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A Study of Pharmacovigilance System Performing Intensive and Monitoring in HIV/AIDS

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Abstract - The objective of the present study is to analyze national and international pharmacovigilance data for potential signals in the pharmacovigilance data analysis. Vigiflow software was used to assess causality, seriousness, severity of spontaneous adverse drug reaction reportage formulas as described in the National Pharmacovigilance Program and to enter the WHO database. WHO experts evaluated these data and certification was made by WHO for the entry of data in Vigiflow. In relation to important information, which led to difficulties carrying out the causality assessment, the ADR forms reported under the National Pharmacovigilance Program were not complete. This is not only because healthcare professionals know about the importance of ADR reporting, but also because there are no columns in the ADR form itself that provide some important facts necessary to evaluate causality. Pharmacovigilance in India hasn't been very advanced. This may be because the health workers are ignorant and the drug safety surveillance is not properly trained. The facts generated in other countries, advisory notes issued and regulatory measures taken by regulators elsewhere depend heavily on India. However, if circumstances differ, information obtained in one country may not be relevant to any other part of the world. This requires us to produce indigenous data that would be more significant and have an educational value and could contribute to national decision-making on regulatory matters. It is therefore important to develop a strong system of pharmacovigilance. The pharmacovigilance system involves minimizing existing risks through health care provider training, secured health care provision, assessment of new risk by different pharmacovigilance methods, such as active or passive supervision, analysis of pharmacovigilance-generated safety data, the identification of preventive risks, and risk development.

Keywords - Pharmacovigilance System, Intensive and Monitoring,HIV/AIDS, pharmacovigilance-generated safety

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INTRODUCTION

The thalidomide tragedy of 1961–62 was the biggest drug disaster. As a safe and effective hypnotic and antiemetic thalidomide has been introduced and welcomed. It was quickly popular in early pregnancy for treating nausea and vomiting. In the countries in which the drug was used in many cases in pregnant women, it was a potent human teratogen that caused significant birth defects in an estimated 10,000 children. This incidence has made people aware of the value of drug surveillance. The science, the assessment, the understanding and the prevention of adverse effects or any other drug-related problem are pharmacovigilance and activities. Guidelines and regulations are available for preclinical, premarketing and post-market assessment in India by the Council for International Organizations of Medical Sciences (CIOMS), the European Medical Agency (EMEA), US Food and Drug Administration (USFDA), the DCGI, etc. The need of pharmacovigilance comes about because during clinical studies in the pre-licensing step not all adverse effects of the drugs are identified and some safety risks are only identified in the general public.

In countries where ADRs (adverse drug reactions) occur (ADRs) and other drug related problems. This may be due to differences in:

- Diseases and prescribing practices
- Genetics, diet, traditions of the people
- Drug distribution and use including indications, dose and availability
- The use of traditional and supplementary drugs, if used alone or combined with other medicines, which can cause specific problems in toxicology.

In India, pharmacovigilance has not well recovered and is at an early age. India is less than 1% compared to the worldwide 5% for adverse events. This is because the subject is ignored and health professionals are not properly trained in the field of drug safety monitoring. Indian countries are heavily

reliant on data generated in other countries, and the advisory notes and regulatory measures adopted by regulators elsewhere may not be pertinent to other parts of the world, but information obtained in one country may differ in circumstances. This makes it essential that Indian data be generated which have greater relevance and educational value and can contribute to the decision-making of national regulations. 3 As an instrument for the detection of ADRs, drug surveillance is therefore of tremendous value to help ensure patients get safe and effective medication. The aims of pharmacovigilance activities are: collecting medicine data and suspected ADRs, analyzing the information, maintaining a track of the incidence and intensity of ADRs, analyzing the information on signals of possible new harms, establishing policies to eliminate or mitigate medicines risk, ensuring implementation of such policies and assessing the results of their application.

