studies. Biostatisticians can prepare and present data with tables and graphics as well as quantities of continuous/discrete variables. Points to consider include epidemiological morbidity and subjects' background data (bias and confounders), investigational comparators, randomization or not, primary/secondary/surrogate endpoint, dropouts and missing data, and data dependency on dose and time (hazard function). All aspects of statistical testing may play a critical role when applying a statistical analysis plan: types of test, probability threshold (p-level), adjustment for multiple testing and confounders, power of test, and confident intervals.

Toward the end of development, all data pooled through clinical trials are reviewed. This may require meta-analysis of individual data of clinical trials as well as meta-analysis of published studies as well. It has been reported that no significant difference exists between meta-analysis of published data and of individual data, and using published data is still considered the norm [19]. From different studies, there needs to be a pooling of numerators (e.g., number of affected patients) and denominators (e.g., number of patients or patient years) for ADR frequency estimation; frequency expression as "number needed to treat to harm," pooling of within-study and between-treatment group differences.

After AE assessment, if necessary, a sponsor should update the investigator's brochure and continue developing the labeling and future surveillance plan. Accordingly, Core Safety Information of an investigator's brochure should be based on the Company Core Safety Information, which in turn will be transferred to the Summary of Product Characteristics. To extend development, phase IV studies are possible, for example, with registers for long-term follow-up, observational studies for safety in clinical setting or using the large clinical database.

3.2. Qualitative data: case narrative

Many algorithms and classification systems on causality have been proposed; however, none has been agreed and accepted by everyone. In recent years, it has been questioned whether it is worthwhile to spend much effort conducting causality assessment on individual suspected ADR reports. The reason why is that ICSRs are considered relatively weaker as an evidence for causality than compared to the frequency of events in the actively treated group with that of the comparative control group. If randomized controlled trials found significant differences with appropriate statistical power, it is likely that pharmacotherapy was the cause of event, that is, the medicinal product directly caused the event under certain conditions of use. It is important to ensure robustness and objectivity of the trial is preserved by blinding (as qualitative assessment of unblinded data is considered subjective). But can even the best conduct clinical trials replace spontaneous reporting? Clinical trials from the early development phase to phase IV cannot replace spontaneous ADR reporting systems for detecting very rare ADRs, and it is not realistic to conduct a large-scale epidemiological survey/study for each new drug. Large databases may consider a signal such a rare ADR as noise and so it may be missed. Therefore, even though information technology has evolved, it remains important to evaluate causal relationship qualitatively on ICSRs individually, using medical inference, taking into account the widely different circumstances in which they arise ranging from clinical trials, registries, to spontaneous reports.

As a tool to assist qualitative evaluation, A to F ADR classes have been proposed and extended since the 1970s. It addresses the characteristics of how to categorize ADRs pharmacologically: Type A—augmented; Type B—bizarre; Type C—chronic; Type D—delayed; Type E—end of use; and Type F—failure of therapy [20, 21].

In addition, the DoTS classification considering dose, time, and susceptibility was also proposed from the viewpoint of elements that are thought to affect how side effects become

manifested rather than the pathology of side effects in isolation (**Table 1**). [21] The authors recognize absorption/distribution/metabolism/elimination to be included as susceptibility factors and, in addition, propose to consider these factors as contributing to medication error (contribution of human factors and other causal and predisposing factors).

WHO-Uppsala Monitoring Center advises that evaluation of causality can be categorized into six stages, such as certain, probable, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable [22], and for that the following major four aspects are to be considered [23]. (1) temporal relationships: What is the temporal relationship between treatment initiation and the beginning of the event? How has the event changed after discontinuing treatment? (negative dechallenge) Did it recur after re-administration? (positive rechallenge) (2) Alternative causes: Have there been exposure factors other than complications, concomitant medications, or medicines that can explain the event occurrence? (3) Nature of the event: Some clinical events are often caused immediately by drugs (e.g., swelling in injection site). (4) Plausibility: Is the reaction already recognized by this medicine? (Is it a known side effect with this class?) Can the explanation for mechanism of event be derived from its known pharmacological action?

As a more specific evaluation criterion, nine criteria by Hill [24] and a number of scoring algorithms such as that devised by Naranjo et al. [25] can be used and applied to as part of causality assessment. Effective use of all these causality techniques requires practical knowledge about how to blend clinical, medical, and pharmacological sciences, which it means it is necessary to have suitably qualified persons with such knowledge actively leading and involved in the assessment team. Behavioral competencies for effective performance in pharmacovigilance have been discussed elsewhere [26].

