Pharmacovigilance: The conscientious today for safe tomorrow

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ABSTRACT
Pharmacovigilance is the Science and activity relating to detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems. There are guidelines and regulations from the Council for International Organizations of Medical Science (CIOMS), the European Medicines Agency, the US Food and Drug Administration (FDA) and other that focus on pre-clinical, pre-marketing and post marketing safety evaluations. The roles of Pharmacist actually have and could have in collecting reports of adverse drug reactions (ADRs) and more widely in Pharmacovigilance. In this review, several ways are mentioned in which the pharmacist, both the community pharmacist and the hospital pharmacist, can contribute to the safe use of drug. In addition to their responsibilities regarding drug dispensing and compliance, they can have a substantial role in ADR reporting.

Keywords: Empirical Byes geometric mean, Pharmacovigilance and Pharmacoeconomics.

INTRODUCTION
Phase IV of the evaluation of a drug starts when the marketing license is granted and extend over many years. It consists of pharmacoepidemiological studies to evaluate the effectiveness, safety, and utilization of the drug in large populations, under real-life conditions. The results confirm or disprove the effectiveness of the drug in clinical practice (confirmation of the therapeutic effect), determine whether approved uses should be expanded or restricted, proved data on the incidence and clinical relevance of adverse events and untoward drug–drug interactions (Pharmacovigilance), and clarify the medico-economics consequences of introducing the drug (Pharmacoeconomics). Pharmacovigilance is particularly concerned with adverse drug reactions.\[^{[1]}\]

World health organisation (W.H.O) Technical Report No 498 (1972). An adverse drug reaction (abbreviated ADR) is an expression that describes harm associated with the use administration of a drug or result from the combination of two or more drugs. The meaning of given medications at a normal dosage. ADRs may occur following a single dose or prolonged this expression differs from the meaning of "side effect", as this last expression might also imply that the effects can be beneficial. The effects of a drug include Pharmacodynamic effects and side effects. Pharmacodynamic effects are the characteristic drug effects that are of interest for treating diseases; examples include an ability to decrease serum uric acid levels or to sup-press inflammation. Pharmacodynamic effects are documented in animal studies then in Phase I and Phase II studies in humans and finally in Phase III
clinical trials. Provided the dosage is adequate, they occur in all individuals. During drug development, the Pharmacodynamic effect that is of greatest clinical relevance is identified. Phase III trials are designed to measure the Pharmacodynamic effect (in the examples above, efficacy against gout or analgesia). Their results are used by regulatory agencies to define the clinical indications of the drug. Side effects stem from documented pharmacological properties of the drug that exist in addition to the selected Pharmacodynamic effect. Side effects may be beneficial or deleterious. For instance, H1 receptor antagonists prevent Motion sickness, and the alpha-adrenoceptor antagonist effect of imipramine antidepressants induces postural hypotension. A drug may also exert toxic effects, which occur in all individuals after exposure to an excessive dose. Toxicovigilance is the set of activities designed to detect and to investigate toxic effects. Pharmacovigilance, in contrast, focuses on adverse drug reactions (ADRs), Which are unwanted side effects, ADRs may occur whether or not the recommendations in the “Summary Product Characteristics” (SPC) are followed. They fall into four categories: category A (“Augmented”) effects reflect augmentation of the Pharmacodynamic properties of the drug (e.g. sedation with a muscle-relaxing benzodiazepine), Category B (“Bizarre”) effects are unrelated to known Pharmacodynamic properties (e.g. unwanted allergic reactions), category C (“Continuous”) effects occur in the long term (e.g. pharmacological dependency or rebound effect), and category D (“Delayed”) effects occur after drug discontinuation (e.g. cancer birth defects, or impaired reproductive capability). Pharmacovigilance is the study of ADRs. In Pharmacovigilance studies, ADRs are classified as expected (listed in the SPC) or unexpected. Pharmacovigilance studies are conducted not only on drugs (both old and new), but also on stable blood products (e.g. albumin, clotting factors, immunoglobulin’s, and biological glues), contraceptives, contrast agents, vaccines, and other products intended to Promote human health.