ADRs, which are noxious and unexpected drug responses occurring at doses normally used for prophylaxis, diagnosis or disease therapy, or physiologic function change, are particularly important to PV[4]. In order to maximize benefits and minimize risks, continuous surveillance of drug effects, side effects and counter substantiating effects which may result in a high degree of morbids and, in some cases, death, is essential. In pre-clinical and clinical testing phases, no degree of care and caution may ensure absolute safety when medication is sold and prescribed to large populations throughout Canada and abroad. Since there are a maximum of several thousand patients involved in clinical trials, less common side effects and ADRs are often unknown when the drug is placed on the market. Post-marketing PV utilizes tools such as data mining and case report research to identify drug-ADR relations. The drug regulators are responsible for the development and later duration of the marketable drug in a well-established PV system to monitor ADRs[5]. The wide range of partners involved in drug safety monitoring practice such as government, industry, health centres, hospitals, academia, medical and pharmaceuticals associations, poisons, health professionals, people, consumers and the media are closely and vital[6–8]. A complex and vital relationship exists. In order to develop and flourish, sustained collaboration and commitment are crucial in order to meet future PV challenges. As very little new drug was discovered in India and little new drug was first launched in India, a powerful PV system to detect ADRs for marketed products was not compelled significantly. Companies and regulatory agencies used the experience gained from the markets where the drug was in use in India for several years prior to its introduction to assess safety parametres, and took corrective actions, such as removal or ban. The evolution of a new patent system as a tradable intellectual property and service (TRIPS) in the Indian pharmaceutical and biotechnology industries makes it the responsibility of India to no longer copy and market patented products without the innovative company's license. The leading Indian companies have made a contribution towards the discovery and development of new medicines, necessary both for the Indian and international markets, by complying with the compulsions of the new regime. This, in turn, will hopeless lead to new drugs based on preclinical and clinical information generated in India in the coming year by the Indian pharmaceutical and biotechnological companies. The Indian regulatory agencies can, in such cases, not count on experience from other markets to evaluate the impact and prevalence of an adequately designed PV system in India. With Indian companies' ability to develop and market new drugs through their own research efforts, the establishment of sufficient PV standards to monitor ADRs for products first launched in India is important.

PHARMACOVIGILANCE SYSTEM

1: Methods for minimizing risks:

The first step of a pharmacovigilance system is to minimize the existing risks. This can be achieved by using various tools.

a. Training and supervision.

The standard guidelines for treatment in the form of easier-to-use tables and diagrams could be applied to include contraindications, precautions, laboratory trials, specific guidelines for pregnancy testing and contraception, particularly in the context of the menstrual cycle. All health professionals must be trained to contribute to pharmacovigilance, risk minimisation, risk evaluation, and documentation at the start of the programme. After the training they could be certified. The village health workers can educate patients by using the material on patient education to emphasize the correct use of the drugs and to inform them of the risks associated with drug use.

b. Use of quality-assured medicine

Good quality medicines should be available to achieve desired therapeutic effects.

c. Safe care delivery:

(i) Use of pediatric formulation for children

Pediatric-strength capsules with a weight-banding chart to ensure correct dose calculation, and documentation of dose administration should be available.

(ii) Provision of dispensing information

Dispensing of a limited number of doses to ensure follow up and early detection of ADRs should be promoted.

(iii) Use of checklist in outpatients

Patient cards to document relevant parts of patient history e.g. menstrual history, pregnancy test results and contraceptive use in case of teratogenic drugs.

(iv) Provision of a patient-held treatment card

An OPD card to determine whether patients have relevant contraindications, including non-permissive laboratory test results, whether they have taken the appropriate patient precautions or received instructions to detect and manage ADRs at an earlier stage.

b. Passive surveillance:

i) Spontaneous reporting

The most common method is spontaneous reporting; it is easy to determine and cheapest to perform, but reporting is low. Passive monitoring may, if available, be done through the use of spontaneous reporting by national ADR reporting forms where active monitoring cannot be done due to manpower and funds restrictions.

c. Assessing the preventability of adverse drug reactions.

Preventable drug-related harm can be assessed by studying:

- The occurrence of adverse events and root-cause tests in active and passive monitoring methods described above for preventable drug-related harm;
- surrogate markers such as results of pregnancy tests, compliance with the contraception procedure; early detection and instructions for defective contraception;
- The knowledge and communication skills of health workers to inform patients about risks, understanding and conformity;
- Retrospective analysis of case files, reports in health centres, hospitals, future active surveillance studies, cohort events monitoring and patient and healthcare workers interviewing will all be helpful in the detection of preventable harm.

2: Analysis of pharmacovigilance data

Study information could enter in a database using the software available, such as a WHO-ART Adverse Reaction Terminology, WHO Drug Dictionary Enhanced (all from the WHO Uppsala Monitoring Centre) and MedDRA, the Medical Regulatory Activity Dictionary (MDRA), and the Vigiflow software (from Maintenance and Support Services Organization, Chantilly, VA, USA). Data could be collected and analysed by pharmacovigilance. Through the review of data and recommendations, a panel could be formed by subject and pharmacovigilance experts from countries and regions. This would allow studies carried out for risk evaluation and risk reduction testing tools to integrate pharmacovigilance within the public health program practices. This would allow. The objective will be to utilize the results of risk reduction, risk assessments and continued pharmacovigilance to improve program practices, modify guidelines, and, where necessary, implement regulatory changes.