As will be described later, it is not uncommon for elucidation of the mechanism of the development of ADR after many years following new drug approval often linked to advances in in scientific technology and research. Benefit-risk assessment that involves scientific review should be considered as standard operational procedures with structured framework to achieve feasible decision-making. However, as there are no perfect causality criteria, we should always bear in mind and not ignore clinical significant events regardless of causality unless there is overwhelming evidence of other causal factors which are obvious.

Dose	Time	Susceptibility
Toxic	Time independent	Age
Collateral	Time dependent (rapid, first dose, and early/intermediate/late/delayed)	Sex
Hypersusceptibility		Physiological variation
		Exogenous factors
		Disease

Table 1. DoTS classification of adverse drug reaction.

3.3. Quantitative data: statistical approach

Statistics are widely used in the drug development as "biostatistics" to validate the efficiency of investigational products entity. What about the application of statistics to assess safety?

In the mid-1980s, the term "pharmacoepidemiology" was used for the first time, which often refers to the academic field of study, drug use and safety on a group level. As you can imagine from the phrase "epidemiology," the "group of subjects" or "population" studied by pharmacoepidemiology is a larger patient group than that of the clinical trial numbering up to tens of thousands or even an entire national population. This academic field has greatly expanded in the 1990s which is underpinned by the increased use of computerized databases including prescription records and clinical outcomes to investigate safety issues quickly and efficiently, as well as sophisticated computer technology, which enables high-enough performance to handle enormous amounts of data.

More recently, the design of pharmacoepidemiologic studies has turned to using big data. No matter the size of study subjects, the most challenging aspect of pharmacoepidemiology is its research design as with clinical trials. The place of "chance" that may lead statistically significant difference, "Bias" by systematic error, and "Confounding" as a third factor associated with both drugs and events, all may contribute to a direct association between drugs and events, which should be considered when designing the research plan and considering their results. Studies on drug safety are often performed further in the post-marketing phase observationally. Because, a double-blind trial to verify whether a serious adverse event will occur to a patient can be ethically dubious as patients cannot be denied an approved effective medicine, and in order to mitigate weakness and strengthen observational studies, pharmacoepidemiological researches inevitably consider new designs. In this academic domain, study designs and statistical techniques have been evolved, such as self-controlled case series, new user design, etc., handling bias and confounding that are classic and common in cohort and case-control studies. Frequently used study designs in pharmacoepidemiology are described further in the regulatory guidelines and the academic proposals [27–29].

New designs seem to be developed and used mainly for retrospective observational database studies. For the question of interest, there is still needs to conduct a traditional epidemiological study design for post-approval, phase IV study. As with the example of Brigham and Women's Hospital epidemiological studies, it may be necessary to plan for a cohort study to assemble from the beginning of development. Recently, many large-scale databases are becoming available and it is prudent to first make use of them. When choosing a database, you should make sure that prescription records, event data, and health-related information, such as gender and age, are available. If you can reconcile patient ID, separate databases may be combined. However, this requires epidemiological knowledge and experience.

3.4. Much to do in the post-marketing phase to fully develop and define a medicine's properties and potential

Based on the principle of ICH E2E, risk management plans have become a part of a new drug approval document to be submitted to the regulatory authorities in many countries/regions.

Most of the processes for evaluating ADRs are similar in the pre- and post-authorization phases, although differences are found in data source for evaluation which impact on the quality and meaning of an adverse event case. One of the significant differences is that the spontaneous reporting system plays a critical role in post-authorization for both qualitative and quantitative analysis, especially for the identification of potential safety issues as soon as possible. This requires the process for quality management of spontaneous reporting so that spontaneous reporting to be improved [30].

One of major challenges of ICSR reporting is its quality variation over time and between different geographical regions, depending on reporting cultures and regulations. This means it is to be expected that the databases of aggregated ICSRs can vary between countries/regions and indicate different drug-event combinations as safety signals. To illustrate these differences, a comparison study was performed on ICSRs databases between the United States and Japan, namely, FDA Adverse Events Reporting System (FAERS) and Japanese Adverse Drug Event Report (JADER) [31]. The ICSR elements and their definitions defined by ICH have been implemented by countries/regions. It is expected that a case should be recorded in the same manner in different countries, however, not in reality. In the study, although both databases limitedly open the data elements, there were discrepancies in the type of reported AEs, reported drugs, reporter type, seriousness, and average number of reported events per case, between the JADER and FAERS. For example, the average number of AEs per case was 1.6 (SD = 1.3, max = 37) in the JADER and 3.3 (SD = 3.5, max = 62) for the Japanese cases in the FAERS; "drug exposure during pregnancy," "no adverse events," and non-serious cases are present in FAERS, but as these are not mandatory for electronic submission in Japan, few reports from non-professionals were found in the JADER.

