Part III

Sources of Data for Pharmacoepidemiology Research

Part IIIa

Spontaneous Reporting

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Postmarketing Spontaneous Pharmacovigilance Reporting Systems

Gerald J. Dal Pan[1], *Marie Lindquist*[2], *and Kate Gelperin*[1]

[1] *Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA*
[2] *Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden*

Potential signals for adverse drug reactions (ADRs) or adverse drug effects most often arise from postmarketing spontaneous case reports, which are collated and analyzed by drug safety experts, evaluated as clinical case series, and considered for potential regulatory action. These efforts are not possible without input from dedicated health professionals and other concerned stakeholders. Adverse events (AEs) thought to be potentially drug related may be reported by a consumer or a health professional to a drug's manufacturer, or they may be reported directly to a health authority through programs such as MedWatch or EudraVigilance [1,2]. In addition, case reports and case series with valuable clinical details may be published in a peer-reviewed journal [3]. Concerned stakeholders – health professionals as well as consumers – are the source of the signals that can trigger hypothesis generation, hypothesis testing, and appropriate regulatory action when needed to protect the public from unnecessary risks or harms. At times, a drug causal association may seem clear due to strong temporal association between exposure to the product and onset of an adverse effect, or when there is confirmation of positive rechallenge (i.e., signs or symptoms resolve when exposure is stopped but recur when reintroduced). But more often, causality assessment is challenging (see Chapter 29), and well-designed pharmacoepidemiology or clinical studies are needed to assess the signal [4,5].

In the United States, the Food and Drug Administration (FDA) issues Drug Safety Communications (DSCs) to alert the public about emerging safety issues, such as investigations into potential safety signals that may alter the balance of therapeutic benefit and risk for a medical product [6]. Recently, the FDA launched a new web portal that enables the public to view summary charts and listings of deidentified cases from the FDA Adverse Event Reporting System (FAERS), a compilation of all postmarketing adverse event (AE) reports received by the FDA [7].

In recent years, the term "pharmacovigilance" has become widely used to denote postmarketing

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safety activities, and is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems" [8].

Monitoring and understanding the safety of drug and therapeutic biologic products is a process that proceeds throughout the product's life cycle, spanning the period prior to first administration to humans through the entire marketing life of the product. Throughout the product life cycle, astute clinical observations made at the point of care constitute an important source of information. While new technologies have enabled more thorough knowledge of a drug's actions, and computerized databases have enabled large-scale, population-based analyses of drug safety investigations, these advancements are adjuncts to, and not substitutes for, careful, well-thought-out clinical observations.

Preapproval drug safety assessment includes animal toxicology and pharmacologic studies, first in humans studies (Phase I), proof-of-principle studies for the disease or condition under study (Phase II), and confirmatory studies of safety and efficacy (Phase III). In each of these stages of drug development, important drug safety information is obtained.

In the preapproval review process, regulatory authorities review these safety data, along with data on the product's efficacy, to determine if the anticipated benefits of the drug are likely to outweigh any risks with its intended use. In the US, as part of the approval process, the FDA reviews the professional labeling (package insert), to ensure that the product's uses and risks are explained adequately.

Although the preapproval testing of a drug is typically rigorous, and the review of the data is thorough, there are still inevitable uncertainties about the complete safety profile of a drug when it is brought to market. Several factors contribute to these uncertainties. First, the number of patients treated with the drug prior to approval is limited, generally from several hundred to a few thousand. Second, patients in clinical trials tend to be carefully selected for inclusion in these trials, and are thus more clinically homogeneous than patients treated in the course of clinical practice once a drug is marketed. Compared to patients in clinical trials, patients treated in clinical practice may have a broader range of co-morbidities, take a wider variety of concomitant medications, and have a wider clinical severity spectrum of the underlying disease being treated. Third, additional populations of patients, such as children or older adults, who may not have been studied in large numbers in premarketing clinical trials, may be treated with the product once it is marketed. In addition, marketed drug products are often used for diseases or conditions for which they are not indicated, or at doses outside the approved range. Because of this "off-label use," patients treated in clinical practice are more diverse than those treated in clinical trials. For these reasons, a postmarketing drug pharmacovigilance reporting system is necessary.

Description

Adverse Events and Adverse Drug Reactions

A key concept in pharmacovigilance is the distinction between the closely related, but nonetheless distinct, concepts of *adverse event* and *adverse drug reaction*. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2D guideline on Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting defines an adverse event as follows [9]:

> An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can

> therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

The same guideline describes an adverse drug reaction as follows:

> All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.
>
> The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a possibility.
>
> A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. If an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction [9].

The principal difference between an adverse event and an adverse drug reaction is that a causal relationship is suspected for the latter, but is not required for the former. In this framework, adverse drug reactions are a subset of adverse events. In some countries, postmarketing pharmacovigilance reporting systems are focused on adverse drug reactions, while in others data on adverse events are collected. In the United States, for example, the scope of reporting requirements is "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug related …" [10].

While many of the principles discussed in this chapter apply equally to adverse events and adverse drug reactions, it is important to understand the distinction between these two concepts. Specifically, some databases may contain only adverse drug reactions, while others may contain adverse events. These databases may behave differently when used for data mining. However, because many of the principles of drug safety surveillance apply to both adverse events and adverse drug reactions, we will use the term "AE/ADR" to refer to these two terms collectively in this chapter, for convenience. When needed, we will use the individual terms if a distinction between the two is required. Although the medical literature may sometimes erroneously use these terms interchangeably, there has been increasing attention to the distinction [11].

The Concept of Spontaneous AE/ADR Reporting

A core aspect of pharmacovigilance is the voluntary reporting of AEs/ADRs either directly to established national or regional centers, or alternatively to pharmaceutical manufacturers, who in turn are obligated to report pertinent information to regulators. National reporting systems are typically run by regulatory agencies (e.g., the US FDA runs the MedWatch program) [1] or by centers designated by the health ministry or the drug regulatory authority. In a few countries, the national pharmacovigilance center is run by a university or other scientific body. In the United States for example, AEs/ADRs in individual patients are generally identified at the point of care. Patients, physicians, nurses, pharmacists, or anyone else who suspects that there may be an association between an AE/ADR and a drug or therapeutic biologic product are encouraged to, but are generally not required to, report the case to either the manufacturer or the FDA.

This system of AE/ADR reporting is often referred to as a spontaneous reporting system; "spontaneous" because the person who initially reports the AE/ADR to either the reporting center or the manufacturer chooses what events to report. Sometimes, spontaneous reporting systems are also labeled as "passive," based on the argument that the reporting

center or manufacturer passively receives this information rather than actively seeking it out. However, this term does not do justice to the proactive way in which many pharmacovigilance centers seek to operate, even if resource constraints often limit the ability to interact adequately with reporters. Moreover, "spontaneous reporting" does not fit well with the reporting situation of today, when most countries have introduced or enacted legislation which mandates reporting from pharmaceutical companies. Reporting may also include canvassed or stimulated reporting of suspected reactions of particular interest.

Underlying the concept of a spontaneous postmarketing AE/ADR pharmacovigilance reporting system is the notion that clinical observations made at the point of care are often valuable pieces of information in further refining the knowledge of a drug's safety profile. This is an important, though frequently underemphasized, idea.

First, after approval, when formal study often ends and marketing of the medicine begins, there is often no further systematic way to continue the study of a medicine's safety, or even to generate drug safety hypotheses. While scientific advances and access to new data sources (e.g., electronic healthcare records) may provide some opportunity to monitor the safety of a marketed medicine, these alternative approaches to safety signal detection remain unproven. Such sophisticated methods are not widely used in many regions, and when used, may cover a limited number of drugs and outcomes. In contrast, existing pharmacovigilance reporting systems apply to all marketed medicines and are relevant to most drug safety issues of interest.

Second, when healthcare professionals, patients, and consumers want to make notification of a potentially adverse effect of a medication, it is useful for this information to be systematically organized, stored, and analyzed. A reporting system fills this need. If such information were not systematically collected, potentially valuable data about medicines would be lost.

Third, this system implies an important role for healthcare professionals in postmarketing safety assessment. Although the practices and systems for healthcare professionals to report AEs/ADRs vary from region to region, the quality of reports is always dependent on the details provided by these professionals.

Spontaneous Reports and Solicited Reports

Another key concept in understanding the contents of a pharmacovigilance database is the distinction between a "spontaneous report" and a "solicited report." While many pharmacovigilance databases are often referred to as "spontaneous report databases," the reports in them are often a mix of spontaneous and solicited reports, as well as reports from other sources. The differences between these two types of reports can explain the quantity and quality of reports in a pharmacovigilance database, and often can explain important distinctions between pharmacovigilance databases.

The ICH E2D guideline on Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting defines a spontaneous report as follows [9]:

> A spontaneous report is an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization (e.g. WHO, Regional Center, Poison Control Center) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme. Stimulated reporting can occur in certain situations, such as notification by a "Dear Healthcare Professional" letter, publication in the press, or questioning of healthcare professionals by company representatives. These reports should be considered spontaneous. Consumer adverse reaction reports should be handled as spontaneous reports irrespective of any subsequent "medical confirmation".

> Regulatory Authorities might require medical confirmation for the purpose of expedited reporting. Emphasis should be placed on the quality of the report and not on its source. Even if reports received from consumers do not qualify for regulatory reporting, the cases should be retained.