DEVELOPMENT OF PHARMACOVIGILANCE SYSTEM IN INDIA

The genetic and ethnic variability in India is vast, with various disease prevalences. There are several pharmaceutical products to prevent or control the different conditions of the disease on the market. New medicines such as vaccines, high-tech pharmaceuticals are currently introduced on the market. Drugs that were commercially available and continue to be available on the Indian market for proven adverse effects were prohibited. Even some drugs still use because the advantages outweigh the risks. The global burden of adverse drug reactions is high, leading to disease, death and public expenditure. Adverse drug reactions simplify the suspicion of any causal link between the drug and the event, implying a suspected relationship to the administered drug. Drug misuse, drug overuse, medication error included error of prescription, misuse of the medicines, errors in dumping, administrative errors and drug abuse, are all tender to cause adverse drug reaction, as is the OTC medicine use (India rankings 11th overall for OTC drug use).

- **Process for Reporting Adverse Drug Reaction in India**

Application of multimodal practices requires ADR monitoring and reporting and poor patient compliance. Due to the potential harmful health effects of drugs, pharmacovigilance becomes increasingly important. In India there is constantly an increase in awareness of monitoring and reporting ADRs. The purpose of Pharmacovigilance is to detect, monitor and report adverse drug reactions, including the severe non-severe, expected or unaffected drug reactions, especially after the marketing of drug products. The incidence, prevalence or use of WHO scale/Naranjo scale are aided by types of adverse drug reactions. Currently India plans to estimate, among other things, the pharmaceutical and pharmaceutical evidence relating to additions to hospitals, prolonged hospital stays, the cost of ADRs (direct or indirect), the cost to hospital and to the nation of adverse drug reactions as well as total morbidity and death to the general level. Subsequently a systematic analysis to obtain data is carried out and is distributed to health authorities, regulatory authorities, drug companies, doctors, pharmaceutical professionals and other healthcare professionals (such as health-care providers, dentists, paramedics, etc.) to provide for

the safety of medications and changes in prescription patterns. In line with the Central Drugs Standard Control Organization, the Government of India initiated the Indian Pharmacovigilance Program (PvPI) (CDSCO). Under the Ministry of Health & Family Welfare Agency, New Delhi has initiated a countrywide pharmacovigilance program. Government of India also liaises and reviews the Periodic Safety Unit Report (PSUre) on pharmaceutical analysis with the international Pharmacovigilance regulatory authority. The PvPI program is co-ordinated by the Ghaziabad Indian Pharmacopoeia Committee (IPC) to publish public documents by adding existing Indian Pharmacopoeia new and updated monographs that improve the quality of medicine. In 2008 the Indian Pharmacy Council (PCI) initiated a Pharmacy (Pharm D) program which determines clinical pharmacists for better drug care by decreasing therapeutic failure in patient safety in clinical activities such as drugs interaction monitoring and reports, prescription analysis/audits and advice on patient pharmaceutical. ADRs to the NCC operating under the supervision of the PvPI Steering Committee have been reported in India to hundreds and seventy-nine adverse drug reaction (ADR) monitoring centres. India shall adopt the recommendation procedures and guidelines for regulatory actions. It builds monitoring capacity, monitoring cooperation with national health programs and WHO's international drug monitoring programme. Health professionals or patients may report directly to the later IPC collected regional ADR monitoring centre. Currently PvPI has set up seven new AMCs at district levels to generate omnibus data on safety of medicine on the grassroots level in eastern Uttar Pradesh. A total of 232 individual safety report(ICSRs) were reported to Vigiflow during a period of a year in recent studies in Raipur, India 63.79% were deemed unserious and 36.21% were serious. The Uppsala monitoring center has also been a PCI member since 1998. CDSCO is the regulatory agencies in India that have been IPC-registered for all forms of ADRs. In 10/dec/2012 hemovigilance was launched as part of PvPI for ADR tracking and the incidence of blood transfusion and administering of the blood product. It also refers to trend identification and advocates best practices. Intervention requires improved care and safety for patients while reducing the overall costs of the health system. A minimum number of valid report criteria for ADR include, for example: patient identification, initials, age or date of birth, sex, the information of the reporter (name, profession, institution or contact details), the names of the suspected medicinal product (e.g. brand name or general name) including medicinal product(s). The reporting form includes concurrent drugs (the drugs used or given simultaneously with the suspected drug) (recovered, not recovered or recovering). Doctors, nurses, pharmaceuticals and residents need to be also more active in ADR reporting. All suspect types of ADRs, whether known or unknown, serious or not and sought after (clinical study) or unwanted (spontaneous). Moreover, the reporting of ADRs for lack of effectiveness (infurious and adulterated medicines), excessive dosage, antibiotic resistance and suspect pharmaceutical defects is recommended.

