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Review Article

IMPACT ON CLINICAL TRIAL STUDIES DUE TO REGULATORY AMENDMENTS IN INDIA: A LATEST REVIEW

Abhimanyu Thakur*, Aishwarya Roy and Sriram Mullapudi

Dept. of Pharm. Science & Technology, Birla Institute of Technology Mesra, Ranchi, Jharkhand-835215, India

ABSTRACT

Schedule Y of Drug and Cosmetic Rule, 1945 plays an important role in regulation of clinical trials in India. There have been various rules there under to regulate the conduct of clinical trials. In spite of these, several incidences of non compensation to the volunteers, non compliance of regulatory requirements, the implementation of unethical procedures, and health related issues, improper documentation procedure being employed by multinational companies and malpractices by the government and private doctors during the clinical trial have been reported. A good number of unethical clinical trials have also been reported in the recent past. From time to time, many regulatory amendments have been done to enforce better laws to safeguard the rights, safety and well being of the trial subjects. This paper reviews the latest regulatory amendments in India and its impact on clinical trials.

Keywords: Regulatory amendment, Clinical research, Schedule Y amendment, Regulatory affairs, Clinical trials.

INTRODUCTION

The Clinical trials in India have recently been a witness to an unexpected and sudden change in the regulatory area encompassing various amendments to the Drug and Cosmetic rules 1945. The approach for the conduct of clinical trials in India, in the recent years is based on an irregular and irrational attitude by the people responsible for the conduct of these trials.[1] There are reports and evidence presented by the media which highlights the violations in clinical trials, the most common being poor patient safety, inefficient ways of handling documents and record keeping. The reason for the recent amendments to schedule Y is that it came to the notice of the honourable Supreme Court of India that the multinational pharmaceutical companies are conducting the trials in an unethical manner and using poor and illiterate Indian patients as "GUINEA PIGS". There has been an inadequacy in the conduct of clinical trial, the process of seeking informed consent, the compensation for the human volunteers in case they meet injury/death during the clinical trial.[2] So, there were amendments to schedule Y of Drug and Cosmetics rules, 1945 which was introduced in January, 2005. There was also adoption of Patent Amendment bill that provided an assurance of Indian patent legislation with trade related intellectual property right patent regime of World Trade Organization (WTO). Along with amendments in schedule Y other measures taken up by regulatory bodies are registration of Contract Research Organizations (CROs), registration of clinical trials, introduction of Pharmacovigilance Program for India (PVPI), review process speed up. These amendments have resulted into increased number of clinical trials being conducted in India on a global basis and at

the same time strict and vigilant approach with which these global clinical trials are conducted. The recent amendments to schedule y are as follows:

- 122 DAB: provides specifications for the procedure of compensation to the subjects of trial in case of injury or death.[7]
- 122 DAC: specifies conditions for conductance and inspection of trials.[8]
- 122 DD: provides specifications about guidelines for ethics committee registration.[9]

Other regulations are:

- Recording of informed consent in audio-video format.
- Dr. Ranjit Roy Chaudhary report which talks about framing of strict policies and guidance for new drug approval, banning of harmful drugs and appropriate environment in which clinical trials are being conducted.
- Reporting of serious adverse events to CDSCO.
- The Drug and Cosmetic (amendment) Bill 2013- yet to be introduced.[13]