Several features of this definition are worth noting. First, by requiring that the report be directed to a pharmaceutical company, regulatory authority, or other organization responsible for surveillance of the adverse effects of medicines, the definition implies, but does not explicitly state, that the reporter specifically intended to report a suspected adverse drug reaction. However, in current practice, most pharmacovigilance reporting systems do not consider the reporter's intent when determining if a report is a spontaneous report. For example, a patient who has been on a chronic daily medicine for hypercholesterolemia for many years may contact that medicine's manufacturer to ask if there are any known drug interactions between that medicine and another product, such as an antiinflammatory agent that may have been recently prescribed for a sprained ankle after a sports injury. The intent of the call was to seek information, not to report a suspected adverse drug reaction. Nonetheless, this report meets the definition of a spontaneous report, at least in those systems in which adverse events, and not only adverse drug reactions, are collected. The consideration of stimulated reports as spontaneous reports is consistent with this logic.

Second, and importantly for pharmacovigilance systems that require reporting of adverse events and not only adverse drug reactions, the definition does not require a causality assessment. For the purposes of meeting adverse event reporting requirements, ICH E2D notes that "spontaneous reports associated with approved drugs imply a suspected causal relationship" [9]. It is important to note that this implied causal relationship is for the purposes of regulatory reporting, and need not represent a scientific or medical conclusion.

Third, the requirement that the report not derive from a study or an organized data collection scheme necessitates existence of another category of report to describe adverse events occurring in clinical trials, other studies, and certain organized programs sponsored by pharmaceutical companies that may collect data on adverse events. CIOMS V (Council for International Organizations of Medical Sciences) recognized the need to describe those adverse event reports derived not only from formal clinical trials or other studies, but also from the increasing number of company-sponsored programs, such as marketing programs and patient-support programs, that promote interaction between the company and patients – and thus the chance for companies to learn about adverse events [12]. CIOMS V proposed the idea of "solicited" reports, which was formalized in ICH E2D as follows [9]:

> Solicited reports are those derived from organized data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance. Adverse event reports obtained from any of these should not be considered spontaneous.
>
> For the purposes of safety reporting, solicited reports should be classified as study reports, and therefore should have an appropriate causality assessment by a healthcare professional or an MAH. Further guidance on study-related issues, such as managing blinded therapy cases, can be found in the ICH E2A guideline.

Unlike its recommendation for spontaneous reports, ICH E2D recommends that solicited reports be subjected to a causality assessment

for regulatory reporting; in general, only those serious adverse events deemed causally related are to be reported. ICH E2D also notes other types of adverse event reports, such as reports from the medical literature, reports from the internet, reports a company obtains in accordance with contractual relationships with another company, and reports a company receives from a regulatory authority. The first two types are considered unsolicited (though not spontaneous) while the latter two are considered solicited [9].

The CIOMS [12] and ICH E2D [9] efforts were initiated to provide a framework for regulatory reporting of adverse events, and many jurisdictions have incorporated the ICH E2D principles in their directives, regulations, guidelines, and guidance documents. While a discussion of regulatory reporting requirements is beyond the scope of this chapter, an understanding of the distinction between spontaneous reports and solicited reports is important because it is essential to understanding the contents of a pharmacovigilance database. For example, if a pharmaceutical company contributes the majority of reports to a particular pharmacovigilance database, that database can be expected to have more solicited reports, as well as spontaneous reports that result from interactions between the company's sales force and healthcare professionals, than a pharmacovigilance database whose reports are derived mainly from hospital-based pharmacovigilance centers. The distinction may also be important in the comparison of adverse event reports between two products in the same pharmacovigilance database. For example, in a single pharmacovigilance database, there may be more adverse event reports for a product that is actively promoted and marketed (and thus has a large sales force and one or more patient-focused marketing programs) than a product for which such an extensive marketing program is not in place.

Overview of Pharmacovigilance Reporting Systems

The goal of a postmarketing, or postapproval, safety program is to identify drug-related AEs or ADRs that were not identified prior to approval, to refine knowledge of the known adverse effects of a drug, and to understand better the conditions under which the safe use of a drug can be assured.

The scope of pharmacovigilance is broad. The core activity is usually the identification of previously unrecognized AEs/ADRs with use of the drug. However, it is not sufficient simply to note that use of a drug can lead to an AE/ADR. Rather, an investigation into not only the potential causal role of the drug in the development of the AE/ADR, but also the conditions leading to the occurrence of the AE/ADR in one person or population and not in others must be the focus of any postmarketing drug safety effort. Factors such as dose–response relationships, drug–drug interactions, drug–disease interactions, drug–food interactions, and the possibility of medication errors must be carefully considered.

A full understanding of the factors that can lead to an AE/ADR may yield ideas for effective interventions to minimize the severity or occurrence of the AE/ADR, and thus enhance the safe use of the drug. For this reason, the approach to detecting and understanding clinically important AEs/ADRs in the postmarketing period must be as comprehensive as possible.

The identification of a new safety issue with a medicinal product often begins with a single observation. Such observations may arise from animal studies, chemical studies and assays, or observations of human experience with the medicine. In the postmarketing period, such observations are usually clinical observations, often made at the point of care in the course of clinical practice. A practitioner or patient notes the development of symptoms or signs that were not present, or were present in less severe form, prior to the patient's using the medicine.

If this sign or symptom is not listed in the product's approved labeling, patients and healthcare professionals may not think to attribute it to the medicine. If further evaluation reveals a clinically significant process (e.g., liver injury, rhabdomyolysis, agranulocytosis), it is important to keep in mind the possibility of a side effect due to a medication in the differential diagnosis of the event. If a medication side effect is not included in the differential diagnosis, a potential association between a medicine and previously unrecognized side effect will not be made, and the patient may not be treated appropriately. If, on the other hand, the practitioner believes the medicine played a role in the development of the new clinical findings, he or she can forward relevant clinical information to either the medicine's manufacturer or to a drug regulatory authority, such as the FDA in the United States or other national or regional authorities, as appropriate.

In the postmarketing period, the investigation of AEs/ADRs is a multidisciplinary effort. The analysis of a complex AE/ADR can involve the fields of medicine, pharmacology, epidemiology, statistics, pharmacy, toxicology, and others. There are several methods of clinical postmarketing safety assessment. These include the review of case reports and case series from spontaneous reporting systems, a wide variety of types of observational epidemiologic studies, and clinical trials. This chapter will focus on spontaneous pharmacovigilance reporting systems. No one method is *a priori* better than another in all settings. Rather, the choice of methods depends on the particular safety question to be answered.

Spontaneous AE/ADR reports have at times served as a necessary and sufficient basis for regulatory actions including product withdrawals. For instance, in August 2001 the manufacturer of cerivastatin withdrew the drug from marketing based on "a markedly increased reporting rate of fatal rhabdomyolysis" compared to the other drugs in the statin class [13]. Additional confirmation of the unacceptably high risk of rhabdomyolysis with cerivastatin was eventually available three years later when results of a well-designed epidemiologic study were published [14]. Clearly, that time frame would have been far too long to delay decisive action, which in retrospect was soundly based on the signal from spontaneous reports. The timely detection of this signal would not have happened without the efforts of the point-of-care clinicians who took the time to report rhabdomyolysis when it occurred in their patients. Some drug safety experts have argued that decisive action could have been taken even earlier based on clinical trial data with a higher unapproved dose of cerivastatin, coupled with early postmarketing experience [15].

Patient Reports and Healthcare Professional Reports

Spontaneous adverse event reports, by their nature, originate at the point of care. While some pharmacovigilance systems were once restricted only to reports from healthcare professionals, there has been growing recognition of the importance of reports from patients, and many systems now accept patient-generated reports. For example, Italy, Denmark, the Netherlands, and Sweden have accepted patient reports since the early 2000s, while Australia has accepted them since 1964 [16]. The United States, which has accepted adverse event reports from consumers since 1969, developed the MedWatch program [17] in 1993 to facilitate adverse event reporting from both patients and healthcare professionals. Nonetheless, as recently as 2012, some countries with highly developed regulatory systems were not actively collecting patient reports. Of 50 countries with developed drug regulatory systems surveyed in 2013, 44 had direct patient reporting systems, 17 of which were started in 2012 or 2013 [16].

There is no internationally recognized definition of a "patient report." ICH E2D defines a "consumer" as "a person who is not a healthcare professional such as a patient, lawyer, friend, or

relative of a patient" and notes that "consumers" can submit adverse event reports [9]. Of note, in 2016 approximately 1.7 million reports were entered into the US FAERS; consumers were the source of about half (845 355) of these reports, the majority of which were submitted via pharmaceutical companies [7].

Despite initial skepticism about the value of patient reports [18], there is growing evidence that they are valuable because they often contain more detail than reports generated by healthcare professionals and can serve to complement those reports [19]. A study of the United Kingdom's Yellow Card system, which allows for AE reporting by both healthcare practitioners and patients, found that reports generated by patients had a higher median number of suspected adverse drug reactions per report compared to those generated by healthcare professionals, had a higher median word count, had more detailed information about symptoms, and more description of the emotional and social impact of the adverse event [20]. A study comparing adverse event reports submitted by patients and those submitted by healthcare professionals to the Dutch National Pharmacovigilance Center Lareb found that reports from patients were comparable to those from health professionals for the purpose of causality analysis [21]. Similarly, a recent UMC-Lareb collaboration assessed the contribution of patient reports to global signal detection in VigiBase, and concluded that patient reports provide unique information valuable in signal assessment, and recommended their inclusion in signal detection processes [22].

In addition to their value in describing adverse drug reactions, patient reports contribute to signal detection. A study of signals sent from the Dutch National Pharmacovigilance Center Lareb to the Dutch Medicines Evaluation Board found that the number of patient reports that contributed to a signal increased from zero in 2003 to 31 in 2008, and that the proportion of patient reports contributing to signal generation equaled their proportion in the database [23]. In one pharmaceutical company's AE database, signals were detected earlier when patient reports were included, compared to when only reports from healthcare providers were included [24]. Experience in the UK Yellow Card system suggests that, when analyzed separately from healthcare professional reports, patient reports may generate additional signals based on disproportionality [25].

