PHARMACOVIGILANCE IN CLINICAL RESEARCH: PAST, PRESENT AND FUTURE

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REVIEW ARTICLE

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ABSTRACT

The growing clinical research after the product patents rights for the pharmaceutical industries as per the trade related aspects of intellectual property rights agreement and adverse drug reaction monitoring of the marketed drugs have raised many ethical and regulatory issues regarding the promotion of new drugs in Indian markets. It becomes vital to understand the history, growth and evolution of the regulatory aspects of drugs which are handled by multiple Ministries and Departments of the Government of India. Although amendment to Schedule Y, registration of Ethics committee, registration of Clinical Trials, Speeding up review process, Pharmacovigilance (PhV) programme for India and Inspection of clinical trial sites have been started by the various regulatory agencies. India's growing partaking in multinational trials, this artifact explores potential areas of Indian pharmacovigilance, requiring reform and provides recommendations for building a robust safety reporting system. (1) Despite global focus on Development Safety Update Report, local regulators are not yet insistent on real-time update of a drug's cumulative safety profile. Issues like reporting requirements for generic trials, pregnancy reporting and lenient timeline for death/life-threatening events need attention. (2)

Keywords: GCP, CDSCO, DSUR, adverse drug reaction (ADR), Development safety update report, Pharmacovigilance (PhV) expedited reporting, serious adverse event, suspected unexpected serious adverse reaction.

INTRODUCTION

Fight with the disease is ever evolving frontier for human beings. Discovery of new drugs and devices through clinical research are the armamentarium to help fight with affliction of mankind. Because of this sustained demand to develop a new therapeutic agent, biomedical research is conducted to enable discovery of more effective and safer medication and discovery of new therapeutic uses of already established drugs. (3) Thus clinical trials are important link between pre-clinical discovery of a new lead and their use. The concept of pharmacovigilance or safety monitoring in clinical trials is relatively new in this country. However, the ever-rising number of global clinical trials being conducted in India underscores the need for a robust pharmacovigilance system that is in line with international norms. (4)

Of late, there is growing interest towards Indian Pharmaceutical Industry in outsourcing pre-clinical and clinical bio-medical research from abroad. (5) There is a great interest in treating this population with upcoming medicines and vaccines, especially given the large burden of disease here. India accounts for 20% of the world's disease burden and 16% of the world's population, but less than 1.4% of global clinical trials is done in India. (6) It is forecasted to grow at a compound annual growth rate of 30%.(7,8) A recent report from the Indian Government's Planning Commission found that the country needs between 30,000 and 50,000 additional research personnel including investigators, auditors and staff qualified to serve on ethics committees and data safety management boards. (9)

Admittedly, a lot of effort had been put in place by Indian regulators to ensure a stringent safety monitoring process. The Indian Good Clinical Practice (GCP) guidelines, published in 2001, provided definition of adverse event (AE) and adverse drug reaction (ADR) and defined responsibilities of the investigator and sponsor

with regard to safety reporting. As per this guideline, investigators should promptly report all ADRs and AEs that are serious and/or unexpected to the Ethics Committee (EC) and the sponsor, while the sponsor should expedite reporting of all serious and/or unexpected ADRs to all concerned, including EC and regulatory authorities. (10) Despite the fact that Indian GCP was not legally binding and did not specify timelines for reporting, it set forth, for the first time, certain requirements for safety reporting.

The Past

The Indian government, realizing the potential of clinical research for new therapies, has modified and amended Schedule Y to the Drug and Cosmetics Rules of 1945. Schedule Y establishes a set of guidelines and requirements for clinical trials. (11) However, Schedule Y was written with the generics industry in mind but increase entry of foreign pharmaceutical companies after the introduction of strict patent rules in the area of clinical research led the government to introduce many changes. The government recognized the importance of their regulation and thus developed Ethical and Regulatory Guidelines. The Indian Council of Medical Research (ICMR) issued the Ethical Guidelines for Biomedical Research on Human Subjects in 2000 (12) and CDSCO released Indian Good Clinical Practice (GCP) guidelines in 2001. (13)

Without a regulatory requirement for GCP compliance, however, most companies did not invest in clinical trials. Low quality data resulted in worsening India's reputation. Also, India's strict bureaucratic system made it hard to manage simple tasks like getting customs clearance for the equipment's. There were regulations which resulted in a phase lag, allowing companies to conduct a Phase II trial in India only if a Phase III study was going on somewhere else. (14) But in 2005, CDSCO made drastic revisions to Schedule Y to try to bring it on at par with internationally accepted definitions and procedures. The changes which took place were

1. Definitions for Phase I-IV trials, which eliminated the Phase lag. (15)
2. Clear responsibilities for investigators; and sponsors.
3. Requirements for notifying changes in protocol.

The Indian Government gave another boost to the drug-development industry by canceling the 12 percent service tax on clinical trials in 2007. (16) In February 2009, the industry applauded new regulations on exporting samples.

Current Scenario

Clinical trials has been defined in Rule 122DAA of the D and C Act in India as “Systemic study of new drugs in human subject(s) to generate data for discovery and/or verifying the clinical, pharmacological (including pharmacodynamics and pharmacokinetics) and/or adverse effects with the objective of determining safety and/or efficacy of the new drugs. (17)

Although every sponsor is mandated to submit developmental safety update report and periodic safety update report but many drugs when exposed to larger masses during the marketing cause newer and unpredictable adverse effects. The government of India has launched the Pharmacovigilance Programme for India (PVPI) in July 2010 through CDSCO to monitor such developments. (18) It was launched in five phases. The first phase was introduced in mid-2010 with an objective of inducting ADR Monitoring Center (AMC) in 40 Medical colleges in one year; 60 more AMC centers are to be added by early 2012 and 100 by 2013. Various hospitals, Medical Colleges and private nursing homes were covered till 2014. CDSCO provided the operational and logistic support such as Internet connection, computer, telephone line and WHO will provide free softwares for ADR monitoring such as VigiBase and PaniFlow for ADRs due to vaccines. The National Coordinating Center (NCC) of PVPI is located at ‘Indian Pharmacopoeia Commission (IPC), Ghaziabad (19) and provides all the technical supports to the CDSCO office. ADR reports generated at AMCs are sent to coordinating center which collate, assess and incorporate them into Pharmacovigilance database. The reports finally conveyed to WHO-Uppsala Monitoring Center ADR database.