CASE REPORTS

In 2012, 436 people died due to serious adverse events during clinical trials; the union health minister Mr. Ghulam Nabi Azad then stated in the parliament that "the deaths could be due to life threatening diseases such as cancer, heart failure or stroke or side effects of drugs or their administration to terminally ill patients or critically ill patients and such deaths are investigated to arrive at casual relationship if any". A health ministry report in 2010 suggested an incidence in which a phase IV clinical trial for an HPV (Human Pappiloma Virus) vaccine was performed on unsuspected tribal girls, it led to death of 7 girls due to which whole trial process was suspended on April 7, 2010. A Committee was constituted to do an enquiry which indicated that an US based NGO named PATH was funded billions of dollars by Bill and Melinda Gates Foundation and it was responsible as they had conducted the trial in an unethical manner, even when the consent forms were scrutinized it was found that there was a statement saying "You will not be charged for your daughter to receive the vaccine". The NGO got away with just a warning letter asking them to be careful in future as stated by an official of health ministry. An incidence which questions India's drug control body is the use of DENXIT, an antidepressant marketed by a Danish company was sold to India and it took 14 years to establish its safety and efficacy until it was questioned. The drug was banned in countries like Britain, Ireland, Canada, Japan, Australia, USA and even in Denmark as it is a combination of two drugs FLUPENTHIXOL & MELITRACEN; MELITRACEN being a banned one. The usage of the drug leads to abnormal heart rhythms when taken with other drugs, so the DCGI on Dec 10, 2013 gave an ultimatum to the company to prove the safety and efficacy of drug in 6 months duration, failing which it will lead to ban on its sale and manufacture in the country.[3]

The ultimatum came out by DCGI as a report was submitted by the parliamentary standing committee in the year 2012 which strictly questioned the regulatory body of India to the approval of an illegal drug for so long and which violated the Drug and Cosmetics act which states that "A drug not being approved in its country of origin cannot be approved in India". Questions on the approval of this drug were raised long back in 2009 by Drug Technical Advisory Board (DTAB), but no decision was taken until the parliamentary standing committee took an initiative. As pointed out by Dr. C.M. Gulhati, Editor of Monthly Index of Medical Specialties (MIMS) "The DCGI made no attempts to explain its part on the approval of a drug for such a long time", the parliamentary standing committee report suggested that DCGI should have looked out for clues like the drug not being marketed in major developed countries e.g., USA, Britain, Japan, Australia instead the concentration of the manufacturers was on tiny markets like Bangladesh, Kenya, Myanmar, Pakistan though the developed countries have a large market pool and profits. When inquired Health Ministry was incapable of providing the documents of approval

of file no. "12-62.95-DC" and date of approval (20-10-1998) was found with no reports of clinical trials being conducted on this drug. In 2011, 438 cases of SAE (Serious Adverse Events) were reported, only 16 was believed to be due to clinical trials and previous 668 reported cases of SAE where 22 was due to trials.[3]

An investigation conducted by The Independent in 2011, exposed various issues for e.g., recruitment of 100's of tribal girls without consent of parents, the use of survivors of the most world's most poisonous gas disaster for trials without any informed consent and the government doctors in Indore who considered themselves as the sole authority and violated all the ethical guidelines for conduct of a clinical trial. All these led to strict actions being taken upon by court and higher authorities in India. The Honourable Supreme Court stated that "the government was in a deep slumber'' when danger prevailed due to clinical trials. Judge R.M. Lodha stated that "foreign companies were treating India as heaven for clinical trials and it was proving to be hell for India''. A Statistic conducted by government revealed that between 2005-2012, 2644 people died during clinical trials out of which 80 deaths were due to the molecules on which they were tested and 500 or more suffered serious adverse reaction.[4]

Even the deaths are not properly recorded in clinical trial government records, a reliable estimate of total number of deaths per year cannot be determined exactly or can vary with number reported in the trial publications, for e.g., in 500 randomly selected clinical trial government records only 123 or 25% were found to be documenting a report on number of deaths.[5]

When Right to Information (RTI) query was filed by medical right activist, it was found that 2000 people in India died as a result of serious adverse events during trial between 2008 -2011, out of which only 22 cases or 1% received compensation. As reported by The Hindu: "The reason for such small number of cases receiving compensation is pharmaceutical companies conducting clinical trial; pay compensation only in cases where it is established that death was due to the trial and not merely during the trial '' but it is the companies that decide whether a death was due to a trial or not, so conflict occurs as the companies want to pay compensation to lowest possible number of cases. Dr. Rai, WHO founded Clinical Trial Victim Association in Madhya Pradesh "we believe all SAE related deaths should receive compensation" so he has filed a petition in the Supreme Court. Also the Indian government is not strictly involved in looking into deaths due to trials, reports of violations for e.g., improper informed consent received by participant or trial on children and mentally challenged people in an unauthorized manner. Although these trials are being conducted by western drug companies like Pfizer & Astrazeneca which has to receive its approval by USFDA but FDA does not have jurisdiction to have access to the confidential records as per international law.[6]

