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Pharmacovigilance in pharmaceutical Industry

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ABSTRACT

Pharmacovigilance professionals from the company are involved early in the product development process. For already-on-the-market products, a Safety Specification and Pharmacovigilance Plan can be produced (e.g., new indication or major new safety concern). The Plan could be used as a starting point for discussions with regulators in the various ICH regions and beyond on pharmacovigilance initiatives.New information will be generated after a product is marketed, which may have an impact on the product's benefits or hazards; examination of this information should be a continuous process, in conjunction with regulatory authorities. To ensure that all products are safe to use, detailed review of information obtained by pharmacovigilance operations is required. The benefit-risk balance can be improved by minimising patient hazards through good pharmacovigilance, which allows for prompt information input to pharmaceutical users. Before a product is approved or a licence is granted, industry and regulators have recognised the need for better and earlier planning of pharmacovigilance efforts. This ICH recommendation was created to promote harmonisation and uniformity, as well as to avoid duplication of effort, and could be of benefit to public health programs throughout the worldas they consider new drugs in their countries.These reviews highlight relationship between the pharmaceutical Industry and pharmacovigilance.

Keywords: Pharmacovigilance, clinical studies, Premarketing trial, good pharmacovigilance practice, post marketing surveillance, Spontaneous reporting, cohort studies

INTRODUCTION

Pharmacovigilance (PV) is in charge of monitoring the safety of medications in everyday clinical practise and during clinical trials. Its main goal is to reduce drug-related risks while maximising their benefits [1]. Pharmacovigilance units collect adverse occurrences from all around the world that were or could have been caused by the use of a specific drug, according to international health agency regulations. Pharmacovigilance units collect adverse occurrences from all around the world that were or could have been caused by the use of a specific drug, according to international health agency regulations [2]. Any undesirable medical occurrence in a patient or clinical trial participant who received a pharmaceutical product that does not necessarily have a causal relationship with this treatment is referred to as an adverse event (AE). A serious adverse event (SAE) is defined as an AE that causes one or more of the following: A medically dangerous condition; death; life-threatening symptoms; necessitates or prolongs hospitalisation; handicap or incapacity; a congenital anomaly or birth defect [3].

Good Pharmacovigilance Practice

The Good Pharmacovigilance Practices were created to "harmonise pharmacovigilance practises and laws around the world," while it is recognised that different countries may have diverse healthcare and regulatory systems, particularly in the area of pharmacovigilance. As a result, every national medicines authority in the globe should view this guideline as a "ideal model" that they should strive to implement as much as possible on a national basis, whether now or in the future. Pharmacovigilance activities are organised into separate but interconnected processes, and each GVP Module focuses on one of these processes. GVP also offers advice on how to perform pharmacovigilance for certain product categories or populations in which medicines are utilised. The GVP Considerations must be used in conjunction with the Modules' process-related ICH guidelines. [4]

Pharmacovigilance system

A pharmacovigilance system is a system designed to monitor the safety of permitted pharmaceutical products and detect any changes in their risk-benefit balance. It is used by an organisation to fulfil its legal obligations and responsibilities in connection to pharmacovigilance. The architecture, procedures, and outputs of a pharmacovigilance system, like any other system, define it. In GVP, a specialised Module is

supplied for each individual pharmacovigilance procedure, containing its necessary structures. [5]

Quality, quality objectives, quality requirements and quality system

The quality of a pharmacovigilance system can be defined as all the characteristics of the system that are considered to produce, according to estimated likelihoods, outcomes relevant to the pharmacovigilance objectives for the purposes of GVP, which provides guidance on the structures and processes of a pharmacovigilance system. Quality, in general, is a question of degree and may be quantified. Pre-defined quality requirements are required to determine if the required level of quality has been met. The qualities of a system that are most likely to yield the desired outcome, or quality objectives, are known as quality requirements. [6]

