International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 103-108 www.ijprajournal.com ISSN: 2249-7781

Pharmacovigilance in Pharmaceutical Companies: An Overview

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Date of Submission: 20-06-2021 Date of Acceptance: 03-07-2021

ABSTRACT
It is an undeniable fact that this and the subsequent centuries will be greatly dependent on drugs because of the unhealthy lifestyle that people are following. Thus the importance of pharmacovigilance is believed to enhance with each passing day, because in order to cure the lifestyle of people , the safety and efficacy of medicines are highly significant. The pharmaceutical companies responsible for drug development are always concerned about the safety of drugs. Hence they make sure to conduct multiple preclinical and post clinical assessments to ensure the safety of people. Additionally the governments of the nations have provided multiple laws/regulations during and after the production of drugs to abide by the health of the general public to be its first priority. Thus, pharmacovigilance has proven to be very beneficial and acts as the sunshade against most ADRs with the pharmaceutical companies giving their one hundred percent contribution in carrying forward.

Keywords: Safety, efficacy, ADRs, industry, drug.

I. INTRODUCTION

Pharmacovigilance is responsible for monitoring the safety of medicines in normal clinical use and during clinical trials.[2] The historical backdrop of pharmacovigilance (PV) started with the German toxicologist Louis Lewin, who published the main book on unfavorable medication impacts in 1881 (ADR). In 1960 FDA started to collect the report of adverse reactions. Appropriate monitoring of ADR is the best way to safeguard public health. Through pharmacovigilance we can get to know about the drug action after the drug is consumed. Spontaneous reporting system (SRS) is most widely used method to report ADR.[8]

The aim of pharmacovigilance in the industry is the same as regulatory agencies that is to protect the patient from unnecessary harm by identifying previously unrecognised drug hazards, elucidating predisposing factors, refuting false safety signals and quantifying risk in relation to benefits.[4] Although the viewpoints of organizations and the regulatory agencies might be diverse they presently work increasingly more intently together and share data. Be that as it may, focal pharmacovigilance units in significant pharmaceutical organizations in numerous occasions are far superior resourced and have a much more prominent 'in-house' mastery on the security of their specific items.[5]

In 1992, the European Society of Pharmacovigilance (ESOP) which was later called International Society of Pharmacovigilance (ISoP) formally marked the introduction of Pharmacovigilance in the field of research and academics, along with giving a wave towards clinical practices.There has been a growing awareness on the scope of pharmacovigilance which extended beyond horizons in the last decade.[6]

WHAT IS PHARMACOVIGILANCE?

Pharmacovigilance as described by the WHO is basically the assessment of any drug and its prevention from causing adverse drug reaction (ADR).[1] The main aim is to observe whether a particular drug during its clinical trial or during use is safe or not.[2]

Adverse Effect (or AE) is basically an unexpected reaction that might tend to occur when the patient or subject has been administered with a drug, which is not supposed to produce such an effect. Thus it is an unfavourable, unintended consequence that a drug might bring along with it, although the medical product might not be associated with causing the effect.[1] There can be Serious Adverse Effect (or SAE) as well that is much more dangerous than thought as it might be fatal, life-threatening,disability or incapable of doing things,might even require prolonged hospitalization, can cause congenital anomaly or birth defects or even might be a medically serious condition.[3]

Adverse Drug Reaction (ADR) is a term that is basically used to describe the unintended

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responses of any drug in a preclinical trial. It is usually categorized in two ways i.e. Unexpected Adverse Reaction and Expected Adverse Reaction, where in the prior one there is absolutely no knowledge about the reaction that might have occurred after taking in the particular drug and the severiarity might be predictable and later means that the severiarity of the drug is unknown.[1]

LEGISLATION /ACT/LAW/EVENT

In 1962, the International Center for Monitoring of Adverse Drug Reaction by WHO was established in Geneva, which was later shifted to Uppsala in Sweden and this is often the start of pharmacovigilance. From then, the WHO-supported Uppsala monitoring Centre has spearheaded many activities of pharmacovigilance everywhere on the planet.