Given the potential importance of patient reporting, efforts have been made to both encourage and simplify it. In 2012, the World Health Organization published a guide for countries to use in setting up a reporting system for the general public [26], which recommends that a patient reporting system ideally be established in the setting of an existing spontaneous reporting system. The reporting form for patients may be a dedicated patient-reporting form or the same form used by health professionals, but it should be understandable by a layperson. Education of the public on the importance of patient reporting as well as training of pharmacovigilance staff in the assessment of patient reports are other elements of the WHO guideline.

At the national level, a law passed in the US in 2008 required pharmaceutical manufacturers to include the following statement in direct-to-consumer advertising: "You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/safety/medwatch, or call 1–800–FDA–1088." This statement, however, did little to increase patient reporting of adverse events. In a sample of 123 drugs, the average monthly increase following the implementation of this statement was 0.24 reports per drug [27]. More recently, in 2013, the FDA introduced a consumer-friendly adverse event reporting form [28], following the introduction of which patient reporting increased by 36% [29].

Because most AE/ADR reporting systems rely on healthcare professionals, patients, and consumers to submit reports voluntarily, it is

generally recognized that there is substantial underreporting of AEs/ADRs via current systems. Two survey-based studies conducted in the US in the 1980s, one in Maryland [30] and the other in Rhode Island [31], examined physician reporting to the FDA and concluded that fewer than 10% of AEs/ADRs were reported to the FDA. These studies were conducted prior to the development of the current MedWatch program [1] in 1993, and do not consider the contribution of reporting from sources other than physicians.

Calculating the proportion of adverse event reports that a reporting system receives requires that the true number of AEs/ADRs in the population be known. For most AEs/ADRs, this number is not known or readily available. In some cases, however, data are available that allow an estimate of the extent of reporting to be calculated. For example, the extent of reporting to the FDA of cases of hospitalized rhabdomyolysis associated with statin use was estimated [32] using a projected estimate of the number of such cases in the US and comparing it to the number of reports of statin-associated hospitalized rhabdomyolysis in the FAERS, a database that houses the FDA's postmarketing adverse event reports. The projected national estimate was obtained by using incidence rates from a population-based cohort study, and applying those rates to national estimates of statin use. Across four statins (atorvastatin, cerivastatin, pravastatin, and simvastatin), the estimated overall extent of AE reporting was 17.7%. For individual statins, the estimated extent of reporting ranged from 5.0% (atorvastatin) to 31.2% (cerivastatin). Further analysis revealed that the high proportion of reporting of cerivastatin cases was driven by reports received after the dissemination of a Dear Healthcare Professional letter notifying physicians of the risks of cerivastatin-associated rhabdomyolysis. The estimated extent of reporting was 14.8% before the letter and rose to 35.0% after. It is important to note that the results of this study apply only to reporting cases of statin-associated rhabdomyolysis. The extent of reporting for different drug-event pairs will be different, and cannot be estimated from the results of this study.

Once reports are received by national pharmacovigilance centers, they are entered into AE/ADR databases. These databases can then be inspected for drug safety signals, which form the basis of further study, necessary regulatory action, or both.

Report Characteristics

The individual case report is the fundamental unit of a postmarketing pharmacovigilance reporting system. The extent to which such a reporting system can address specific drug safety questions depends, in large part, on the characteristics and quality of the individual reports. Specific report formats differ across jurisdictions, though many countries and regions collect information compatible with the ICH E2B format. The updated electronic messaging standard ICH E2B (R3) [33] specifies both administrative and product identification information, as well as information on the case. The standard is designed to work with a variety of national and international systems and incorporates endorsement of standards by participating standards development organizations such as the International Standards Organization (ISO), Health Level Seven (HL7), European Committee for Standardization (CEN), and Clinical Data Interchange Standards Consortium (CDISC) to enable wider interoperability across the regulatory and healthcare communities. Although potentially comprehensive in scope, the format also allows for limited data to be submitted. The principal domains of case information in the ICH E2B standard include patient characteristics, reaction(s) or event(s), results of tests and procedures relevant to the investigation of the patient, drug(s) information, and a narrative case summary and further information.

Regardless of the specific formatting requirements across jurisdictions, there are some fundamental components of an individual safety report that are important for a thorough review.

Product identification, in as much detail as possible, is essential for an assessment of a case report. For pharmaceuticals, the identification of the active ingredient(s) is critical to product identification. However, other factors can also be important, depending on the specific safety question. For example, the formulation of the product can be important, as certain active ingredients may be present in a variety of formulations. Many opioid agents come in oral, injectable, and transdermal formulations. Because the pharmacokinetic and other pharmaceutical properties can differ across these formulations, information on the formulation is important in determining if there are formulation-specific effects, including those that may result from medication errors. Additionally, if the drug safety question involves the assessment of an AE/ADR related to a product quality defect, information on both manufacturer and lot/batch number can be very important, as product quality problems typically involve specific lots from an individual manufacturer.

Reports describing medication errors, or the potential for medication errors, ideally contain information on the product involved, the sequence of events leading up to the error, the work environment in which the error occurred, and the type of error that occurred [34].

Characteristics of a good-quality case report have been published [33,34]. As discussed below, these characteristics include adequate information on product use, patient characteristics, medical history, and concomitant treatments, and a description of the AE/ADR, including response to treatments and clinical outcome. Our experience, based on many years of reviewing case reports, is that while a substantial amount of useful clinical information can be written in a succinct narrative, most narratives are incomplete, many to the extent that they are uninterpretable. While follow-up with the reporter is sometimes feasible for drug safety analysts during case review, this has been the exception rather than the rule, often due to resource constraints. Incomplete and uninterpretable case reports limit the effectiveness of postmarket pharmacovigilance reporting systems. Attempts to improve the systems will need to address the problem of poor case report quality rather than merely increasing the number of reports. Unfortunately, it is not unusual for the FDA to receive potentially important spontaneous reports which cannot be evaluated because of missing key information. For instance, 13 (2%) of a total 675 reports of hypersensitivity AEs/ADRs associated with heparin administration during an investigation of tainted heparin were excluded from an analysis of AERS data because the reports were "not interpretable" [35].

Information on product use should include the start date(s), stop date(s), doses, frequency of use, and indication for use. Dosage information is important in exploring dose–event relationships. Duration of use is important for characterizing the time course of AEs/ADRs relative to initiation of product use. Indication for use is also an important piece of information, as many products are used for more than one indication (either on-label or off-label). Certain AEs/ADRs may be related to specific indications. Alternatively, concomitant medications and other factors related to one indication but not others may confound interpretation of the AE/ADR. For these reasons, indication for use is an important element of a case report.

Patient information should include age, gender, medical history, and concomitant medication usage. The presence of factors that could confound the relationship of the drug to the AE/ADR, especially elements of the medical history and concomitant medication usage, are critical to the interpretation of individual case safety reports.

A description of the AE/ADR that allows for independent medical assessment is critical. A simple listing of coded diagnostic and procedure

terms is generally insufficient for adequate assessment of the report. A narrative of the event that includes the temporal relationship of drug usage to the development of the AE/ADR, the clinical and diagnostic features, the clinical course, any measures instituted to treat the AE/ADR, the response to these measures, and the clinical outcome are all essential components of a high-quality case report. Results of laboratory tests, imaging, and pathology results facilitate an independent interpretation of the report. Information on dechallenge (the resolution of the AE/ADR when the medication is withdrawn) and rechallenge (the redevelopment of the AE/ADR when the drug is reintroduced), if available, can be invaluable.

Social Media

Social media are a range of computer-based technologies that allow the creation and sharing of information, ideas, photographs, and other messages via electronic communication. User-generated content is a defining feature of social media. This content can be made available to others via computer-based networks that connect one user with other users or groups to form social networks. Depending on privacy settings, which in some cases may be chosen by the user, the user's content may be widely available to other users or it may be restricted to only certain users or groups. Given the widespread use of the internet and, to a lesser degree, of social media for health-related topics, there is interest in whether social media can be a source of drug safety signals or otherwise shed light on adverse drug reactions [36]. Because social media posts describe individual experiences, they can, in theory, describe adverse reactions to medicines. The use of social media for pharmacovigilance presents both opportunities and challenges [37,38].

With an estimated 2.5 billion users of social media worldwide [39], including in parts of the world where formal pharmacovigilance programs are not highly developed, social media have the potential to be a source of patient- and consumer-generated information about adverse events [37]. The ability to tap into this potential source of information is especially relevant given the growing importance of, and attention to, patient- and consumer-generated reports in pharmacovigilance.

The challenges of identifying drug safety signals in social media include all those inherent in traditional spontaneous reporting systems (e.g., underreporting, duplicate reports, lack of relevant details, and stimulated reporting) as well as additional ones posed by the unique features of social media. These latter challenges include the general lack of structure of social media posts, the often informal nature of writing, the use of "street names" for established pharmaceuticals without corresponding use of standard brand names or active ingredient names, the use of slang or other informal language to describe symptoms or other medical concepts, and the diffuse audiences in social media. A further challenge is that while there are millions of social media posts, only a small percentage will concern adverse drug reactions. These challenges might be expected to pose more problems in large general social media sites than in smaller, health-related social media sites. For example, a study using the general social media site Twitter to identify adverse drug reactions found that of 10 822 tweets that mentioned a drug of interest, an adverse drug reaction, determined by expert annotation, was present in approximately 1200 [40]. By contrast, a similar study based in the health-related social media site DailyStrength found that approximately 24% of posts that mentioned a drug also mentioned an adverse drug reaction [41].

In traditional adverse event reporting systems, data are entered using a structured format, such as the ICH E2B standard, and drug and adverse event information are coded using standard dictionaries and terminologies. Importantly, data collection methods in these traditional systems

usually are designed to collect relevant information and have the final data structure in mind. Social media do not share these characteristics. Because most social media posts do not concern drugs or drug-related adverse events, techniques to identify adverse events in social media must first identify mentions of drugs, and then must further identify mentions of drug–adverse event pairs. Once these pairs are identified, further analyses can begin.