Although it is currently recognised as a separate subject, pharmacovigilance is linked to a variety of scientific disciplines, the most important of which are clinical medicine, clinical and pre-clinical pharmacology, immunology, toxicology, and epidemiology. The discovery and study of drug safety characteristics is divided into two steps. During the initial stage, prior to marketing, the major tactic is experimentation with clinical studies comparing the new medicine to a placebo or current alternative treatments In general, experimental data are of significantly higher quality than observational data, with superior confounding factor control. The issue in pharmacovigilance is thus to analyse and develop well-founded inferences from post-marketing observational data. Furthermore, data from observational epidemiological research are becoming increasingly essential. [5]

Pre Marketing Trial

In clinical studies, safety monitoring includes gathering adverse events, laboratory investigations, and clinical examination records from participants. Pharmacovigilance personnel may be involved to varied degrees in all phases of clinical trials, including design, execution, data analysis, and safety information reporting. Animal pharmacology and toxicology studies, phase I study findings, known ADRs with similar medications, signals from other research, and particular patient groups (e.g., the elderly) must all be addressed. The practise of gathering all adverse events rather than suspected ADRs developed from clinical trials' failure to discover significant reactions with practolol, and after several years of experience , this is currently the strategy used by most companies in most studies.[6]

A well-conducted clinical trial should be able to identify and characterise common type A (pharmacologically mediated) [6] ADRs, indicate how these are tolerated by patients, establish a relationship between ADRs and dose or plasma concentration, and, if possible, identify predisposing (risk) factors. These issues will typically be presented and discussed in an integrated safety analysis and clinical expert report in the company's Marketing Authorisation Application, and will serve as the basis for ADRS, warnings, and precautions included in the prescribing information, i.e. Summary of Product Characteristics (SPC) or data sheet. However, clinical trial programmes before to marketing have a limited ability to detect unusual, particularly type B (non-pharmacologically mediated) ADRs. This is due to the small number of patients studied prior to marketing [6], the frequent exclusion of patients who may be at higher risk, such as the elderly and those with significant concurrent disease, and the structured nature of clinical trials, in which drugs are given at specific doses for limited periods by an experienced investigator.[7]

Process of Post Marketing Surveillence

The broad procedure is similar to that used by regulatory authorities and other parties concerned with drug safety. The first phase is signal creation, which refers to mechanisms that can detect potential new ADRs. There may then be a period of signal strengthening before such signals are subjected to hypothesis testing in the second step, i.e. determining whether the signal indicates a new process that ADR or whether it is untrue. Whereas signal generation is, in theory, quite straightforward if the necessary mechanisms are in place, hypothesis testing is difficult, time consuming, and may necessitate a variety of methodologies. The main issue encountered is'signalvs noise-many adverse events recorded in treated patients eventually turn out to be false positives.'[8]

Spontaneous reporting

Spontaneous or voluntary reporting is the process of recording and reporting clinical findings of a suspected ADR with a marketed medicine. In the United Kingdom, the "yellow card" scheme encourages doctors, dentists, and, more recently, hospital pharmacists to report all suspected adverse reactions to new drugs and major suspected adverse responses to existing medicines. Pharmaceutical companies collect and compile similar reports in conjunction with their licenced goods [8]. Often, an enquiry from a prescribing physician or pharmacist to Medical Information or a sales representative regarding whether a product could be the source of a patient's illness leads to a report to a company. Following the provision of such information, pharmacovigilance staff will look for details of the case to add to the database of reports. Companies must report suspected ADRS to the MCA and other authorities; some authorities, including MCA, make anonymised data available to licence holders. There is also a move towards electronic exchange of data between authorities and companies.[9]

Published Case Reports

Publishing suspected ADRS case reports in medical journals is a well-established method of alerting people to potential medication dangers. It does, however, have limitations in that only a tiny percentage of instances are published, reports are sometimes inadequately documented, publishing is dependent on editorial selection, and there is frequently a significant time lapse between occurrence and publication. Companies and some regulatory agencies keep a close eye on the literature for such stories. This will entail screening major journals for ADRs, monitoring publications like ADIS International's Reactions Weekly, and conducting frequent standard searches on databases like Medline and Excerpta Medica. Because of effective regulatory and industry safety surveillance, it is currently uncommon for a novel ADR to be reported solely through published cases. However, publication of vellcharacterised ADRs still fills an important function in alerting physicians. A more recent development is reports of possible ADRS appearing on the Internet and many companies are still determining how they should best handle them. [10]