According to a studied research data, a study led by a group of researchers came in to Journal of Medical Ethics; these researchers reviewed around 84 warning letters issued by FDA to clinical investigators, sponsors and IRB (Institutional Review Board) in year 2005-2012 to find out the violation of rules during trial. Most common of them was for investigators, shifting of the plan of investigation (93%), failing to protect the volunteers involved in trial, failing to lodge a report to IRB in case of adverse events, failure to maintain and handle records (40%). In case of sponsors, they fail in monitoring how the trial is being conducted i.e., its progress, they fail to obtain agreement from Principal Investigator (34.8%). Recent violations that have come to limelight are failure to obtain approval by IRB before initiating a study and submission of false data to FDA and trial sponsors.[11]

There have reports of clinical trials being conducted on mentally challenged patients in Indore unethically by doctors of government medical colleges and private practitioners.[10] It has also been reported that from 2008 to 2010, the ethics guidelines have not been followed. A fine of Rs. 5000 was charged by Madhya Pradesh government on the doctors involved which can be

regarded as an insufficient punishment .[11] This incidence raises questions on the part of regulatory bodies, ethics committees, irregularities in documentation, informed consent by the participants.

LATEST AMENDMENTS TO SCHEDULE Y

Rule 122- DAB, Rule 122 DAC and Rule 122 DD in the Drug and Cosmetic Rule, 1945 [2, 8-10]

With the introduction of the concept of Good Clinical practices (GCP) the standard has been set for designing, conducting and recording the clinical trials involving human volunteers. Earlier the norms encompassing the compensation to the volunteers who suffer any sort of injury or death while participating in clinical study of a new drug were not discussed clearly under the Drug and Cosmetics Rule, 1945. According to the latest amendment, new rules 122-DAB, 122 DAC and 122 DD have been inserted to bridge the gap in context of the provisions for compensation.

Rule 122-DAB: The Drug and Cosmetic (First Amendment) Rules, 2013[7]

According to Rule-122-DAB, free medical support should be given to the clinical trial subjects in case of any injury during the conduct of clinical trial. If the injury is related to the trial by any way, the financial compensation should be given to the subject as per order of Licensing Authority. In case the subject died due to the clinical trial, the nominee(s) should be compensated by financial compensation. The sections preceding this rule elaborates the circumstances which is referred as a "direct nexus" to an immediate cause of injury/death, fate of non-payment of compensation. Earlier the reporting of serious adverse effects (SAEs) within 24 hours was only limited to sponsor by the investigator whereas after the amendment, the reporting of SAEs have been extended to Licensing Authority, sponsor and the Ethics Committee (EC). After the amendment, the sponsor is required to send the reports of SAEs by their medical affairs team where as prior to the amendment this task was done by Bioequivalence centres. The SAEs report has to be done in colour coded binding as per the latest amendments which involve red cover for SAEs of death, blue cover for SAEs of injury other than death and white cover for remaining cases.

Rule 122-DAC: The Drug and Cosmetic (Second Amendment) Rules, 2013[8]

This rule entail the requirements for a clinical trial to be considered as adequate so that permission from the Licensing Authority can be granted for the conduct of clinical trial on human subjects. Moreover, any additional condition if laid down by the Licensing Authority is required to be fulfilled for the grant of permission to conduct any specific clinical trial. As per this amendment, the Licensing Authority has the right to investigate the sponsor which includes investigation of all the staffs, subsidiaries, contractors, trial sites and investigators for seeking the compliance of the regulatory requirements and applicable guidelines. It is necessary that all the stakeholders comply with the regulatory requirements where knowledge of Good Clinical Practices (GCP) is required.