The use of social media for pharmacovigilance is an area of active research to address these challenges [38]. Current research focuses on the use of natural-language processing and other techniques, such as supervised machine learning, to identify drug-related adverse events in social media [42]. One of the biggest challenges in this regard is the distinction of drug mentions associated with an adverse event from those with no association to an adverse event, a task complicated by the fact that though the former group is the relevant one, it is usually notably smaller than the latter group.

Another area of research is determining the utility of social media in pharmacovigilance. In 2014, the Innovative Medicines Initiative (IMI), a public–private partnership between the European Union and the European Federation for Pharmaceutical Industries and Associations, launched WEB-RADR: Recognising Adverse Drug Reactions to develop new technical tools to facilitate the detection and analysis of potential adverse drug reactions in social media sites. It also aimed to develop a mobile phone app for the reporting of suspected ADRs to regulatory authorities in the European Union (in the context of traditional adverse event reporting). One of several planned outgrowths of these efforts is the establishment of a regulatory framework for social media mining for adverse drug reactions [43].

Preliminary results of IMI WEB-RADR, based largely on analyses of posts in Twitter, suggest that some medicines receive more attention in social media relative to their frequency in VigiBase, while others receive much less. Individual Twitter posts were deemed to be not valuable, perhaps due to Twitter's character length restrictions; however, combining information from multiple posts generated by the same user was not examined [44]. Preliminary recommendations from IMI WEB-RADR for a regulatory framework note that data from social media should be treated as a "secondary use of data," the use of social media for signal detection and validation should be optional, reporting of individual case safety reports of adverse drug reactions from social media sites should not be required, and follow-up with social media users should not be required. Rather, drug manufacturers should include insights gained from social media regarding the safety of their products in the product's periodic safety update report or risk management plan [45]. In conclusion, more work is needed to refine the methods of extracting and analyzing data from social media for detection of adverse drug reactions.

National Pharmacovigilance Systems

The organization of postmarketing safety reporting systems and national pharmacovigilance systems varies around the world. The fundamental feature is that health professionals, and in some cases patients or consumers, are encouraged to send reports of AEs/ADRs to one or more specified locations. These locations can be the drug regulatory authority, an academic or hospital-based pharmacovigilance center (often working with or on behalf of a drug regulatory authority), or the drug manufacturer. The roles of these institutions vary from country to country, and depend greatly on the regulatory and national drug monitoring system in the country.

In low- and middle-income countries, with varying regulatory infrastructure, the focus in pharmacovigilance has been different from that in the more affluent parts of the world. Reports can result from counterfeit and substandard

drugs, known ADRs and drug interactions of concern to reporters, and ADRs resulting from medical error. In some countries, responding to queries about adverse reaction incidence, diagnosis, and management is a major part of the work of pharmacovigilance centers. In developing countries, there are often deficiencies in access to up-to-date information on drug safety that need remedying. On the other hand, large donations of new drugs to combat the endemic scourges of malaria, HIV/AIDS, tuberculosis, infestations, and other diseases, along with vaccines, have led to the high priority of monitoring their use for both safety and efficacy.

However, in many low- and middle-income countries there is currently not enough capacity for effective drug safety monitoring, and the improved access to new medicines adds additional strain on already overburdened or nonexistent pharmacovigilance systems. A survey from 2010 of pharmacovigilance systems in low- and middle-income countries found that seven of 55 responding countries indicated that they had no designated system in place, and fewer than half of the respondents had a budget for pharmacovigilance [46]. Consequently, lack of funding was mentioned as a hindrance to the development of pharmacovigilance, together with lack of training and a culture that does not promote AE/ADR reporting. Suggested key developments included training for health workers and pharmacovigilance program managers; active surveillance methods, sentinel sites and registries; and better collaboration between pharmacovigilance centers and public health programs, with a designated budget for pharmacovigilance included in the latter.

The WHO is now working together with major donor organizations to address the urgent need for capacity building in low- and middle-income countries. The strategy is focused on sustainable development, covering not only the implementation of reporting systems, technical support, and training of healthcare professionals, but also improvements in governance and infrastructure to support pharmacovigilance activities in the broader context of regulatory systems strengthening.

The perceived responsibility of healthcare professionals to report AEs/ADRs often varies around the world. Because the largest gaps in drug safety knowledge are believed to be for recently approved medicines, most countries emphasize the need to report AEs/ADRs, even less serious ones, for this group of medicines. For example, in the United Kingdom, recently approved drugs containing new active ingredients are marked in the British National Formulary with a black triangle [47], a symbol used to denote a product whose active ingredient has been newly licensed for use in the UK. In some cases, drug products meeting certain additional criteria are also marked with a black triangle, even if the active ingredient has been previously approved. The aim of the black triangle program is to prompt health professionals to report all suspected adverse reactions associated with the use of these products. In some countries, it is mandatory for physicians and dentists to report cases of suspected adverse drug reactions to the regulatory authority. Most countries, however, do not have such specific programs or requirements, but health professionals are encouraged to report and the national reporting centers provide general advice to health professionals on what events to report.

In a majority of countries, including countries in the ICH regions, other high-income countries, and 33 of 55 low- and middle-income countries responding to a 2008 survey [46], pharmaceutical companies that hold marketing authorizations are obligated to report AEs or ADRs to the regulatory authority. In some countries, the event is reportable only if an attribution of causality has been made. In other countries, the event is reportable even if no attribution has been made. For example, in the United States, pharmaceutical companies are required by law to submit spontaneous reports

of AEs/ADRs, regardless of attribution of causality, on an expedited basis if they are serious and unexpected. The AE/ADR is considered serious [1] when the patient outcome is death; life-threatening; hospitalization (initial or prolonged); disability; congenital anomaly; or requires intervention to prevent permanent impairment or damage. Periodic reporting of other types of AEs/ADRs, such as those considered serious and expected (labeled), or nonserious, is typically required as well. The periodicity of such aggregate reports is determined by the length of time the drug has been marketed, with increased frequency for newly approved drugs, and decreased frequency (e.g., annual) with older drugs.

While spontaneous reports of AEs/ADRs usually originate initially from the point of care, the more proximal source of reports coming into the national pharmacovigilance centers may vary from country to country. In countries outside the ICH regions, the majority of reports are received directly from physicians in hospital and in general practice. Cumulatively over the past 40 years, most reports in the ICH region have come from the point-of-care initial reporter via the pharmaceutical companies to the regulatory authority; however, in several EU countries (e.g., all the Nordic countries), reports coming directly from health professionals to the regulatory authority greatly exceed company reports during this period. The patterns are likely to change towards a higher proportion of company reports in those many countries where pharmaceutical companies are legally obliged to report AEs/ADRs. Some countries restrict reports to those received by physicians. Other countries accept reports from pharmacists, nurses, and patients. There is a current trend towards encouraging direct patient or consumer reporting, replacing the notion held by many in the past that such reports would not be a reliable and useful source of information.

In most countries, the national pharmacovigilance center is part of the drug regulatory authority; in some, the monitoring is carried out jointly by the drug regulatory authority/Ministry of Health and an independent institution. In Germany, the Federal Institute for Drugs and Medical Devices (BfArM) maintains a joint database for recording reported adverse drug reactions, together with the Drug Commission of the German Medical Profession. According to the professional code of conduct of physicians in Germany, all adverse drug reactions should be reported to the Drug Commission. In The Netherlands, the practical responsibility for postmarketing surveillance is shared between the Medicines Evaluation Board (MEB) and the Netherlands Pharmacovigilance Centre (Lareb). The MEB handles communications with market authorization holders; the role of Lareb is to process and analyze reports from health professionals and patients.

Decentralized drug monitoring systems exist both within and outside the ICH region. In France, the French Medicines Agency coordinates the network of 31 regional centers that are connected to major university hospitals. In the UK, there are four regional centers connected to university hospitals which have the special function of encouraging reporting in their regions. The reporting system in China involves 31 regional centers reporting to the National Center for Adverse Drug Reaction Monitoring in the China Food and Drug Administration (CFDA). In India, the Pharmacovigilance Programme of India has been in operation since 2010, with the Indian Pharmacopoeia Commission (IPC) running the National Coordinating Centre. The system is now operating nationwide, with 250 local monitoring centers in medical institutes.

National and International Postmarketing Safety Databases

Once submitted to the national drug safety monitoring program, individual case safety reports are stored in computerized postmarketing safety databases. Many national drug regulatory

authorities have databases which include suspected AE/ADR reports derived from a postmarketing reporting system, as well as reports from other sources, such as the published medical literature, and sometimes certain types of serious adverse events (e.g., those considered by a clinical investigator to be potentially caused by a study drug) from clinical trials. Examples of national reporting systems and databases include the Blue Card system (Australia), Canada Vigilance (Canada), the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) database (Canada), the French Pharmacovigilance Spontaneous Reporting System database (France), the Adverse Drug Reaction Information Management System of the Pharmaceutical and Medication Devices Agency, Ministry of Health, Labor, and Welfare (Japan), the Lareb database (Netherlands), the BiSi database (Sweden), the MHRA ADR database (United Kingdom), the FDA Adverse Event Reporting System (FAERS) database (United States), and the Vaccine Adverse Event Reporting System (VAERS) database (United States). In addition, there are two international reporting and database systems: EudraVigilance [2] in the European Union (run by the European Medicines Agency, EMA) and VigiBase [48] pooling data from the more than 120 member countries of the WHO International Drug Monitoring Programme (run by the Uppsala Monitoring Centre, UMC). VigiBase is also the system used as the national database by around 70 pharmacovigilance centers around the world; reports are stored directly in VigiBase but entered, managed, and analyzed remotely through an internet-based data management tool, VigiFlow.