Cohort Studies

Companies can set up or finance prospective, non-interventional cohort studies to solve safety problems that occur after a product is launched, or as a general hypothesis generation and testing tool that can be employed whenever the need arises. Previously, company-sponsored studies were thought to be ineffective at detecting new safety problems, owing to delayed recruitment and a lack of control groups [9]. Since 1994, similar studies in the United Kingdom have been governed by the SAMM (Safety Assessment of Marketed Medicines) rules [10], which have resulted in a stronger working relationship between corporations and the MCA. Cohort studies are ineffectual as signal generation methods in general, owing to size limits. Furthermore, data from such studies are prone to the signal vs noise problem in the same way. [11]

Post marketing Clinical trials

Large randomised clinical trials with broad entry criteria can be useful in determining the safety and efficacy of marketed products. Because patients are randomly assigned to various therapies, they avoid some of the issues that plague cohort studies, such as whether the control group is actually equivalent. Companies can opt to conduct or support such research to address specific safety concerns. Making them large enough to provide more information than trials conducted for product registration purposes could be prohibitively expensive, so a simple protocol and research plan with few observations is preferable. [12]

The Hypothesis testing process

A common occurrence in firm pharmacovigilance is the receipt of a limited number of reports indicating that patients had a dangerous medical condition, such as liver function disturbance, convulsions, or blood dyscrasia, while using a particular product. As much information as possible about the cases must be acquired, and any new instances must be thoroughly investigated, but the notion that this condition was caused by the drug, i.e. constitutes an ADR, must be raised. There are several approaches to analysing this subject, the most popular of which is to use spontaneous reporting data in a variety of ways. Another option is to do formal epidemiological research, such as case-control studies. Clinical trial experience and preclinical pharmacological and toxicological data should also be included. [13]

Spontaneous Reporting data for testing Hypothesis

In clinical practise, it is customary to make choices and conduct actions based on individual case assessments of causality between an incident and a certain medicine. However, in general, pharmacovigilance experience has shown that determining causality in particular cases is fraught with uncertainty. Attempts to build a methodology for assessing causality, such as by utilising a Bayesian approach, have given fascinating results [11], but have had little influence so far. However, there are some exceptions to this ambiguity, such as the condition of positive rechallenge, in which symptoms and objective results that had subsided after treatment discontinuance reappear after fresh exposure. The other circumstance is when an adverse event occurs in a number of individuals and has a highly consistent pattern in terms of symptomatology and duration of treatment prior to onset of symptoms, such as zimeldine and Guillain-Barre syndrome [14].

These arguments highlight a key parallel between clinical medicine and pharmacovigilance: there is no replacement for meticulous observation and study of individual situations. In some cases, biochemical markers or pharmacokinetic data from particular individuals may be used to help determine whether or not observed symptoms or problems are an ADR. Data from spontaneous reporting can be used to compare the frequency of a certain incident in a treated population to the background incidence of that event. This may be especially true in the case of unusual diseases like blood dyscrasias. Even if there is a lot of underreporting, if the reporting rate for a specific occurrence, which can be thought of as a minimum frequency, obviously exceeds the expected frequency, it generates a lot of scepticism about a causal association. This is a rather uncommon event, mainly due to the lack of solid background incidence data for many illnesses. [15]

Hypothesis testing can be a rather simple process in real life. A simple approach is that once the number of reported events of a certain type reaches a certain threshold, regulatory authorities and company pharmacovigilance units may conclude that the numbers most likely reflect a true adverse reaction, unless other causative factors are sufficiently convincing. The fear of litigation is increasingly influencing the public mindset in this field, particularly in the United States. Most businesses adopt a cautious approach and, for legal reasons, mention a number of suspected ADRs in the prescription instructions that have not been confirmed to be true. This is gradually having a more detrimental effect on the value of the prescribing information to practising health care professionals.[16]