TRADITIONAL PHARMACOVIGILANCE METHODS
Post marketing drug surveillance has historically relied on data from clinical trials or epidemiological studies. Post-marketing “randomized controlled trials” (RCTs), such as the “Adenomatous Polyp Prevention on Vioxx” (APPROVe) trial that prompted the global withdrawal of Vioxx (rofecoxib) [3], are expensive and are not routinely powered to detect rare ADRs, those with a long latency or events occurring in specific (and often excluded) patient groups [4-7]. As such, epidemiological methods, such as spontaneous reporting systems (SRS), have long been recognized as useful tools in drug-safety monitoring. The Yellow Card scheme adopted in the United Kingdom more than 40 years ago has become an important detection system for prescribers, and now patients, to voluntarily report ADRs. Spontaneous reporting has proven useful for capturing ADRs occurring in the initial period after treatment; however, this method does not define the population from which reports arise (the “denominator”), leading to poor estimation of the incidence of ADRs especially in long-term drug use. Despite previous success of SRS schemes in identifying rare ADRs, some have questioned the future legitimacy of this method, citing its low position in the hierarchy of evidence and persisting problems of underreporting [4-8].

NEW APPROACHES TO STRENGTHEN PHARMACOVIGILANCE
Spontaneous adverse reaction reports
Spontaneous reporting of suspected adverse drug reactions relied traditionally on health care professionals but has been strengthened over recent years by broadening the reporter base, including to patients [9, 10]. Spontaneous reports are mainly used for hypothesis generation in a context of detecting signals of new or changing safety issues and this process can be made more efficient by screening large volumes of reports kept in databases using quantitative analysis. Early methods for quantitative signal detection used reporting rates derived from sales or prescriptions [11], but such denominators are not readily available. Recent methods are therefore based solely on spontaneously reported data using the concept of disproportionality of reporting and a derived measure, the “proportionate reporting ratio” (PRR), better known under its acronym, the PRR [12]. Measures of disproportionality quantify unexpectedness, as they look at whether the observed
number of reports for a specific drug-adverse event combination in the database is higher than expected, the ‘expected’ being derived from the total database[13]. Unexpectedness does not demonstrate causality, and the term ‘signals of disproportionate reporting’ (SDR) has therefore been suggested to emphasise the need for clinical review in the process of finding signals[14]. Other methods use Bayesian framework and calculate measure known as the “information component” (IC)[15] and the “empirical Byes geometric mean” (EBGM) estimate[16]. Their implementation is different but both reduce risk estimates towards the null value of no association, more strongly at low values of either the observed or expected value. Thus combinations with spuriously highly observed/expected ratios due to limited data are much less apparent. None of the quantitative methods is universally better than the others. Recently, a comparison of the number of spontaneously reported cases with the number of cases of a particular event that would be expected to be seen in the exposed population based on epidemiological data has been frequently employed to support signal detection and evaluation. This methodology, known as observed versus expected analysis was used during the recent influenza H1N1 pandemic to help to assess spontaneously reported events following vaccination[17-18].

OBSERVATIONAL DATA

The availability of electronic patient data has had a marked impact on research into the safety of medicines. The last two decades have witnessed the development of key data resources, expertise and methodology that have allowed the conduct of landmark studies in the field[19]. Electronic medical records and record linkage of administrative health records Examples of the first and second are the General Practice Research -database in the UK and the national or regional databases in the Nordic countries, Italy, Netherlands and other countries, respectively.

The development of guidance for post-authorization safety studies making secondary use of data collected for another purpose have established methodological standards in this field (examples are guidelines developed by the International society for Pharmacoepidemiology and the German Society for Epidemiology). The number of such studies will therefore probably increase. There are, however, important limitations to the use of electronic health care records. A first one is the validation of data recording and coding. Although several methods had been used to assess the validity of these processes, the quality of reporting of the validation has often been inadequate to permit a clear interpretation of the results[20]. Another limitation concerns the ability of studies based on electronic health care records to assess rare reactions, delayed reactions or reactions following chronic exposure, for which prospective studies with direct data collection from patients, such as case control and cohort studies, are still often needed[21-24].

Observational data play an increasing role throughout the product life-cycle. In the drug development phase, they are useful to assess the need for medicines, to characterize frequency and distribution of disease, there by identifying the population to be treated and their medical needs. An important application is the identification of potential or phanmedicines. The EU orphan regulation stipulates a prevalence level of five per 10,000 persons in the EU as a limit for access to incentives and this prevalence can be measured using administrative health care databases, electronic medical records, registries and surveys[25]. Electronic health care record databases can also be used in clinical trials for recruitment of patients before treatment allocation and their long term follow-up, and provide background event rates needed to interpret adverse events occurring in clinical trials[26,27].