Rule 122 DD: The Drug and Cosmetic (Third Amendment) Rules, 2013[9]

According to this amendment, the Ethics committee should be registered with the Licensing Authority as defined in clause (b) of rule 21 prior to the conduct of review and approval of any clinical trial protocol. It also describes the procedure of registration as per the requirements as specified in Appendix VIII of Schedule Y of the rule.

IMPACT OF REGULATORY AMENDMENTS ON CLINICAL TRIAL INDUSTRY

The amendments made to schedule Y have made our regulatory organization strong, vigilant and active, for e.g., Central Drugs Standard Control Organization (CDSCO) is constantly putting its efforts by introducing guidance document submission of application in Common Technical Document (CTD) format, compulsory registration of clinical trial and CROs' duty free import of clinical trials product so as to highlight transparent and accountable picture of CDSCO,

being one of the highest regulatory bodies in India. All these efforts have led to a boom in the clinical research industry. Due to amendment in Drug and Cosmetic rules, 1945 in relation to compensation given to clinical trial patients, a pre screening of all clinical trial application is done so as to have a complete submitted file. There has been a checklist available on CDSCO's website for enlisting and submitting drugs and other medical devices. The Indian government on its part has appointed 12 NDACs (National Drug Advisory Committee) and MDAC (Medical Device Advisory Committee) to advice CDSCO on issues like new drug approval and clinical trials conducted by multinational drug companies in India. There has been an ongoing review on issues related to compensation of patients on clinical trials by all the stakeholders and expert committee members on a global platform. The working of whole organization and committee is basically a simultaneous process, after pre-screening application is accepted by CDSCO and after the review of application on a technical basis is forwarded to advisory committee for their respective opinions. The expert decision comes within 6 weeks of time and on receivable of opinion CDSCO takes further action. A meeting is called for between committee members and CDSCO members, when no response comes from the expert even after 45 days.[12]

Registration of clinical trials with the clinical trial registry on a central basis has been approved for India as well as other nations. There is a committee called International Committee for Medicinal Journal Editors (ICMJE) which played a major role in establishing this new regulation. As per this new regulation, the ICMJE member journals need a trail registration not to be submitted prior to publication of a clinical trial data. Further publication appeared on Indian Journal of Medical Research and it came to the notice of Drug Controller General of India and the trial registry was made compulsory within effective date of 15th June 2009. The amendment have resulted into reporting of SAE (Serious Adverse Events) that includes death as well as the amount that is paid as a compensation by the sponsor timely to the clinical trial patients. This is looked into by a panel of expert committee members which does a strict scrutiny of the report and passes its assessment to DCGI within 30 days. DCGI then solely decides the amount to be paid as compensation to the victims of clinical trial by the sponsor and thereby passes a verdict on to the report within 3 months of submission of its report. A formula was found for deciding the compensation amount as follows:

C=B*F*R/99.37

C= Compensation,

B= Base amount (8 LAKHS),

F= Factor depending on age of subject,

R= Risk factor depending on scrutiny of disease, co-morbidity and duration of disease at the time of enrolment in clinical trial ranges between scale of 0.5 - 4, where, 0.5= Terminally ill patients, 1.0= Highly risky patients, 2.0= Moderately risked patients, 3.0= Patients at mild risk, 4.0= Healthy volunteers.

Estimated amount can vary from 4 to 73.60 Lac and it depends on factors stated above. This amendment made to schedule Y as rule 122 DDC, drafted by GSR 63 OF Drug and Cosmetic rules as per date 1st Feb 2013 requires a prior approval for conductance of clinical trial by Licensing Authority (LA) and in accordance with protocol. Added specifications are prior approval by Ethics Committee (EC) before initiation of trial and registration with CTRI.[1] Annually, a report is submitted to DCGI in approved format as given in Appendix -XI of schedule Y. Registration of EC was notified by the GSR 72 (E) on 8th Feb 2013, rule 122 DD in Drug and Cosmetic rule, 1945. The validity of registration is for 3 years unless terminated. The EC generally is involved in approval and review of protocol, investigators and facilities, obtaining methods of study and collection of adequate information for proper framework of informed consent. This made EC much more systematic, reliable, clear and transparent, confidentiality of patients being an important aspect. As drafted by GSR 364(E) dated on 7th June 2013 and proposed in Drug and Cosmetic rule, 1945 about compulsory audio-video recording of the complete procedure of