The major objectives laid down by PvPI are:

1. To create a nation-wide system for patient safety reporting
2. To identify and analyse the new signal (ADR) from the reported cases
3. To analyse the benefit - risk ratio of marketed medications
4. To generate the evidence based information on safety of medicines
5. To support regulatory agencies in the decision-making process on use of medications
6. To communicate the safety information on use of medicines to various stakeholders to minimise the risk
7. To emerge as a national centre of excellence for pharmacovigilance activities
8. To collaborate with other national centers for the exchange of information and data management
9. To provide training and consultancy support to other national pharmacovigilance centers located across globe

The primary objective of DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period, related to a drug under investigation and not to provide initial notification of significant new safety information. (20) DSUR, being a cumulative report spanning over entire clinical development period, has unique value in identifying trends and patterns of safety issues related to an investigational product, which cannot be derived by looking at individual serious event reports in isolation.

Since CDSCO does not require DSUR, for Indian pharmaceutical companies undertaking global trial for a locally developed drug, Indian regulators will not have real-time update of the drug's developing safety profile, while foreign regulators (such as ICH countries) having requirement of DSUR will have this information. This underscores the relevance of DSUR to Indian pharmaceutical companies undertaking indigenous drug development. With the global focus on DSUR, Schedule Y needs to be revised incorporating similar provision of providing cumulative safety updates to the regulators during clinical development phase.

Recent initiatives unveiled by PvPI include provision of a toll-free number, a revolutionary mobile application which simplifies the process of ADR reporting, adverse event reporting forms in six regional languages to encourage consumer reporting and a mandate to the pharmaceutical industry to submit reports in XML-E2B (Extensible Mark-up Language) format. It is worth noting that various Indian headquartered global pharmaceutical companies have established in-house PV units that operate by adopting global standards even before PvPI rolled out any mandates, in order to remain compliant with PV regulations outside India. PvPI has also set up a PV system in tuberculosis and HIV/AIDS-related health programmes with WHO support. The IPC is all set to become the first WHO Collaborating Centre for safety of medicines and vaccines in South-East Asia. It is evident that, by being a progressive program of the CDSCO and without the controls for any executive jurisdiction, PvPI has made positive strides. Earlier in 2015, the Drugs Technical Advisory Board (DTAB) recommended mandating pharmaceutical companies to report adverse effects of marketed medicines. Although recommendations were proactive, the legislation for mandate came in only in March 2016. The periodic communications and interactive discussions between PvPI and its stakeholders have brought progression in receiving ADR reports as many pharmaceutical companies consider reporting ADRs as an industry practice. As a result, the ADR reporting rate by the pharmaceutical industry to PvPI was 18.80 per cent in the year 2015.

The Future: A way forward

Though the PvPI is a huge step forward in the right direction for accumulating Indian pharmacovigilance data, it is currently restricted to the approved medical college hospitals in India, public health programmes, and autonomous institutes like the Indian Council of Medical Research (ICMR).

Figure 3: Roadmap of Pharmacovigilance Programme of India

The data received by PvPI is shared with the WHO through their VigiFlow and PaniFlow software but not shared with the concerned pharmaceutical companies, which misses the opportunity for understanding and managing the risks identified.

However, it is understandable that, being the beginning, it is not possible to set up a holistic pharmacovigilance system overnight and hopes are bright that the PvPI will become the centre of excellence for Pharmacovigilance in the Asia Pacific, as it targets, in due course.

It is strongly felt that, apart from the PvPI, Indian pharmaceutical companies also should educate all their staff on adverse event reporting and ensure that a proper pharmacovigilance plan is put in place for the products they market in India, as they do for their international operations in the regulated markets. (21)

The long term goals may include the expansion of pharmacovigilance programme to hospitals (govt. & private) and centers of public health programs located across India. The development and implementation of electronic reporting system (e-reporting) may take PvPI to other heights for adverse event reporting in India. The reporting culture amongst healthcare professional and making ADR reporting a mandate for HCPs in country can further add value and help potentially the public health.

Perspective

Sponsors of human drug and biologic products subject to an investigational new drug (IND) application are required to distribute expedited safety reports of serious and unexpected suspected adverse reactions to participating investigators and MoH to assure the protection of human subjects participating in clinical trials. The submission of uninformative expedited safety reports by commercial sponsors of INDs continues to be a significant problem that can compromise detection of valid safety signals which continues to be an issue in India. The common questions to consider this perspective may include how can we envision an alternative model for reporting important new safety information to investigators and patients during the conduct of a clinical trial or how can we better evaluate safety of an investigational product across multiple clinical trials and indications for use.

CONCLUSION

For obvious advantages, global players view India as a favored destination for conducting clinical trials. The activity, in the long run, has the potential to help our citizens, professionals and society. However, our infrastructure and systems are not yet in the optimal state to meet this challenge. Indian policy makers, administrators and professionals should initiate positive steps to ensure that this opportunity is exploited to its maximum potential.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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