To understand the results of an analysis of individual case reports from a postmarketing safety database, it is necessary to understand the unique features of the database, as each large postmarketing safety database differs from the others. It is necessary to understand if, and how, the data are coded. Many databases code drugs according to a local or national standard drug dictionary, while others use a standard international dictionary, such as WHODrug [49]. Similarly, many databases code individual AE/ADR reporter verbatim terms which describe the AE/ADR according to a standard medical dictionary, such as the Medical Dictionary for Regulatory Activities (MedDRA) [50]. In the ICH regions (Europe, Japan, and the United States), use of MedDRA is mandatory for coding of AEs/ADRs.

Beyond coding, several other features of the database are important to understand. First, does the database include only reports from postmarketing systems, or does it include reports from other sources, such as the medical literature or clinical trials? Second, does the database include reports only from health professionals, or does it also include reports from patients and consumers? Third, what is the range of medical products included in the database – drugs, biologics, blood, blood products, vaccines, dietary supplements? Fourth, does the database include reports from only one country or region, or does it include reports from regions outside the jurisdiction of the regulatory authority? Fifth, does the database include both "nonserious" and "serious" AEs/ADRs; if so, what proportion of the reports have been classified by the health authority (or other database manager) as serious? Sixth, does the database include all adverse events (i.e., events which may or may not be judged to be causally related to a medicine) or does it include only adverse drug reactions (i.e., events for which a likely causal relationship has been determined prior to entering the report into the database)? Seventh, how many individual case reports are in the database? Each of these factors is important in determining the utility of a particular database in answering a specific drug safety question.

Detecting Signals from a Postmarketing Safety Database

The impetus to use a postmarketing safety database to evaluate the potential relationship of an AE/ADR to a drug may come from various

sources. For example, postapproval animal studies may suggest that a certain AE/ADR may be associated with a drug. The finding that a particular member of a drug class is associated with a specific adverse effect may prompt a search for the same reaction in other members of the class. Publication of case reports or case series, or unanticipated safety findings from ongoing clinical trials can be important sources of new safety questions for a marketed product. These stimuli for more intensive review of AE/ADR reports are external to the database.

Identifying potential associations of AEs/ADRs to drugs using only information within the database involves the detection of signals. According to the WHO, a signal is "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously" [51]. While there have been many definitions of a signal put forth over the years, the important underlying principle is that a signal is a hypothesis that calls for further work to be performed to evaluate that hypothesis. Signal detection is the act of looking for or identifying signals from any source.

In the setting of a relatively small number of reports, review of groups of reports or periodic summaries of reports has been a standard method of signal detection. For example, one could look at a list of all reports in which the outcome was "death" to see if this outcome was reported more frequently for some drugs than others. Summaries based on specific organ class toxicities could be reviewed to examine whether reports in one system organ class were proportionately more frequent for one drug than others. These methods depend on the ability of a drug safety specialist to recognize new or unusual patterns of case reports. While an astute specialist can identify signals using this method, this manual review is often neither practical nor reproducible for detecting signals from large postmarketing safety databases, some of which contain several million records.

In an effort to address this challenge, data mining techniques have been applied to pharmacovigilance AE/ADR databases. In broad terms, data mining refers to a process of analyzing data to find patterns. In the case of AE/ADR databases, most of these patterns would not be visible without the use of statistically based, computerized algorithms. A variety of specific algorithms have been applied to safety signal detection in AE/ADR databases (see Chapter 27) [52,53].

The fundamental feature of data mining techniques used to analyze adverse event databases is that each is based on finding "disproportionalities" in data; that is, the finding that a given AE/ADR is reported for a particular drug more often than would be expected based on the number of reports of that AE/ADR for all other drugs in the database. Several features of these methods are worth noting.

First, the methods are transparent. While the total number of reports for a drug varies over time (and may be highest in the first few years of reporting), this temporal trend will not necessarily alter the proportion of specific reactions for the drug. Thus, a given reaction may still be found to be disproportionately reported even as the total number of reports for the drug changes.

Second, these methods rely exclusively on reports within the database; no external data are needed. For this reason, understanding the characteristics of the database, as discussed above, is important. This feature has several consequences. Because the expected number of reports of a specific AE/ADR for a given drug (and thus the disproportionality of the drug–event pair) depend on the reports within the individual database, the degree of disproportionality for a given drug–event pair may vary from one database to the next. In the extreme, a given drug–event pair may have a strong signal of disproportionality in one database and no such signal in another. A second consequence is that as the background information for all drugs in the database changes, so does the expected number of reports of a specific AE/ADR for a given drug (and again the disproportionality of the drug–event pair).

Third, a signal of disproportionality is a measure of a statistical association within a collection of AE/ADR reports (rather than in a population), and it is not a measure of causality. In this regard, it is important to underscore that the use of data mining is for signal detection – that is, for hypothesis generation – and that further work is needed to evaluate the signal.

Fourth, the absence of a signal of disproportionality in a postmarketing safety database is not evidence that an important AE/ADR is not associated with a particular drug.

Data mining is sometimes done using a subset of an AE/ADR database; for example, a portion of the database limited to a specific class of drugs might be used to find relative differences in the frequencies of specific AEs/ADRs across the class [54]. Some of the data mining techniques used in pharmacovigilance have included the proportional reporting ratio, the reporting odds ratio, the Bayesian Confidence Propagation Neural Network (BCPNN), and the empirical Bayes method (also known as the Gamma Poisson Shrinker or the Multi-item Gamma Poisson Shrinker) [55]. As part of the IMI, a public-private partnership in Europe, the EMA established the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI PROTECT) with a goal of conducting research to develop and test new tools for the benefit–risk assessment of marketed drugs. A range of signal detection algorithms were compared across seven spontaneous reporting databases, with no method found to be better than the others. Findings were inconsistent across databases. The choice of signaling criteria had a greater impact on signal detection performance than the choice of disproportionality methods [56,57].

Review of Case Reports

The review of individual case reports of AEs/ADRs is a complex process that has been described elsewhere [58,59,60]. It typically begins by identifying one or more case reports with the outcome of interest. Because the case reports that form a case series often come from disparate sources, it is usually necessary to develop a case definition. The case definition centers on the clinical characteristics of the event of interest, without regard to the causal role of the medicine whose relationship to the adverse event is being investigated. Once a case definition is established, each report is reviewed to determine if the event meets the case definition and if the report is to be included in the case series. Depending on the specific question(s) to be answered by the case series, other exclusion criteria may also apply. For example, one would always exclude a case in which the report suggests that the patient never took the medicine of interest. In other cases, one may restrict the case series to only certain formulations of the medicine (e.g., include case reports in which an intravenous formulation, but not an oral formulation, was used, if such exclusion is appropriate for the question at hand), or to certain age groups (e.g., limit the case series to only case reports describing the suspected adverse events in pediatric patients, if such exclusion is appropriate for the question at hand), or to certain indications for use (e.g., limit the case series to case reports in which the medicine was used for a certain off-label indication, if such exclusion is appropriate to the question at hand). Exclusion criteria for a case series must be carefully considered so that potentially relevant cases are not excluded, and all available information is fully assessed. In general, if the purpose of the case series is to examine the relationship between a medicine and a suspected AE/ADR that has not been previously associated with it, it is best to err on the side of inclusion to avoid missing clinically relevant, though incomplete, information about cases of interest.

Once the case series has been developed, it is next necessary to review each case report individually to determine whether there is a

plausible causal relationship between the medicine and the adverse event. At the level of the individual case report, it is often difficult to establish with certainty that the medicine caused the adverse event of interest (see Chapter 29) [61,62,63]. For example, if the AE/ADR of interest is already common in the population that takes the medication, establishing a causal role for the medicine in the development of the condition is generally not feasible using individual case reports or case series. For example, the incidence of Parkinson disease is much higher in persons over age 60 years than it is in persons below that age [64]. In this situation, review of a report describing a myocardial infarction in a 70-year-old patient on an antiparkinsonian agent will generally not be informative in determining if the agent played a causal role in the development of the myocardial infarction, as myocardial infarction occurs commonly in this age group. Similarly, review of a case report is not likely to shed light on the causal relationship between a medicine and an AE/ADR when the AE/ADR is a manifestation of the underlying illness which the medicine is treating. For example, review of case reports of worsening asthma in patients taking an antiasthma medication is not likely to be sufficient to establish a causal link between the worsening asthma and the medication.

Review of a case series to establish a causal relationship between a drug and an AE/ADR is most straightforward when the suspected AE/ADR: (1) is rare in the population when the medication is not used, (2) is not a manifestation of the underlying disease, (3) has a strong temporal association with drug administration, and (4) is biologically plausible as a drug reaction or is generally the result of a drug reaction based on other clinical experience. Examples of AEs/ADRs that often meet these criteria are acute hepatic failure, aplastic anemia, agranulocytosis, rhabdomyolysis, serious skin reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis, and certain arrhythmias, such as torsades de pointes.

The approach to assessing the causal role of a medicine in the development of an AE/ADR has evolved over recent decades. In general, the approach relies on a systematic review of each case report to ascertain the temporal relationship between drug intake and development of the adverse reaction, an assessment of any coexisting diseases or medications that could confound the relationship between the medicine and the AE/ADR, the clinical course after withdrawing the drug (dechallenge), and the clinical course after reintroduction of the drug (rechallenge), when applicable. Naranjo and colleagues described a method based on these general principles for estimating the likelihood that a drug caused an adverse clinical event [65]. The WHO has developed a qualitative scale for categorizing causality assessments [66].