- **Biologics Control Act:** which was passed in 1902 by USA this act was passed because many deaths were deported due to diphtheria vaccines tainted with tetanus
- **Pure Food and Drug Act:** this act was passed by the US congress, for preventing the manufacturing, sales and adulterated or poisonous foods, drugs, medicines and liquors.
- **Sulfanilamide Elixir:** used to treat streptococcal infections, which had been used with none issues in powder and tablet form.
- **Federal Food and Drug Cosmetic Act:** this act was passed in 1938, federal food and drug cosmetic acts were passed after the incident of sulfanilamide.
- **Council for International Organization of medical sciences (CIOMS):**Established jointly by WHO and UNESCO with the target to facilitate and promote international activities within the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary.
- **Thalidomide tragedy:**Thalidomide first entered the German market as an over-the-counter remedy in 1957. A German newspaper soon reported 161 babies were adversely suffering from thalidomide, leading the manufacturers of the drug—who had ignored reports of the birth defects related to it—to finally stop distribution within Germany. Other countries followed suit and, by March of 1962, the drug was banned in most countries where it had been previously sold.
- **Yellow Card Scheme:** Again within the wake of thalidomide tragedy the Yellow Card Scheme (UK) was established for collecting information on suspected adverse drug reaction (ADRs) of drugs to supply an early warning of possible hazards.[9]

IMPORTANCE OF PHARMACOVIGILANCE

The several underlying reports of adverse drug reaction is one of the major problems faced by the world today. It is a well noted fact that the development of a drug is a complex procedure and undergoes multiple steps, but as soon as the product is manufactured, it is marketed and is consumed by the general public. Here, comes into play the importance of pharmacovigilance. Before any drug is consumed by the general public, it has been stated by the WHO that it should undergo tests which are helpful in determining any new adverse reaction of the drug, whether it is sensitive to a group of patients or not, and in case such risks are found, to eliminate the risk factors. Additionally it is very important to monitor the safety and efficiency of any newly marketed drugs. Furthermore, there are specific groups of people like children, pregnant women, people who already consume multiple drugs for chronic disorders, might not be compatible with the newly marketed drug. Hence, pharmacovigilance assure the safety of drug from any kind of adverse reaction before its consumption.[10]

ACADEMICS : In relation to pharmacovigilance

The popularity of pharmacovigilance has now increased the curiosity among students to know about everything after a drug has been processed, its risk, safety, effectiveness, sensitivity etc. This has paved a way among the students to gain more knowledge. Clinical researches, studies, training and teaching in institutions have led to great advancement in the field of pharmacovigilance and has led to the increase in the effectiveness of drug safety. [2]

HEALTH PROFESSIONALS: In relation to Pharmacovigilance

The safety of any drug is basically determined by the reports provided by the health care workers. They are responsible for monitoring the array of side effects that follow the administration of drugs. After digging into the history of the relation of health care professionals and pharmacovigilance it is found out that only the physicians were allowed to report any ADR. This in turn limited the monitoring process as a

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physician cannot monitor a particular patient for the entire period of time. Thus this was changed for better good. All health care professionals including general physicians and nurses were given the responsibility of monitoring and further reporting anything that they noticed after drug intake. [1]

PATIENTS: In relation to Pharmacovigilance

The actual advantage/ disadvantage of any medicine is actually interpreted best by the patient itself. The reports that healthcare professionals provide is actually what the patient has informed. It is believed that the reports can be upto 90% correct if it is reported by the patients themselves.

It is also said that a patient's recording response is considered faster drug safety signals as compared to health care professionals. [1]

PHARMACOVIGILANCE PRACTICE WITHIN INDUSTRY

PRECLINICAL TRIAL OF MEDICINE DEVELOPMENT

Before introducing any pharmaceutical product into the market, it is necessary to undergo multiple clinical trials to make sure that the product is free from harm. General four trials are conducted before a product is permitted with market authorization, namely Phase I, II, III and IV.

The trials are conducted under the surveillance of highly expert investigators and the pharmaceutical company involved in the manufacture.