Epidemiological studies

Pharmacoepidemiology, the study of medication use and effects in large populations [13], has emerged as a growing discipline in the last decade and has made significant contributions to our understanding of drug safety. The confirmation and quantification of the link between NSAID medication and gastrointestinal ulcers and bleeding [14] is a notable illustration of this. Pharmacoepidemiology expertise is now a must for any research-based pharmaceutical company, and there has been a significant increase in knowledge in several areas in recent years. In addition, numerous firms have formed pharmacoepidemiology research relationships with academic institutions. Pharmacoepidemiological studies are largely based on observational rather than experimental data and have some important methodological problems, particularly con founding and bias. The recent debate about studies with third generation oral contraceptives is a good example of this. It is possible that the observed differences between third generation oral contraceptives as compared with second generation ones are due to confounding or bias or both rather than on real differences , although this is still controversial [17].

In pharmacovigilance, there is a broad scientific and ethical challenge associated to the significant public attention that drug dangers receive. When should information about a potential hazard be provided during the evaluation process? Patients may be denied useful drugs if communication is made prematurely, before a hypothesis has been validated. I patients may be exposed to unnecessary hazards if it is too

late. Obviously, there is no simple answer; each case must be assessed individually, taking into account a variety of factors such as not only the potential ADR under consideration, but also the risks associated with the disorder being treated, as well as the risks associated with alternative treatments and inappropriate treatment cessation.[18]

International Regulatory requirements

Pharmaceutical companies have been required to provide safety data from clinical trials and marketed medicines to regulatory agencies for many years, but each national authority has distinct requirements. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [19], which brings together regulatory authorities and other experts from Europe, the United States, and Japan, has recently attempted to harmonise reporting. Despite this, and despite European Directives and Regulations, there is still a wide range of requirements, and the CPMP Pharmacovigilance Working Party's guidelines is still in the works. [20]

One element of the European standards is that holders of Marketing Authorisations, i.e. corporations, must have an adequately certified pharmacovigilance person. Their responsibilities include establishing and maintaining a system that ensures that all ADRS reported to company personnel are collected and collated so that they can be accessed at a single point within the community, preparing various reports, and responding to requests from authorities for additional information. Meeting global regulatory reporting requirements is a critical business need in pharmacovigilance, and corporations have spent a lot of money on people, computers, and procedures to meet them. This should not, however, overwhelm the importance of sound research and judgement in detecting and analysing critical product safety risks. [21]

Issue and Crisis Management

The signal creation and hypothesis testing processes are often long-term and ongoing throughout a product's lifetime, leading in a progressive accumulation of knowledge about the safety qualities. However, there are occasions when the process must be accelerated, resulting in a crisis. This could be because a safety signal signals the prospect of a new and significant risk, but regulatory efforts and/or mass media activities could also set off such events. [22]

The most significant feature of the crisis situation is the scarcity of time. A potential serious risk to patients, as well as the fear of regulatory action or media pressure, necessitates quick action. At the same time, analysis of all available data, discussions with various experts, internal discussion within the organisation, dissemination of information to other parties, and other activities are required. [23] This is usually handled by a task force, with pharmacovigilance expertise playing a key role. In most cases, a task force is required to conduct an analysis of all available data, interact with specialists, manage internal and external information, and, in the end, make well-considered benefit-risk judgments and recommend actions. [24]

CONCLUSION

Before a product is approved or a licence is granted, industry and regulators have recognised the need for better and earlier planning of pharmacovigilance efforts. This ICH recommendation was created to promote harmonisation and uniformity, as well as to avoid duplication of effort, and could be of benefit to public health programs throughout the world as they consider new drugs in their countries. These reviews highlight relationship between the pharmaceutical Industry and pharmacovigilance.

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