informed consent. Two important aspects of the informed consent process are that it should always include a statement clearly specifying the chances of failure of Investigational Product (IP). Also it should include that in case of Placebo Controlled Trial; there is no therapeutic effect as such on patients with placebo. There was an introduction of a bill in Rajya Sabha on 29th Aug 2013, named the Drug and Cosmetic (amendment) bill, 2013 which acts to establish a committee called CDA (Central Drug Authority), comprising of 19 members that would regulate overall drugs and cosmetic industry supervised and headed by Health Family Welfare and Secretary.[1]

The clinical trial applications are currently being observed and evaluated by new drugs advisory committee/ IND Committee, revised by Technical Committee and approved by Apex Committee. Other measures taken to strengthen the regulation other than amendment to schedule Y is submission of Dr. Ranjit Roy Chaudhary Committee Report, it was framed by authorities from Ministry of Health and Family Welfare, for preparation of policy, guidelines and SOPs for approval of Clinical Trial Study. It framed formula for deciding the amount of compensation given in case of death due to clinical trials. There are Independent Ethics Committee which reviews BABE study of the molecules which has already been approved and a periodic checking and review of clinical trial being conducted currently for which approval was given earlier.[13]

There has been an introduction of PVPI in which a sponsor has to compulsorily submit Periodic Safety Update Report (PSUR) as there are several drugs which on post marketing, on administration to large masses can cause unexpected and serious adverse events (SAE). There was a launch of PVPI on July 2010 by CDSCO in five phases with an objective to establish Adverse Drug Reaction (ADR) monitoring centres in 40 medical colleges in 1st year, 60 or more to be added by 2012 and 100 by 2013. It aims to cover hospital, medical colleges as well as private nursing homes. The CDSCO acts as a support system and provides all technical assistance for e.g., internet connection, telephone line and availability of free software by WHO viz., VIGIBASE, PANIFLOW (ADR due to vaccines). The NCC of PVPI is located at IPC in Ghaziabad; aids to provide technical support to CDSCO office. ADR reports are then forwarded to coordinating centre which receives, assess and compiles it to PV database and finally forwarded to WHO. The review process has been updated and speeded by division of application in two categories viz., Category A and Category B.

Category A Application is received from the countries where in exists this form of speedy review process and international ethical rules and guidelines are being followed. Category B is other countries application form. It has decreased the duration of various processes from 16 weeks to 10 weeks and further aim is to set at 45 days. Also introduction of E-Tracking system of government files. From 2010 onwards, a strict and vigilant system of inspection is led by USFDA, comprising of trained Indian inspectors and authorities from central regulatory bodies.[14]

CONCLUSION

In the era of globalization, Pharmaceutical sector is witnessing tremendous developments. India seems to be a hub for a good number of Multinational Companies for drug innovation because of relatively economic cost and skill base to accomplish the purpose of conducting clinical studies. But along with this it has also been seen that India is unable to enforce and implement a strict and vigilant norms for the companies who are conducting such trials at the cost of lives of poor and vulnerable subjects. Many subjects are not even acquainted with norms pertaining to their safety and laws related to their right. Hence with recent regulatory amendments this can be assumed that these amendments have brought light of hope to many vulnerable subjects participating in clinical studies and it can be expected that the various regulatory guidelines will be a reality and not just on papers.

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Correspondence Author:
Abhimanyu Thakur
Dept. of Pharm. Science & Technology, Birla Institute of Technology Mesra, Ranchi, Jharkhand-835215, India

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