These differences are mostly due to regulations and customs. In addition to these, social factors and healthcare systems also have a considerable impact. Interstitial lung disease (ILD) is an example of how an AE can be differently reported in Japan based on social-induced reporting bias. Japan has experienced serious social concerns with ILD related to several drugs and simultaneously, diagnosis with x-ray imaging is available in Japanese clinics and hospitals so it would appear that ILD could be more efficiently detected than other countries. Coding rules also may affect ICSRs data, because medical terminologies of ICSRs are submitted using codes inputted by a reporting company, where the company culture may have been embedded in the process so that bias may arise. All these unresolved biases threaten internal and external validity of the ICSR databases.

Nevertheless, the ICSR database is still very useful for review in the post-approval phase. It gives an opportunity to detect any safety signal (a combination of a medicine and an event considered to require more detailed examination) that would require a closer scrutiny. Collecting individual cases in the post-approval phase is said to be particularly suited for capturing suspected cases of serious and rare adverse drug reactions; however, if healthcare professionals, especially physicians, do not report the event, the potential safety risk cannot be noticed. In order to complement this, those who evaluate actively post-marketing data are extending their activities to include looking for signals from a large amount of information, which is out of scope of this chapter.

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Data management and statistical methods draw attention to the need to press forward by improving the efficiency of data analysis. However, it is hard for database analyses to identify issues such as dependency problems of medicines such as benzodiazepines and many delayed side effects unless they are flagged as a safety problem by patients' complaints in the first place through spontaneous reporting.

4. Remaining issues and the future for pharmacovigilance

4.1. Characteristics of phase IV studies

Phase IV studies, either interventional or observational studies, have to be appropriately designed, according to the purpose/hypothesis about drug efficacy, effectiveness, or safety. To say that "the medicine is safe" in regulatory science means that the probability of hazard is low and acceptable, as compared to the disease to be treated and the benefit expected by the drug. In that sense, the safety concerns of the marketed drug are always linked to the benefit of the drug which has been accepted in the approval process. Unlike "efficacy" review, observational studies prevail in drug safety due to ethical reasons. Clinical trials are designed to reduce a statistical erroneous conclusion that efficacy exists when it really does not (Type I error). It defines "efficacy" to be tested, and statistical analysis is planned on the basis of a single hypothesis of the efficacy, thus the testing of multiple hypothesis within a single study is discouraged. However, there are a lot of potential types of ADRs that would be inappropriate to examine in a randomized trial. This is another reason for using surveillance to catch any signs of hazard and using prospective/retrospective longitudinal observational studies and pharmacoepidemiological database studies to assess the occurrence of ADRs. In addition, population-based design is of significance to compensate limited generalizability in clinical trials. "Effectiveness" in real-world clinical settings of a drug is scrutinized normally by non-interventional study or trial where the drugs are prescribed as per usual based on the terms of a drug marketing license. Definition of "effectiveness" may be prone to chance of subjective variation of the prescribing physician, which would make designing a study difficult.

Some registration systems provide an overview of clinical trials and studies: purpose, study type, intervention, recruitment criteria, etc. One such system in regulatory use is ClinicalTrials.gov, where information on phase II to IV studies of drugs, biological products, and medical devices regulated by the FDA is submitted [32–34]. Approximately 20,000 phase IV studies, over a half of which were interventional, have been registered in ClinicalTrials.gov; among over 250,000 studies in 203 countries, noticeably, registered phase IV studies include studies without drugs and observational studies [35, 36]. Those interventional studies examine various aspects of efficacy, pharmacodynamics, pharmacokinetics and other pharmacological aspects. Safety is often focused along with efficacy as described above, and 4392 of 4722 safety studies were aimed at efficacy as well as safety from 2004 to 2014. Of those which were interventional studies, 226 (68.5%) of them recruited less than 300 patients. Again, from a public health view point of generalizability, safety profile cannot be efficiently informed through clinical studies alone.