VACCINES AND BIOLOGICAL MEDICINES

Modified safety control systems are necessary for vaccines and biologic medicines. It is often given to healthy kids. This is especially true of vaccines used under a national immunization programme. The whole cohort of birth and therefore a large proportion of all the population in many countries are exposed to a particular vaccine. People's safety expectations are high and even a small risk of adverse events are reluctant to face. Real or imagined concerns about vaccine safety may lead to confidence loss throughout the vaccine programmes. This can lead to bad compliance and the resulting resurgence of vaccine-preventable disease morbidity and mortality. Vaccine safety monitoring and management difficulties are complicated by the causal association issues between an adverse event after immunization and vaccine [10,12]. Vaccine safety issues are also complicated. For instance, de-challenge and re-challenge information is often missing and vaccines are delivered to most birth cohorts in the country at the age where coincidence is likely. Multiple vaccines will likely be given simultaneously. Never overlook the possibility of programmatic errors. A medical incident that results from errors in vaccine transport, storage, handling or administration is a programmatic error. The Regulatory Authority's responsibility is not limited to the safety of immunization programmes' vaccines. In specific patient populations, several biological products are used as preventive or curative measures. Efficient regulation of these products is crucial to avoid the potential damage to the public arising from poorly produced vaccines and biologic medicinal products or inadequate transportation and storage of them. The safety of biologics and blood products has been subject to public scrutiny in recent years. Substances of concern about the safety of animal medicinal products related to varied CJD and to infectious organisms such as HIV and hepatitisB contamination of blood and blood products were raised[12]. The quality of screening, sterilization and the proper selection of donors are related to the contamination risks. The use of plasma-based medicinal products should be aligned with the PV programs in these safety issues. In order to do this, PV centers would have to take the specific safety issues of these products into account. Expertise is necessary in biotechnology, virology and medical microbiology. In order to test the efficacy and safety of biological medicine, clinical trials in large patient populations are under consideration.

CLINICAL TRIALS IN INDIA

Global pharmaceutical companies have found India to be a preferred destination for clinical trials because India's clinical research space and opportunities are very attractive. Some of the advantages for clinical trials that India has as are as follows:

- High degree of compliance to international guidelines such as the International Conference on Harmonisation (ICH) / WHO Good Clinical Practice (ICH-GCP) and the regulations lay down by the US Food and Drug Administration.
- Availability of well qualified, English speaking research professionals including physicians.
- Ongoing support and cooperation from the government.
- Lower cost compared to the west.
- Increasing prevalence of illnesses common to both developed and developing countries.
- Availability of good infrastructure.
- Changes in Patent Laws since January 2005.

The scientific feasibility, medical infrastructure, clinical trials, regulations, commercialisation potential and cost competitivité are, in recent times, the main drivers of the metamorphosis of Indian clinical research, as stated in a recent report by the Federation of Indian Chambers of Commerce and Industry (FICC I). The benefits of better understanding the Indian scenario, offering services at more competitive pricing, and improving our knowledge of the research sites in the countries in comparison with the new entrants to the market were offered by Indian-born contract-for-research organisations. India's current favorable regulatory framework and international standards regulations, increased awareness of the guidelines of good clinical practice, and their application by clinicians are some of the main reasons for India's growth in clinical research. Figure 1shows the rational therapeutic division of clinical studies and the availability of various patients across key therapeutic segments in India.

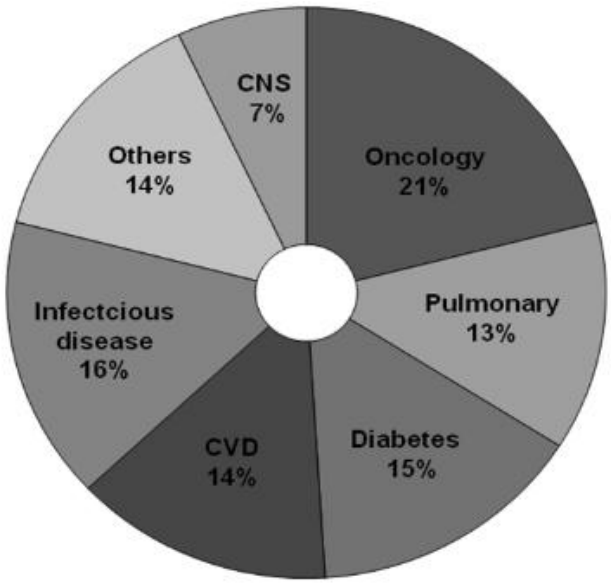

Figure 1: Therapeutic area wise distribution of clinical trials outsourced to India