In the post-authorizations phase, observational studies are now increasingly used in the context of risk-management plans to assess the incidence and risk factors of identified risks, detect or strengthen signals of potential risks and evaluate the safety profile of medicines in specific population groups for which information is limited[28]. An example is the Vaccine Safety Data link in the United States, which can quickly respond to concerns on emerging health outcomes and support regulatory decision making by providing timely data on large populations. Furthermore, this system has been used effectively to refute potential safety signals and concerns which had threatened vaccination programmed[29-31]. In Europe, the EU-ADR project is developing an
innovative Computerised system to detect adverse drug reactions supplementing the spontaneous reporting system. To achieve this objective, it exploits clinical data from electronic healthcare records of over 30 million patients from several countries (The Netherlands, Denmark, United Kingdom, and Italy).

PHARMACOVIGILANCE FOR EVALUATING ADVERSE DRUG REACTIONS
Classification of ADRs
A. Dose-dependent ADRs related to the pharmacological effect of the drug:
   • Increased pharmacological effect
   • ADRs that occur secondarily to the desired pharmacological effect
   • ADRs due to other well-known pharmacological effects
B. Sensitivity reactions – not dose-dependent
   • Allergic reactions
   • Idiosyncratic reaction
C. Long-term ADRs
   • Carcinogenic
eases
   • Teratogens
   • Chronic organ damage
D. Drug-drug interactions
   • Pharmacodynamic
   • Pharmacokinetic
   • Non-classifiable

EVALUATION PARAMETERS
1. Need for pharmacovigilance activities
2. Organization of pharmacovigilance activities
3. Mode of operation and objectives of pharmacovigilance centers

Need for pharmacovigilance activities
Pharmacovigilance studies of drugs that are on the market (Phase-IV studies) produce crucial information. Phases I through III are conducted in a limited number of individuals (a few hundred), usually under favorable conditions, i.e., in the hospital, under close surveillance, over a short period, with few concomitant medications, and with few high-risk individuals (e.g., children, older individuals, pregnant women, or patients with renal or hepatic failure).

Marketed drugs are used in a far broader range of patients and circumstances, which may lead to the emergence of previously unrecognized ADRs. Rare ADRs (occurring for instance in 1/1000 individuals) are unlikely to be identified in pre-marketing studies. If the unrecognized ADR is serious, it may have devastating consequences. A drug that belongs to a widely used pharmacological class may be used in up to 100,000 individuals within the first month, so that a rare (1/1000) but serious ADR may occur in 100 patients. There is no clinical trial design or other evaluation method that is capable of eliminating the risk of serious ADRs occurring after marketing. Therefore, pharmacovigilance studies are essential to identify and to measure ADRs in order to prevent further occurrences.[32] In sum, clinical trials are well suited to the validation of clinical effects but are of limited value for identifying ADRs.

Organization of pharmacovigilance activities
The World Health Organization set up an International Drug Monitoring Program based in Uppsala, Sweden, in 1968. Since 1995, the European Medicines Agency in London has been assembling pharmacovigilance data from European Union countries. In France pharmacovigilance activities are carried out by 31 regional centers based in clinical pharmacology departments of university hospitals (listed in the Vidal Drug Compendium). These centers collect ADR reports (which serve as alarm signals), develop pharmacovigilance studies and surveys, and provide information on drugs. Concerns about possible ADRs and requests for information about a drug should be directed to the appropriate regional pharmacovigilance center (not the pharmaceutical company). In recent years, regional centers have expanded their pharmacoepidemiology activities. For instance, they now look for associations between specific ADRs and factors such as age, gender, drug dosage, environmental factors, concomitant medications, and population phenotype. “The heads of the 31 regional centers constitute the Technical Pharmacovigilance Committee, which meets once a month at the offices of the French Agency for Healthcare Product Safety (AFSSaPS) in Paris”. The committee plans and conducts pharmacovigilance surveys then reports the results to the National Pharmacovigilance Committee. This last
is composed of healthcare authority representatives, pharmacologists, hospital- and office-based physicians and pharmacists, and a pharmaceutical industry representative. The national committee reviews the data and advises the AFSSaPS about specific measures such as removing a drug from the market, changing the classification of a drug, restricting the approved uses of a drug, or supplying physicians with additional information on ADRs and the risk/benefit ratio.