In the development of a case series, once the individual cases are reviewed, it is important to integrate the findings across the cases to determine patterns that may point to a relationship between the drug and the AE/ADR. For example, does the AE/ADR appear at some doses but not at others? Does the AE/ADR appear after one or a few doses, or does it appear only after a more prolonged exposure? Is the spectrum of severity of the event homogeneous or heterogeneous? Are certain co-morbidities or concomitant medications more likely to be present in patients with the event? In the review of a case series, there are no prespecified answers to these questions that establish or exclude the possibility that the drug led to the AE/ADR. Rather, the characteristics of the individual cases, taken together with the patterns observed in the case series itself, can lead the analyst to determine if the medication has a reasonable possibility of causing the condition of interest.

Reporting Ratios

Because postmarketing safety reporting systems do not capture all cases of an event of interest, it is not possible to calculate an incidence rate for

a particular drug–event pair. However, analysis of AEs/ADRs based simply on numbers of reports, even after thorough analysis of these reports, does not in itself put these reports into the context of how widely a medicine is used.

To adjust for the extent of drug utilization in a population in the analysis of AE/ADR reports, a reporting ratio can be used. A reporting ratio is defined as the number of cases of a particular AE/ADR reported to a drug safety database during a specific time period divided by some measure of drug utilization in the same time period. Across drugs, the reporting ratios measure the relative frequency of the AE/ADR reports adjusting for differences in level of drug utilization. The numerator is derived from counts of AE/ADR reports associated with the drug of interest that are recorded in the postmarketing safety database during a specified time period. In the past, the denominator typically consisted of the number of dispensed prescriptions, used as a surrogate measure of drug exposure in the population over that same time period, and often estimated from proprietary drug utilization databases. The number of dispensed prescriptions was used because data on the number of unique individuals using the drug in a specified time period were generally not available.

More recently, such data have become available, and reporting ratios based on persons using the medication, and not prescriptions, are being calculated. In some cases, information is available on not only the number of persons receiving the drug or the number of prescriptions dispensed, but also on the duration of use. When such data are available, the denominator for the reporting ratio may be expressed in person-time. When using denominators based on person-time, it is important to be mindful of the assumptions of the person-time method, especially the assumption that events in the numerator occur uniformly over time. Because AEs/ADRs may not occur uniformly over time after a drug is started, this assumption does not always hold.

Because the reporting ratio (sometimes referred to as "reporting rate") is not a measure of incidence or prevalence, it must be interpreted cautiously. For AEs/ADRs that are rare in the general population (e.g., aplastic anemia), reporting ratios are sometimes compared to the background rate (incidence or prevalence) of that event in a defined population. In other situations, individual reporting ratios of a particular AE/ADR across different drugs used for a similar indication or within the same class are calculated and the magnitude of the differences in reporting ratios is compared. Interpretation of the comparison of reporting ratios across drugs must be undertaken with caution, since such comparisons are highly sensitive to variation in AE/ADR reporting and thus it is necessary to consider the differential underreporting of AEs in the postmarketing safety reporting system. The underlying assumption in estimating reporting ratios for comparison across a group of drug products is that each of the respective manufacturer's reporting practices for the drug of interest is similar over the reporting period. However, this assumption may not hold true in some cases, and a comparison of reporting ratios across drugs may not be valid.

Strengths

Signal Detection

The principal strength – and, arguably, the principal purpose – of a postmarketing safety reporting system is that it allows for signal detection, the further exploration of drug safety hypotheses, and appropriate regulatory decision making and action when necessary. As noted earlier in this chapter, signals can be detected by data mining methods, review of individual case reports, or assessment of case series. In many instances, further work is needed to determine with more certainty the relationship of the drug to the AE/ADR. The

capability for timely and effective signal detection is a key strength of a postmarketing pharmacovigilance reporting system.

Another key strength of a well-designed and effectively utilized postmarketing pharmacovigilance reporting system is that, in certain cases, the relationship of a drug to an AE/ADR can be established with sufficient confidence, usually by a case series, that necessary regulatory action can be taken. AEs/ADRs for which the relationship to a drug can be established with reasonable certainty are generally those that have a strong temporal association with drug administration, a low or near absent frequency in the underlying population, are not part of the underlying illness being treated, are generally the result of exposure to a drug or other toxin, and have no other likely explanation. Aplastic anemia, agranulocytosis, acute liver failure, rhabdomyolysis, certain arrhythmias such as torsades de pointes, and serious skin reactions such as Stevens–Johnson syndrome are examples of adverse events whose relationship to a drug can often be established by case series [67,68,69]. However, relative to all signals detected in a postmarketing safety reporting system, those about which a reasonably firm conclusion can be made on the basis of AE/ADR reports alone are few in number.

Opportunity for the Public to Report AEs/ADRs

Postmarketing safety reporting systems allow healthcare professionals to report suspected AEs/ADRs to national pharmacovigilance centers, drug regulatory authorities, and/or manufacturers. Such systems allow for direct engagement of healthcare professionals in the drug safety monitoring system. The advantage of this involvement is that it allows for careful clinical observations, made at the point of care, to inform drug safety surveillance. Clinicians can provide succinct but detailed accounts of relevant symptoms, signs, diagnostic test results, past medical history, concomitant medications, and clinical course of an AE/ADR, including information on dechallenge and rechallenge. Such a synthesis of clinical information is generally not available from automated data sources. For those AEs/ADRs that are serious, rare, and often the result of a medication exposure, the ability to obtain detailed information directly from the point of care is an essential feature of postmarketing pharmacovigilance reporting systems.

Postmarketing safety reporting systems also can accept reports from consumers and patients, though this practice is not a feature of all reporting systems. In the US, where consumers and patients can report either to the manufacturer or directly to the FDA, the percentage of reports in 2016 that originated from consumers was about 50% [7]. When consumer- and patient-generated reports do not contain sufficient medical detail for meaningful review, subsequent follow-up with health professionals may be possible in potentially important cases, so that more complete clinical information (e.g., hospital discharge summary) can be obtained.

Scope

The scope of a postmarketing safety reporting system is quite broad. The system can cover all medicines used in the population, and it can receive reports of AEs/ADRs occurring in any member of the population. Because it need not restrict the reports it receives, it can receive AE/ADR reports throughout a medicine's marketed life cycle. Thus, AEs/ADRs recognized late in a product's life cycle, such as those resulting from prolonged exposure to a medicine, can, in theory, be ascertained. In practice, such ascertainment is difficult to achieve, because healthcare professionals may be less likely to ascribe an AE/ADR not known to be associated with a medicine that has been marketed for several years. In addition, patients who take a medicine for several years may also receive other treatments during that

time, making it difficult to conclude that there is an association between the medicine and the AE/ADR.

Despite this broad scope, a postmarketing spontaneous reporting system can be relatively inexpensive. Most of these pharmacovigilance systems rely on voluntary reporting, and those who report AEs/ADRs are generally not paid. Thus, information collection is not expensive from the perspective of effective pharmacovigilance, given that the system has the capacity to handle all medicines and all outcomes. This is in contrast to other data used to study drug safety questions, such as data from clinical trials, registries, and electronic healthcare data, each of which is relatively expensive to operate.

Limitations

Quality of Reports

Perhaps the major potential limitation of a spontaneous postmarketing safety reporting system is that it depends quite heavily on the quality of individual reports. Although data mining and other informatics methods can detect signals using coded bioinformatics terms in safety databases, each individual case report must still be carefully reviewed by a clinical analyst to determine if there is a plausible relationship between the medicine and development of the AE/ADR. The quality of the report, as described earlier in this chapter, is critical for an informative and meaningful review. Report quality depends on the care, effort, and judgment of the person submitting the report, as well as the diligence of the person receiving and/or transmitting it to the health authority. Reports without sufficient information for an independent determination of the relationship between the medicine and the AE/ADR are problematic for drug safety surveillance. However, with successful follow-up, sometimes even such deficient reports can yield useful information.

Underreporting

Another well-recognized limitation of spontaneous postmarketing reporting systems is underreporting. Because most systems are voluntary, not all AEs/ADRs are reported. A consequence of underreporting is that population-based rates of AEs/ADRs cannot be calculated, because all such occurrences in the population are not reported and the extent of underreporting for any individual AE/ADR is not known. Reporting ratios, discussed earlier in this chapter, allow the reported number of AEs/ADRs to be put into the context of drug utilization, though this measure is not an incidence rate.

Nonuniform Temporal Trends in Reporting

Another limitation of spontaneous reporting systems is that temporal trends in the number of AE/ADR reports for a drug–event combination may not reflect actual population-based trends for that combination. This is because multiple factors can affect the number of AE/ADR reports received for a given drug–event pair.

First, the number of reports for a medicine is thought to peak in the second year after approval and decline thereafter, even though the drug may be used more widely. This phenomenon, known as the Weber effect, was originally described in relation to nonsteroidal antiinflammatory medicines [70]. A more recent analysis of reporting patterns for the angiotensin II receptor blocker class of medicines revealed no discernible trend when the number of reports over time was examined [71]. Specifically, this analysis did not confirm that the number of reports increased toward the end of the second year and declined thereafter. Rather, it indicated that additional factors, such as the approval of additional indications and modifications of the firms' reporting requirements, affected the total number of reports received. However, when the

number of reports in a year was adjusted for the number of prescriptions dispensed in that period, it was found that the adjusted number of reports was highest in the first years after approval and declined thereafter. The frequency of AE/ADR reports per estimated unit of drug utilization may not be constant over time, although a recent analysis of FAERS data for 62 drugs did not confirm a reporting pattern over time as described by Weber [72].

Second, publicity about an important new AE/ADR often gives rise to a large number of reports shortly after the publicity, with a decline in the number of reports shortly thereafter. This phenomenon is known as stimulated reporting and was observed, for example, in the reporting pattern of statin-induced hospitalized rhabdomyolysis after publicity of this risk. For these reasons, changes in the number of AE/ADR reports for a given drug–event pair cannot reliably be interpreted as a change in the population-based frequency of the AE/ADR.

