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REVIEW ARTICLE

Handling of Clinical Trials in India: Recent Amendments and Its Impact

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ABSTRACT

India has been considered as a hub for conducting various multi center trials, the Central Drugs Standard Control Organization (CDSCO), headed by the Drug Controller General of India (DCGI), lays down the regulations for the conduct of clinical trials in India. This trend has but changed from 2011 when most of the trials are being outsourced to other countries like China and Philippines. The conduct of trials, regulations in India and quality of data generated may be the cause for this development. Updating our knowledge about these is of utmost importance in today turbulent scenario that prevails in the pharmaceutical industry. The path was smooth until 2011 when a dramatic drop in conducting and delivering the international RCTs outsourced to India was noticed. According to certain calculations, this drop is up to 50%. At the same time international outsourcing of RCTs to China, Russia and Philippines has increased. In a pursuit to find an answer to this drastic decline-the conduct of trials, ethics, regulatory environment and the quality of data – all are challenged. This review focuses on the changes in regulatory aspects introduced subsequently and their impact on clinical trials in India.

KEYWORDS

Clinical Trials, India, CDSCO, ICMR

INTRODUCTION

In pharmaceutical field, the main regulatory law operating is the Drug and Cosmetics act (1940) and the Drugs and Cosmetics Rule (D&C) (1945). The act and Rules are binding on allopathic and other system of medicine and regulate imports, manufacture, distribution, and sale of drug in India. The clinical trial on new drugs is regulated under the provision of D&C rule 1945 as amended from time to time[1]. The rule provides that no clinical trial can be initiated without the grant of permission by the licensing authority & the condition prescribed there in. The detailed requirement & guideline for undertaking the clinical trials are specified under schedule Y of said rule and this schedule further provide that clinical trials are required to be conducted and data generated, documented and reported in compliance with the approval protocol and Good clinical Practices (GCP) guidelines published by Central Drug Standard Control Organization (CDSCO) Directorate General of Health Services, Govt. of India as well as application regulations. The changes should be made to the existing law to address and resolve these evolving issues. Recently changes in Schedule Y,

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and how clinical trials or pharmaceutical industries affected are discussed. Since Jan. 2013 to last update of 28 June 2014, The Indian regulatory authorities have announce the spit of laws and guidelines, which will have a huge impact on the clinical trial sector in India[2]. RCT is a study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to group's means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best. It is the patient's choice to be in a randomized trial.

The important changes were a 50% drop in operational cost, low per-patient trial cost, large number of qualified English speaking professionals, large patient pool with diverse ethnicity, extensive network of hospitals and laboratories, good communications with information technology and above all, easy and fast recruitment of patients.[2]

Regulatory Body of India in Clinical Trials[3]

In India, the central government's CDSCO under the Ministry of Health and Family Welfare develops standards and regulatory measures for drugs, diagnostics and devices; lays down regulatory measures; and regulates the market authorization of new drugs as per the Drugs and Cosmetics Act. The Department of Chemical and Petrochemicals of Ministry of Chemicals and Fertilizers, through National Pharmaceutical Pricing Authority (NPPA) sets the prices of drugs; maintains data on production, exports and imports; and enforces and monitors the supply of medicines and also gives opinions to parliament on the related issues.

The CDSCO office regulates the clinical trials via its central office at New Delhi and four zonal offices situated at Mumbai, Chennai, Kolkata and Ghaziabad.[4] These zonal offices work in close collaboration with the state offices to bring about uniform enforcement of the regulations imposed by the central government. Despite having many principles and bodies to regulate clinical trials, nothing much is seen in practice. The 59th report of Parliamentary Standing Committee on Health and Family Welfare stated gross lack of qualified staff, lack of co-ordination between various agencies, improperly conducted trials for 39 drugs and 33 new drugs approved without conducting clinical trials on Indian patients in the period of January, 2008 to October, 2010.

Status of Clinical Trials in India

As you may look at the status of clinical trials in India, you will be shocked to know about the fact that the number of deaths resulting from clinical trials has increased in the past few years. The number of deaths from clinical trials in India is threatening when on the other hand; the decrease in the number of clinical trials as well as approval given for the clinical trials is equally shocking. When we want to look at the reasons and causes for all these, we are in need to know about the clinical trial regulatory agencies in India.