THE CHALLENGES OF PV IN INDIA

The greatest challenge to the PVPI is to report seriously negative effects. There are many reasons for this including the absence of medical knowledge and adequate skills of photovoltaics and the national insufficient knowledge of photovoltaics. The other challenges are still conservative infrastructure with a wide time interval between directions and legislation, an orthodox attitude towards new pharmaceutical research, and almost nonexistent PV and regulatory inspections. The system must be refined with the help of PV experts and IT, because India boasts a highly-designed IT industry. Since PV is responsible for many ADRs the development and construction of a robust system would be wise for PV experts to work with the software professionals. Developed software programs are suitable for data sets to be collected, analyzed, drug usage trends determined in different disease areas, compliance with the rules, drugs errors, and ADR-related drug interactions. Furthermore, with more clinical research and photovoltaic outsourcing in India, the DCGI's investment in a solid PV system was useful for assessors and decision-makers to analyze safety data and take legislative decisions without having to rely on others. Sometimes, however, admission doctors fail to recognize ADRs and ADRs can be responsible for many patients' deaths. In addition, the health system also has enormous financial costs for ADRs. On the market, patients self-medicate and switch between prescription-only medicines (POM) and over-the-counter medicines (OTCs) more broadly, and this is the primary reason for exposure of them to ADR, when new medications are started without long term safety studies. India's regulatory agencies and drug companies in the earlier period based their safety assessments on long-term experience. In recent years, many Indian companies have increased their research and development investments and have increased their ability to develop and commercialize new medicines through their own research efforts. Once a product is marketed, new information is generated that can affect the product's risk-benefit profile. For all products, a detailed assessment is important for ensuring their safe use of the new information generated by PV activity. DCGI should therefore take some tough decisions and undertake to make PV mandatory and to begin the culture of photovoltaic inspections.

CONCLUSION

National and international pharmacovigilance data for potential signals have been analyzed for the analysis of pharmacovigilance data. Vigiflow software has assessed for its causehood, gravity and severity the forms of spontaneous adverse drug reaction reporting reported under the National Pharmacovigilance Program and entered the WHO database. These data have been evaluated and certified by WHO experts for WHO Vigiflow data entry. Forms of ADR reported under the NPP were incomplete with important information that caused difficulty in the conduct of the causality evaluation.

Not only are healthcare professionals unaware of the importance of ADR reporting, but also because there are no columns in the ADR form itself which provide important information needed to evaluate their causality. The complete procedure for performing pregnancy tests before isotretinoin was observed by very few dermatologists and practitioners. Without a prescription for women (including visibly pregnant women) pharmacists dispensed isotretinoin without instructions to not pregnant during taking this medicine. The package inserts mention two pre-pregnancy tests before a female patient is placed on the drug; however, no mention of double contraception, i.e., one hormonal or other barrier method, was given to avoid remote chances for pregnancy in the patient's information sheet. This ignorance by healthcare professionals puts India's women at risk; therefore, awareness of the potential preventable damage from teratogenic drugs needs to be educated and diffused among patients, prescribers and pharmacists. Thus, a simpler and more practicable risk reduction method has been developed to minimize women who are married and unmarried, in which a doctor can avoid prescribing teratogenic medicines where other medication options can be used and if isotretinoin is required, they must interact with the patient's family to explain precautions during therapy.Vigiflow was previously used only for adverse events related to drugs. The software did not contain specific fields necessary for entry of vaccine-related adverse events. Such fields have therefore been identified and developed in Vigiflow. For official use by the WHO and then Indian health professionals, a detailed instruction guide on how to enter AEFI in Vigiflow was prepared In order to make the training program more interactive, PowerPoint presentations and hands-on training were included. Practical training helped the participants, because many practical problems were encountered when they entered the case which was easily resolved. Various types of sample cases have been requested in order to help participants in the different scenarios understand the data entry process for a range of cases. The evaluation scored 50% and higher for all participants. These training courses should be conducted on a regular basis for healthcare professionals to evaluate and, where necessary, provide further training.

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