In the **Phase I** approximately 20-50 healthy volunteers are subjected to the drug for preliminary data.Also, animals are used for analysis of acute toxicity, organ damage, dose dependence, metabolism, kinetics, carcinogenicity, mutagenicity/teratogenicity. In the **Phase II** approximately 150-350 people with disease are monitored to determine safety and dosage recommendations. In the **Phase III,** 250 – 4000 more varied patient groups are tested to determine short-term safety and efficacy.[11]

After the third phase the analyst sends this information to the Research and development wing of the pharmaceutical company, where they make all the necessary changes and make sure that the drugs are safe to be marketed and suitable for consumption by the general public. [4]

Phase IV is Post-approval studies which is used to determine specific safety issues including continuous reporting for the efficacy of the drug. [11]

METHOD OF POSTMARKETING SURVEILLANCE USED BY THE PHARMACEUTICAL INDUSTRY

(1)THE SIGNAL GENERATION PROCESS

The early detection of safety signals is important and of great interest to the pharmaceutical industry, the public domain and regulators. The signals have both qualitative and quantitative aspects if there is a different kind of adverse event that needs different methods for detection. The important function of pharmacovigilance is early detection of signals. In the 1960 thalidomide tragedy was due to late signal detection. Signal detection is generated by one of the most usable methods of spontaneous reporting which have now been developed and used all around the world. The signal generation process is generated by various processes such as spontaneous reporting, case control, and cohort studies preclinical as well as clinical studies.[12]

- **Spontaneous Report:** Current pharmacovigilance is based upon the spontaneous reporting system (SRS). case report and case series are generally considered as a part of spontaneous reporting systems. Recording of the clinical observation of a suspected ADR with a marketed drug is known as spontaneous report or voluntary reporting.[14]Reactions, during the clinical trials they supply less information about the medication due to strictly controlled conditions. Post marketing studies (Phase-IV studies) are wont to observe the adverse drug reactions of a replacement drug in a large population and in specific patients thanks to a disease and specific concomitant medications. To detect the unknown and unexpected signals as soon as possible from the market is the major challenge in pharmacovigilance. Spontaneous reporting is play a key role in signal detection, detecting type B adverse effects and unexpected adverse effects.[16]
- **Published Case Report:** Publishing case reports of suspected ADRs in medical journals is a longtime way of alerting others to possible drug hazards. However, its limitations as only a really small proportion of cases are often published, reports are sometimes poorly documented, publication depends on editorial selection and there is often considerable delay between occurrence and publication. Companies and a few regulatory authorities actively monitor the published litera-ture for such reports.[17]

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- **Cohort studies:** A cohort study may be a prospective, observational study during which group of individuals having similar characteristics are followed so as to work out the sort and extent of exposure.[18] during a cohort study, a population-at-risk for the disease (or event) is followed over a time for the occurrence of the disease. In many cohort studies involving drug exposure, comparison cohorts of interest are selected on the idea of drug use and followed over time. Cohort studies are useful when there is a requirements to understand the incidence rates of adverse events additionally to the relative risks of adverse events.Cohort studies also are wont to examine the security issues in special populations (the elderly, children, patients, pregnant women).[19]
- **Post marketing clinical trials :** Large randomized clinical trials with wide entry criteria (similar to SPC indications) are often valuable in assessing the security of marketed products and also as confirming efficacy.[14] Adverse reactions that occur in fewer than 1 in 3,000 – 5,000 patients are unlikely to be detected in phase 1 clinical trial – III investigational clinical trials, and should be unknown at the time a drug is approved. The adverse reaction is more likely to be seen in the large number of patients when exposed to a drug.[4]

(2)THE HYPOTHESIS TESTING PROCESS

A situation in pharmacovigilance is that a small number of reports are received by the company which shows that the patient has a serious medical condition while receiving a product. Much more of the report must be reported and new cases will have to be reported rigorously and hypotheses also be raised that the condition has been caused by the drug (ADR). For the analysis of this kind of question a number of approaches have been taken and the most used process is spontaneous reporting data and the other process is formal epidemiologica.[14]