**Mode of operation and objectives of pharmacovigilance centers**

Pharmacovigilance centers pursue four objectives: to detect ADRs, to evaluate them, to study them what is the difference between evaluate and study? and to inform prescribing physicians. ADR detection relies on mandatory spontaneous reporting. By law (article R-5144-19), “a physician, dentist, or mid-wife who observes a serious or unexpected event potentially related to a drug must immediately report the event to the regional pharmacovigilance center, irrespective of whether he/she prescribed the drug”.

A serious ADR is defined as an ADR that causes death, is life threatening, requires hospital admission or prolongation of a hospital stay, or causes disability or incapacitation. All serious ADRs must be reported, including those described in the SPC or elsewhere. All unexpected ADRs, i.e. serious and non-serious events that are not listed in the SPC, must also be reported. The regional pharmacovigilance centers are in charge of recording, evaluating, and exploiting data on ADRs. An important task of the regional pharmacovigilance center is evaluation of causal relationships between unwanted events and drugs. Documented ADRs are recorded in the national pharmacovigilance database at the AFFSaPS, which communicates the data to the World Health Organization.

Causality is assessed using a probabilistic approach. The method used in France distinguished between intrinsic causality and extrinsic causality \[33\]. Intrinsic causality is assessed based on the timing and features of the event. Timing criteria include the time from drug exposure (challenge) to occurrence of the event, the time from drug discontinuation (dechallenge) to resolution of the event, and the time from further drug exposure (rechallenge) to recurrence of the event. These criteria are used to determine a chronological score (C) that can range from 0 (causality is excluded) to 3 (causality is likely). Four features of the event are considered in the causality assessment: suggestive symptoms, precipitating factors, causes other than the drug, and specific investigations performed in the patient. Combining these four criteria produces a semiological score(S), which can range from 1 (dubious) to 3 (likely). A final decision Table serves to determine the intrinsic causality (I) score based on both the C and the I score. The I score can have five values: 0, excluded; 1, dubious; 2, plausible; 3, likely; and 4, very likely. Extrinsic causality is evaluated by reviewing published reports of identical events seen with the same drug. These reports may be found in reference books, published articles, or national and international pharmacovigilance databases. The B (bibliographic) score is then determined; it can range from 0 (no previous reports of the event) to 3 (widely documented event). The regional pharmacovigilance centers conduct surveys on drug safety and drug-induced iatrogenic events. For instance, the effects of one or several drugs may be evaluated using data in the French pharmacovigilance database, or pharmacoepidemiological studies (e.g. case–control and cohort studies) may be conducted to measure the risk of an ADR occurring with a specific drug. As part of their efforts to minimize iatrogenic events, the regional pharmacovigilance centers contribute actively to information campaigns on the proper prescription of drugs.

The regional pharmacovigilance centers are also drug information centers that disseminate and explain the results of pharmacovigilance surveys. They publish independent, validated, and objective newsletters on drugs (e.g. the Toulouse newsletter at http://www.bip31.fr). They take calls 24 hours a day 7 days a week to supply information on ADRs, contraindications, drug-drug interactions, and appropriate precautions in high-risk populations. Regional pharmacovigilance centers are developing a proactive approach based on national and European Risk Management Programs. These programs are established during discussions held by the pharmaceutical company, AFSSaPS, and regional pharmacovigilance centers at the time the marketing license application is submitted. They aim to apply a
surveillance and risk-minimization strategy that is appropriate for each specific situation. Thus, the field of pharmacovigilance, which previously focused on detecting alarm signals, is expanding to encompass risk prediction, management, and surveillance throughout the market life of the product.