Another limitation of a postmarketing reporting system is that it is usually not well suited to ascertaining the relationship of a medicine to an AE/ADR that is common in the treated population, especially if the condition is a manifestation of the underlying illness. In such cases, the combined effect of confounding of patient factors and indication makes causality assessment of individual cases difficult.

Finally, duplicate reports of the same AE/ADR may be received by drug manufacturers and health authorities and if undetected as duplicates, may be entered into the database as multiple occurrences of the same event. Algorithms have been developed and various methods can be used to identify such reports; nonetheless, this issue is a potential source of bias and limits the utility of data mining or other calculations which rely on "crude" case counts which have not been "deduplicated."

Particular Applications

Fingolimod

Fingolimod, a sphingosine-1-phosphate receptor modulator that reduces the number of lymphocytes in peripheral blood, is used to reduce the frequency of clinical exacerbations and delay the accumulation of physical disability in patients with relapsing forms of multiple sclerosis. When the product was initially approved in the US in September 2010, the product label noted a dose-dependent reduction in peripheral lymphocyte count of 20–30% of baseline values and warned of the risk of serious infections. Based on experience in premarketing clinical trials, the label described the specific risk of fatal herpetic infections in two patients who received a dose higher than the recommended dose for multiple sclerosis. The label also noted that while the overall rates of infections and serious infections were similar in fingolimod-treated and placebo-treated patients in clinical trials, bronchitis and pneumonia were more common in fingolimod-treated patients.

Approximately three years after approval in the US, a patient in Europe was reported to have developed progressive multifocal leukoencephalopathy (PML), a demyelinating central nervous system disease caused by the JC virus. PML is a rare disease; when it occurs, it is usually in the setting of immunosuppression. Because the patient in whom PML was reported had received prior immunosuppressants, the PML could not be conclusively linked to fingolimod. At the time this case was reported, approximately 71 000 patients worldwide had received fingolimod, according to the manufacturer.

Two years after the initial case report of PML, the US FDA announced that it had received two case reports of fingolimod-treated patients with no prior immunosuppressant treatment [73]. In the first case, a 49-year-old patient with a five-year history of multiple sclerosis was suspected to have PML when results of a routine magnetic

resonance imaging test (MRI) showed lesions, not present at the time fingolimod treatment was initiated, that were atypical for multiple sclerosis and more consistent with PML. The patient had prior treatment with interferon beta-1a and intermittent corticosteroids. Cerebrospinal fluid analysis was positive for JC virus DNA. Based on the MRI findings and cerebrospinal fluid analysis, a diagnosis of probable PML was made, in accordance with the diagnostic criteria of the American Academy of Neurology consensus statement [74].

The second case concerned a 54-year-old patient with a 14-year history of multiple sclerosis who had been taking fingolimod for 2.5 years when PML was diagnosed. The patient had previously been treated with interferon beta-1a for 11 years, and was then switched to treatment with fingolimod. At the time of the PML diagnosis, the patient had been receiving treatment with mesalazine for ulcerative colitis for four years. After 2.5 years of treatment with fingolimod, the patient developed walking instability, clumsiness, inattention, and somnolence. A brain MRI was suggestive of PML, and cerebrospinal fluid analysis was positive for JC virus DNA. Based on the symptoms, MRI findings, and cerebrospinal fluid analysis, a diagnosis of definite PML was made, in accordance with the American Academy of Neurology diagnostic criteria. On the basis of these two cases, the product label for fingolimod in the US was updated to include a warning for progressive multifocal leukoencephalopathy.

This example illustrates some important features of the analysis of individual case safety reports. First, individual reports can be used to establish a causal relationship between a drug and an adverse event when the adverse event is rare in the population. In this example, PML is extremely rare, and when it occurs, it is usually in the setting of immunosuppression due to treatment with certain medicines or certain malignancies. If PML occurred spontaneously (i.e., in the absence of these particular conditions) in the general population or in patients with multiple sclerosis, it would be quite difficult to establish a causal relationship between PML and fingolimod therapy. Second, detailed, though not necessarily lengthy, case reports are important for robust case analysis, and especially for causality assessment. The two case reports in this example included detailed information about prior and concomitant medications (none of which is known to cause PML). Without information on prior and concomitant medications, the uncertainty about exposure to immunosuppressants would have limited the conclusions that could be made from the case reports. Third, the inclusion of relevant clinical information used to establish the diagnosis of the adverse event allows reviewers of the case report to come to an independent conclusion about the diagnosis. In this case, the details of the diagnosis were applied to the published consensus-driven diagnostic criteria set forth by a professional society. While use of such criteria is ideal, formal, established diagnostic criteria are not available for all adverse outcomes of interest, and reviewers of individual case safety reports should establish their own criteria.

Finally, this example is unusual in that a causal relationship between a drug and a serious AE was established based on two individual case reports. Because establishing a diagnosis and evaluating causality are difficult with individual case safety reports, a higher number is usually needed.

Dabigatran

Dabigatran is an oral direct thrombin inhibitor approved in the US in October 2010 to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It was the first oral anticoagulant approved for this indication since warfarin had been approved for a similar indication. In the clinical trial that supported dabigatran's approval, 6076 patients were randomized to dabigatran 150 mg twice daily, and 6022 were randomized to warfarin

treatment. The rates of major bleeding were 3.3 per 100 person-years in dabigatran-treated patients and 3.6 per 100 person-years in warfarin-treated patients (hazard ratio 0.93, 95% confidence interval (CI) 0.81–1.07). The corresponding rates for life-threatening bleeds were 1.5 per 100 person-years and 1.9 per 100 person-years in the dabigatran and warfarin groups, respectively (hazard ratio 0.80, 95% confidence interval 0.66–0.98). Gastrointestinal bleeding was more common in dabigatran-treated than in warfarin-treated patients (1.6% vs 1.1%, hazard ratio 1.5, 95% confidence interval 1.2–1.9). In the first 14 months after dabigatran's approval, the US FDA received 2347 case reports of bleeding with dabigatran (348 with a fatal outcome), compared to 647 case reports of bleeding with warfarin (46 with a fatal outcome) [75].

On its face, this disparity in report numbers between the two agents suggested that dabigatran might be responsible for more bleeding in actual practice, a finding that was contrary to the preapproval observations. These numbers also raised the possibility of increased mortality with dabigatran relative to warfarin. A population-based analysis using administrative claims data, however, found that the rates of bleeding associated with dabigatran use were no higher than those associated with warfarin use [76]. A subsequent study using data from the US Medicare system found that, in actual practice settings, dabigatran was associated with a lower risk of ischemic stroke, intracranial hemorrhage and death and a higher risk of major gastrointestinal bleeding, relative to warfarin – findings that were consistent with those of the preapproval clinical trial data [77].

This example illustrates some important limitations concerning use of aggregate spontaneous report data to estimate population-based risk or relative risk of an adverse event between two drugs. A comparison of raw numbers of adverse event reports generally cannot be used to estimate the relative frequency of the adverse event in a population between two drugs. Population-based rates of an adverse event generally cannot be estimated from spontaneous reporting data because of underreporting and lack of a reliable measure of population exposure. Importantly, there often is a differential extent of underreporting of adverse events across a product's marketed life. Studies of adverse event reporting patterns of angiotensin receptor blockers and antiepileptic drugs have shown that, after adjustment for drug utilization, there were more adverse event reports in the first year after approval compared to subsequent years [71,78].Thus, even though a newly approved drug may not be widely used, there may be more spontaneous adverse event reports received for the newer drug compared to an older, widely used drug, even if there is no true difference in risk between them.

Peginesatide

Peginesatide, a novel synthetic peptide which was considered to be an important breakthrough for treatment of anemia in patients with dialysis-dependent chronic kidney disease, was withdrawn from marketing in 2012, within months of becoming commercially available, when the manufacturer received an unexpected number of case reports of fatal anaphylaxis [79]. Subsequent analyses suggested that the root cause of the reactions may have been a preservative present in the commercially available multiple-use vials but not in the single-use formulation that had been used exclusively in clinical trials [80,81].

Anaphylaxis, whether mediated by immunologic or nonimmunologic mechanisms, is a rare, unpredictable adverse reaction that can occur within minutes of exposure to an offending agent. Such reactions can alter the benefit–risk balance of newly approved drugs or biologics. Because fatal anaphylaxis is a rare occurrence with a strong temporal relationship between a triggering exposure and the onset of severe

symptoms, it represents a good example of the type of adverse drug reaction for which postmarketing spontaneous reporting systems are the primary means of timely signal detection. Although the decision to withdraw peginesatide from marketing was relatively swift, the results of subsequent nonclinical analyses suggesting an unexpected root cause illustrate the role of multiple data streams [82].

Drugs to Treat Attention-Deficit/ Hyperactivity Disorder

In other examples of postmarketing pharmacovigilance issues, spontaneous reports have provided actionable information about the clinical spectrum of adverse drug effects that may not have been well recognized in more restrictive clinical trial settings. An FDA safety evaluator became aware of several spontaneous reports describing psychiatric adverse events in otherwise normal children who were being treated with an extended-release formulation of methylphenidate for attention-deficit/ hyperactivity disorder (ADHD), and presented her findings at a Pediatric Advisory Committee meeting in June 2005. Committee members expressed concern, and a comprehensive evaluation of psychiatric adverse effects with drug treatments of ADHD was undertaken with the full cooperation of the drug's manufacturers. The results of the analysis were presented at a subsequent Pediatric Advisory Committee meeting in March 2006 and were also later published in a peer-reviewed journal [83]. Data were analyzed from 49 randomized controlled clinical trials. Results showed a total of 11 psychosis/mania adverse events which occurred during 743 person-years of double-blind treatment with the drugs of interest, compared to no similar adverse events during 420 person-years of placebo exposure in the same trials. Analysis of postmarketing spontaneous data yielded a total of 865 unique reports of psychosis or mania-type adverse events associated with these drugs. These findings were the basis for a MedWatch Alert in 2007, and for the addition of new warnings and medication guides for all of the ADHD drug treatments which were studied [84].