4.2. Utilizing and making sense of new data sources

Real world data (RWD) refers to all the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources [37]. They are collected under day-to-day circumstances and not through international trials with a control or comparative group. This means data are outside the controlled constraints of conventional randomized clinical trials. Especially occurring in the post-approval setting, the data can be used to evaluate what happens when a medicine is used in normal clinical practice. Such data can arise from a number of sources, not only in the clinical settings, but also social settings. Therefore, RWD can be found in electronic health records (EHRs), claims and billing activities, product and disease registries, patient-related activities in out-patient or in-home use settings, health-monitoring devices and even blogs if possible [38]. In addition, RWD can include data on outcomes (both clinical and patient-reported), resource use (medical institutions, patient, and societal), treatment pathways, service models, patient preference, experience, and compliance. Secondary research data derived from routinely collected data is also applicable. Real-world evidence in drug development is, in turn, the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from the analysis of all of this RWD.

RWD and RWE may not be the best thing for collecting efficacy data, and interventional trials are essential and inevitable to prove efficacy of medicinal entity. The methodology to utilize RWD would elaborate the better use of RWD for the monitoring of safety information in the post-approval phase to add further information on benefit-risk balance [39]. As of today, the majority of studies with RWD are safety-focused, and real-world pharmacovigilance is one of the main drivers currently for collection of RWD for many companies, based on post-authorization requirements for safety evaluation in real-world patients. It is reported that registries, in the form of a cohort study, have not sufficiently enrolled participants [40], and it should bear in mind that any type of data source has difficulties and limitations in collection and quality of its data.

4.3. Necessity of pharmacovigilance for the development of pharmaceuticals

Access to new therapies in oncology has depended on the results of post-approval RWD. There are some drugs approved based on progression-free survival using Kaplan-Meier survival analysis with no difference in overall survival time. Can the data of progression-free survival really support a clinically meaningful effect of anticancer drugs? Would not data about the overall survival period be better? It may be agreed with regulators that data on the overall survival time derived from post-approval observational research be evaluated with the results fed back to healthcare professionals through updates to the package insert, etc. Such an approach may well lead to increase in utilization of conditional approvals.

Beginning with imatinib, the development of molecular-targeted drugs and utilization in clinical practice became popular especially in the twenty-first century. However, it has been noted in recent years that many genetic mutations are present in the signal transduction system and from this scientist can more easily predict outcomes concerning effectiveness and safety. Even though we cannot fully clarify molecular targeted drugs at the time of approval, research for confirming gene mutation should continue to be recommended after marketing by using

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companion diagnostic agents often as personalized medicine. As the tragedy of thalidomide was one milestone, the lessons learned after gefitinib's marketing in Japan can be considered a further milestone for molecular targeted drugs. Gefitinib was the second molecular-targeted drug that was launched in Japan ahead of the world in July 2002 based on the approved indication of lung cancer. Some years later, it was confirmed that the effectiveness is valid for small cell lung cancer patients with EGFR gene mutation (L858R or Exon 19 deficiency), and that the mutation of the ATP binding site is more common in Oriental women such as Japan and China [41]. In terms of safety, many adverse reaction cases of Interstitial Lung Disease were reported at the time of clinical trials, but the mechanism of action that caused such an adverse reaction had not yet been elucidated.

However, there remains a huge question about the feasibility for a company being obliged to obtain even more data during development by investing in post-marketing safety studies and effectiveness studies. In recent years, regulatory authorities have streamlined reviews for approval, such as FDA's Accelerated Approval Program, and there are increasing numbers of applications requiring post-approval safety measures at the time of approval. It is considered as one possible solution to replace conducting many phase IV studies and in vitro studies with utilizing RWD, as described above. However, it should be noted that profiles of each database vary so much that they produce different results even if you study with the same objective, for example, pioglitazone [42]. Therefore, it is necessary to sufficiently clarify the risk minimization actions in a RMP, and to keep these in mind when choosing a database for quantitative assessment.

5. Conclusions

Pharmacovigilance can be defined as a multidisciplinary science consisting of systematic activities and processes relating to the detection, assessment, understanding, and prevention of adverse effects or any other problems related to medical healthcare products and their handling throughout their lifecycle, thus mitigating risk and maximizing benefits for patients. These activities include those required to monitor and assess a quality system embedded in a just and fair culture that facilitates reporting, communication, and organizational learning to demonstrate that the system is performing according to guiding safety principles agreed by all stakeholders. What has been learned from the history of various medicines is that the balance between benefit and risk can change from time to time based on the obtained experience and information, and that taking multiple approaches to a certain safety research objective can often result in different answers. Therefore, pharmacovigilance is a challenging and evolving multidisciplinary science that has to be applied logically throughout drug lifecycle. This chapter presented what are available in practice to assess and profile safety with a central aspect of adverse drug event/reaction throughout the development phase to the post-marketing phase.

Conflict of interest

No potential conflict of interest was reported by the authors.

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