- Using spontaneous reporting data for hypothesis testing
- Epidemiological studies

NATIONAL AND INTERNATIONAL REGULATORY REQUIREMENTS FOR DRUG APPROVAL

INDIA

To regulate the import, manufacture, distribution and sale of drugs and cosmetics the Indian Parliament proclaimed the Drug and Cosmetic Act 1940 and Rules 1945 and along with that the Central Drugs Standard Control Organization (CDSCO) and the office of its leader, the Drugs Controller General (DCGI) was also established. Scheme Y was added to the Drug and Cosmetics Rules 1945 by the Indian Government in 1988,which provided the guidelines and requirements for clinical trials. This was further enhanced in 2005 in order to comply with Internationally accepted procedures.[13]

In order for any pharmaceutical company in India to manufacture/import new drugs, the company has to take permission from the licencing authority (DCGI) by filling up the Form 44 and by submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945.To ensure the efficacy and safety of the drug in India, it has to conduct clinical trials in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format.[15]

Rules

Rule- 122A of the Drug and Cosmetics Act says that the clinical trials can be ignored in the case of new drugs which are already approved and being used for several years in other countries. Section 2.4 (a) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that all phases of clinical trials are required for those drug substances which are discovered in India. Section 2.4(b) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that those drug substances which are discovered in countries other than India, the data available should be submitted by the applicant in order for the licensing authority to repeat all the studies or permit him to proceed from Phase III clinical trials. Ensuring the safety and efficacy of the drug product for human consumption, safety demonstration by the applicant is necessary before the drug product can be approved for import or manufacturing of new drugs to the Central Drugs Standard Control Organization (CDSCO). The information required for approval of an application to import or manufacture a new drug for marketing is described in the regulations under Drugs and Cosmetics Act 1940 and its rules 1945, 122A, 122B and 122D.

Stages of approval

1. Submission of Clinical Trial application in order to evaluate safety and efficacy.

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2. Requirements in order of permission of new drugs approval.
3. Post approval changes, quality,safety and efficacy documents in biological products.

4. Preparation of the accurately correct information for drug submission for approval of new drugs. Since most countries follow the CTD format, CDSCO has also decided to follow CTD format for technical requirements for registration of pharmaceutical products for human use.[13]

INTERNATIONALLY

In the year 1995, the European Medicines Evaluation Agency (EMEA) was established in London, which aimed at coordinating the European Union (EU) member states in order to evaluate and supervise the medicinal products for both Human and Veterinary use. This body was concerned with the safety and proper guidelines associated with all pharmaceutical products in order to gain complete efficiency on implementation. [15]

The drug approval in the european countries majorly include two steps:

1. Clinical Trial
2. Marketing Authorization

A clinical trial application (CTA) is filed, in order to conduct the clinical trial within European Union (EU) to the competent authority of the state. This authority evaluates the application and only on approval clinical trials. Only after the three phases of clinical trials the Marketing Association can be filed.[13]

In the UK, the CTX/CTC guidelines are the current requirements for investigation of drugs. The MCA publication Medicines Act Information Letter No. 87 outlines the licensed products. In case there is an individual suspected reaction for a marketed product, it must be reported to the MCA within 15 days of receipt by the company. This rule is applicable only to the UK and the European member states. Cases which originate outside European states should be reported only when they are very serious. Other than this periodic safety reports should be submitted after every stipulated amount of time. In case any product is marketed in the USA, it needs to undergo strict FDA regulations with strict deadlines.[21]

II. CONCLUSION

Despite its 40-yr history, pharmacovigilance remains a dynamic medical and medical discipline. It maintains to play a vital function in assembling the demanding situations posed with the aid of using the ever-growing variety and efficiency of medicines, all of which convey an inevitable and sometimes unpredictable capacity for harm. When negative results and toxicity do seem, particularly while formerly unknown — it's miles critical that those are reported, analyzed and their importance communicated successfully to a target market that has the understanding interpreting the information.[11]

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