THE PROTECT PROGRAMME

The PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) programme, funded by the Innovative Medicines Initiative (a public-private partnership between the European Union and the European Federation for Pharmaceutical Industries and Associations), aims to strengthen the monitoring of benefit–risk of medicines in Europe by developing innovative methods. These methods will enhance early detection and assessments of adverse drug reaction from different data sources (clinical trials, spontaneous reporting and observational studies) and enable integration and presentation of data on benefits and risks. These methods will be tested in real life situations. The PROTECT project is a unique public private partnership bringing together medicine regulators, academic institutions, small and medium sized enterprises, pharmaceutical companies and other organisations. It has an important package of work relating to the use of electronic databases in pharmacoepidemiological studies. Based on the observation that studies on the same issue sometimes provide conflicting results, even when they are carried out in the same data source [34,35], objectives are to develop and test methodological standards for the design, conduct and analyses of pharmacoepidemiological studies applicable to different safety issues using different data sources. Five adverse event–drug pairs with known association will be studied in different EU databases using different study protocols. By comparing the results of the different studies and identifying the sources of discrepancies it is hoped to produce improved methods for the future. The five adverse event and drug pairs selected are antidepressants and hip fracture, antibiotics and acute liver injury, beta-2 agonists and myocardial infarction, anti-epileptics and suicide, and calcium channels blockers and cancer. Innovative methods to control for confounding will be developed, tested and applied, based on the creation of simulated cohorts.

A work stream on drug utilisation will evaluate and disseminate methodologies for drug utilisation studies (including the identification of relevant data sources) to promote their use in research and in regulatory activities to evaluate the potential health impact of adverse drug reactions. PROTECT also aims to improve early and proactive signals detection from spontaneous reports, electronic health records and clinical trials. The objective is to develop new methods for signal detection in individual case safety reports, and fully test those that already exist, to foster the use of electronic health care records for signal detection and signal strengthening, to evaluate signal detection based on suspected unexpected serious adverse reactions from clinical trials, and to make recommendations for good signal detection practices.

The research programme also assesses the feasibility, efficiency and usefulness of modern methods of data collection using web based data collection and computerised interactive voice responsive systems by telephone. This will be achieved through a prospective non interventional study which recruits pregnant women directly without the intervention of health care professionals and then collects drug exposure data from these women using either the web based system or the voice recognition telephone system. The study will be conducted in Denmark, the United Kingdom, the Netherlands and Poland. Another work package within PROTECT will study benefit–risk integration and representation with the objective to assess and test methodologies of benefit–risk assessment of medicines and to develop tools for the visualisation of benefit and risk of medicinal products.

CONCLUSIONS

The process of post authorisation medicines regulation has been based on Spontaneous reporting of suspected adverse drug reactions and placing obligations on the industry to conduct studies and then regulators judging the results of those studies. The New approach of medicines regulation including pharmacovigilance draws on all relevant data Sources including studies conducted by academia, industry, health authorities and regulators. Excellence in
pharmacovigilance is based on a patient focused, proactive, proportionate, Multi-disciplinary, benefit-risk balancing transparent and science based approach. Health data and epidemiology support medicines regulation throughout the medicines life cycle. They are most established, however, in the post authorisation monitoring of the benefit risk Medicines Here, through electronic health records, record linkage, claims databases, and registries, signal strengthening, causality and effectiveness or risk minimisatistudie can be conducted. Drug utilisation studies are proving more and more useful in post authorisation product monitoring and experience over the last 15 years has shown that we should embrace. All data sources with spontaneous report, epidemiological method of data collection, clinical Trials and meta-analysis all playing their role in product monitoring and decision making. New Legislation in Europe provides an excellent opportunity to further strengthen the Science and Capacity for post authorisation benefit risk monitoring and important new European projects to improve the scientific methods available and capacity for post Authorisation research will lead to better protection and promotion of public health.

ABBREVIATIONS
Council for International Organization of medical science (CIOMS)
Uninated state food and drug administration (US-FDA)
Adverse drug reaction (ADR)
World health organisation (WHO)
Summary product characteristics (SPC)
Randomized controlled trials (RCT)
Adenomatous polyp prevention on Vioxx (APPROVE)
Spontaneous reporting system (SRS)
Proportionate reporting ratio (PRR)
Signals of disproportionate reporting (SDR)
Information Component (IC)
Empirical Byes Geometric Mean (EBGM)
European Union adverse drug reaction (EU-ADR)
The heads of the 31 regional centers constitute the Technical Pharmacovigilance Committee, which meets once a month at the offices of the French Agency for Healthcare Product Safety (AFSSaPS) in Paris.

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