Medication Errors

The detection of medication errors is now an established area of pharmacovigilance [85,86]. An analysis of the EudraVigilance database revealed that between 2002 and 2015, a total of 147 824 cases of medication errors had been reported, with the annual number of such reports increasing throughout that period. Between 2010 and 2015, case reports of medication errors accounted for 1–2% of all reports in EudraVigilance [87].

For the purposes of pharmacovigilance, there is not an internationally accepted definition of a medication error. In the US, the National Coordinating Council for Medication Error and Reporting defines a medication error as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer" [88]. In the European Union, the Good Practice Guidance defines a medication error as "an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the patient." Regardless of the specific definition used, preventability is a key concept underlying the detection of medication errors. Careful analysis of case reports of medication errors can lead to changes in the design of a product, changes to its instructions for use, changes to carton or container labeling, or other changes aimed at reducing the frequency of preventable errors.

Because a medication error can occur at many points in the drug use process, attentive healthcare professionals, patients, and others can detect the error (such as a wrong drug or wrong dose) before it reaches the patient – a so-called "near miss." Thus, unlike case reports of adverse

events, which describe an adverse outcome associated with use of a medicine, a case report of a medication error describes a medication error along any point in the medication use process, whether or not the patient receives the medication or experiences harm. Analysis of case reports of medication errors focuses on the product(s) involved, the sequence of events leading up to the error, the work environment in which the error occurred, the personnel involved (healthcare professionals, patient, family, and others), the type(s) of errors that occurred, and other contributing factors. For these reasons, case reports of medication errors should include detailed information on these factors [34]. The Medical Dictionary for Regulatory Activities (MedDRA) [50] contains terminology for medication errors, which allows for both broad and narrow searches of reports of medication errors in pharmacovigilance databases.

For example, the antidepressant vortioxetine was approved in the US in September 2013 and carried the proprietary name Brintellix®. By June 2015, the US FDA had received 50 case reports describing medication errors in which the name Brintellix was mistaken for Brilinta®, the proprietary name of the antiplatelet agent ticagrelor. Review of the case reports indicated that the wrong medication was dispensed in at least 12 cases, though there were no reports of ingestion of the wrong medicine. The case reports also indicated that this medication error occurred both when prescribing the medication and when dispensing it. Based on analyses of the two proprietary names, the confusion was likely due to the drugs' having the same first three letters, being presented near each other in a computerized order entry system, lack of pharmacist familiarity with the recently approved medication Brintellix, and the drug names looking and sounding similar to each other.

Between the analysis of these cases and a subsequent regulatory action, the FDA received an additional five case reports of Brintellix being confused with Brilinta. In one case, the medical record of a patient undergoing a lung biopsy indicated that the patient was taking Brilinta but the medical staff confused it for Brintellix. Not aware that the patient was taking an antiplatelet agent at the time of the lung biopsy, the medical staff did not take the necessary precautions and the patient experienced bleeding and a collapsed lung. In May 2016, the FDA approved a change in the proprietary name from Brintellix to Trintellix [89].

Data Mining Signals

According to the UMC glossary of pharmacovigilance terms, a signal is "a hypothesis of a risk with a medicine, with various levels of evidence and arguments to support it" [8]. Signals are identified by UMC analysts from the WHO Global Individual Case Safety Report (ICSR) database (VigiBase) by applying a predefined triage algorithm (data mining). The disproportionality measure used by the UMC is the information component (IC), originally introduced through the BCPNN, which is a logarithmic measure of the disproportionality between the observed and expected reporting of a drug–event pair. A positive IC value means that a particular drug–event pair is reported more often than expected, based on all the reports in the database. Signals from VigiBase are reported quarterly in the Signal document, which is circulated in restricted fashion to national pharmacovigilance centers for the purpose of communicating the results of UMC evaluations of potential data mining signals from the WHO database. A recent analysis found that of 43 UMC signals disseminated between 2007 and 2010 for products with approved labeling, 15 (35%) were labeled, and eight of the labeled signals were subsequently updated after the signal communication, supporting the relevance of routine data mining [90].

Below is an example of a WHO program signal identified by data mining applied to the WHO Global Individual Case Safety Report Database, VigiBase.

Topiramate and Glaucoma

Topiramate was approved in the US in 1996 as an anticonvulsant drug [91]. In the second quarter of 2000, reports of topiramate and glaucoma in VigiBase reached the threshold of an "association" (i.e., the lower limit of a 95% Bayesian confidence interval for the IC exceeded zero). When potential signals are identified, the available information is reviewed by the UMC staff and an expert review panel. At the time, there were six cases reported to VigiBase. After review, a summary of the findings were circulated in the Signal document in April 2001 to all national pharmacovigilance centers in the WHO program. On September 26 the same year, the Market Authorization Holder issued a Dear Healthcare Professional letter warning about "an ocular syndrome that has occurred in patients receiving topiramate. This syndrome is characterized by acute myopia and secondary angle closure glaucoma." By August 17, there were 23 reported cases according to the company. The FDA issued a warning in the revised labeling on October 1, 2001 [91].

Signals from Developing Countries

At the annual meetings of the WHO program members, country representatives are invited to share problems of current interest in their countries. Below are two examples illustrating the kind of issues that have been investigated in developing countries, presented at the 2017 meeting in Uganda [92].

Blindness and Retinal Disorder Associated with Clomifene Citrate: Case Series Assessment

A case of retinal detachment with the use of clomifene citrate that caused irreversible blindness triggered an assessment by the Eritrean Pharmacovigilance Centre. A search of VigiBase identified 24 cases of blindness and retinal disorder. All cases were evaluated using Austin Bradford Hill considerations to assess the causal relation. In all cases, clomifene was reported as the sole suspected drug and in all but three cases, no concomitant drugs were reported. There were two cases of blindness in which the reaction abated with sequelae following withdrawal of clomifene. The conclusion was that the findings support a causal relationship and warrant further investigation to substantiate the signal [93].

Signal of Alpha-Chymotrypsin and Anaphylaxis

Alpha-chymotrypsin is a biological product commonly used in Vietnam for numerous conditions. The efficacy of the oral product was questioned because this product is a large molecule product and the potential for safety issues of the injectable form warranted an investigation. From the national spontaneous reporting database, significant signals related to hypersensitivity, including anaphylactic reactions (reporting odds ratio [ROR] 2.12; 95% CI 1.46–3.07). Since 2010, 249 reports were received nationwide, of which 65 cases were related to anaphylactic reactions, and this is approximately equal to all spontaneous reports related to alpha-chymotrypsin obtained from VigiBase. The National Centre sent an official letter to the Drug Administration of Vietnam, Ministry of Health to advocate a safety effectiveness revision for this product [92].

Deployment of Pharmacovigilance During Mass Drug Administration in Sierra Leone

The specific challenges for pharmacovigilance in a developing country during a public health emergency were illustrated by Wiltshire Johnson, Registrar and CEO of the Pharmacy Board of Sierra Leone during the May 2016 Uppsala Forum conference [94]. Pharmacovigilance during the Ebola crisis in 2014 meant not only the safety surveillance of experimental treatments, but also of products such as disinfectants, rubber gloves, and other equipment. Treatment of malaria, as well as pneumonia and diarrhea, became difficult due to the reluctance to seek medical help; many feared that the similarity of symptoms with Ebola would prevent them from returning home. The surveillance of the antimalarial mass drug administration

of over 5 million doses of artesunate-amodiaquine that needed to be rolled out during the peak of the Ebola outbreak stretched all capacity, but became a success story. In collaboration with the National Malaria Control Programme, the Pharmacy Board's National Pharmacovigilance Centre actively participated in real-time pharmacovigilance by going into the communities and searching for, identifying, and managing adverse events. The data analysis led to changing first-line treatment of malaria from artesunate-amodiaquine to artemether-lumefantrine [94].

The Future

Spontaneous AE/ADR reporting is an important component of drug safety surveillance. The widespread availability of electronic healthcare data may, at first, seem to undermine the importance of AE/ADR reporting. This is not likely to be the case. Because careful observation at the point of care is an essential component of pharmacovigilance, electronic systems may be able to facilitate AE/ADR reporting in the future but will not replace it. It is technologically and administratively feasible for carefully designed systems to allow clinicians to report AEs/ADRs directly from electronic medical record systems. If designed properly, these systems could allow for the accurate, complete, and efficient inclusion of laboratory, radiologic, and other diagnostic test results, information which is often incomplete in current AE/ADR reports. The challenge of such a system will be to encourage reporters to routinely provide a clinically meaningful narrative that explains concisely the clinical course of the AE/ADR and its relationship to medication usage.

There is also interest in using modern informatics techniques to facilitate review of adverse event reports, especially in large AE databases. For example, the use of natural language processing techniques is being explored to determine if they can identify individual case safety reports that warrant further evaluation, or individual case reports that suggest a causal association between a medicine and an adverse event. Postmarketing safety reporting systems depend on the involvement of healthcare professionals and, in some areas, consumers and patients as well, for high-quality AE/ADR reports.

As new medicines become available, it will be increasingly necessary to monitor postmarketing safety. Postmarketing safety reporting systems will continue to be the cornerstone of this effort, because of their unique advantages. As social media, active surveillance, and the use of large healthcare databases begin to play a role in drug safety surveillance, demonstrate their utility, and realize their potential, they could become valuable adjuncts to existing pharmacovigilance reporting systems worldwide.

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