Regulatory Agencies of India

There are four main regulatory agencies for clinical trials in India:

(1) Ministry of Health and Family Welfare

(2) Central Drug Standards Control Organization

(3) Indian Council of Medical Research

(4) Ministry of Chemicals and Fertilizers

Ministry of Health and Family Welfare

This regulatory agency which is primarily deals with healthcare. This government body has several bodies under its administrative control. Some of them are:

- Medical Council of India
- Dental Council of India
- Pharmacy Council of India
- Central Drug Standards Control Organization

- Hospital Services Consultancy Corporation Limited

This regulatory agency acts by prescribing the standards in order to ensure the safety, efficacy as well as the quality of the following products:

- Drugs

- Cosmetics

- Diagnostics

- Devices

In addition, this regulatory agency is also regulating the following aspects of clinical trial:

- Market authorization of new drugs

- Clinical trials standards

The role of Ministry of Health and Family Welfare in a clinical trial does not stop with this alone. This body will also supervise the drug imports. Furthermore, it is this regulatory agency which will approve the license to drug manufacture.

1. Central Drug Standards Control Organization

This is the national regulatory authority that is being operated under the 'Ministry of Health and Family Welfare'. This is the primary regulatory authority for the pharmaceuticals as well as medical devices in the nation. The Central Drug Standards Control Organization is serving the parallel function to the U.S. FDA, Japan's PMDA and European Union's EMA.

With this regulatory agency, it is the Drug Controller General of India who is regulating all the pharmaceuticals and medical devices. As such, the DCGI is being advised by two other bodies which are:

- Drug Technical Advisory Board

- Drug Consultative Committee

As such, the whole regulatory agency has been divided into zonal offices to perform the following functions:

- Pre-licensing inspections

- Post-licensing inspections

- Post-market surveillance

- Recalls (if required)

The Central Drug Standards Control Organization is maintaining a good track record with 'World Health Organization'. At present, this agency is planning to open its international offices in China.

2. Indian Council of Medical Research[5]

This is one among the oldest research bodies of the country. This agency is being funded by the Indian Government. The governing body of this organization is presided by the Union Health Minister. This regulatory agency is being assisted by the scientific advisory board. Various eminent experts in biomedical disciplines will assist ICMR in both scientific and technical matters. This regulatory agency is acting to promote biomedical research in the country and is considered as the apex body for the following activities:

- Formulation of biomedical research

- Coordination of biomedical research

- Promotion of biomedical research

ICMR is the regulatory body which has formulated guidelines for several aspects that are relating to national health. Treatments for conditions like malaria, cancer, type 2 - diabetes and retinoblastoma have been covered by various guidelines by Indian Council of Medical Research.

3. Ministry of chemicals and Fertilizers

The Department of Chemicals and Petrochemicals was under the Ministry of Industry until December 1989, when it was brought under the Ministry of Petroleum and Chemicals. On June 5, 1991, the Department of Chemicals and Petrochemicals was transferred to the Ministry of Chemicals and Fertilisers.

The Department is entrusted with the responsibility of planning, development and regulations of the chemicals, petrochemicals and pharmaceutical industry sector, inducting:

- Drugs and Pharmaceuticals

- Insecticides
- Molasses
- Alcohol
- Petrochemicals
- Synthetic rubber

The main activities of the Department of Fertilisers (DOF) broadly cover planning, promotion and development of the fertiliser industry, planning and monitoring of production, import and distribution of fertilisers and management of financial assistance for indigenous and imported fertilisers.

Need for changes in Schedule Y

A) To frame guidelines for the current scenario of clinical research.

B) Schedule Y 1988 is relevant to generic industry predominantly

C) Integration of India in global clinical development and legal support to global GCP guidelines

D) Improvement in Quality of clinical Trials

Significant Amendments in Schedule Y during 2013

A) Three Amendments in Schedule Y of the Drugs and Cosmetics Act

1. The first gazette notification is G.S.R. 53 (E) dated January 30, 2013, with insertion of Rule 122 DAB which specifies procedures to analyze the reports of SAEs occurring during clinical trials and payment of compensation in case of trial related injury or death as per defined timelines.

2. The second gazette notification is G.S.R. 63(E) dated February 01, 2013 with insertion of Rule 122 DAC which specifies conditions under which application for conduct of clinical trials shall be approved by licensing authority, which includes a very important point that the sponsors, their subsidiaries, agents, sub-contractors, and clinical trial sites shall allow inspectors authorized by CDSCO to inspect their premises.

3. The third amendment is related to mandatory registration of the Ethics Committees (EC) in the Drug and Cosmetic act vide G.S.R. 72(E) dated February 08, 2013 with addition of Rule 122 DD

B) Recent Amendment in the Regard of Responsibility of Sponsor

Prior to amendment, the report of SAE occurring during clinical trial have to forward to Licensing Authority within fourteen calendar days of occurrence of the SAE. But now timeline for this is within ten calendar days of occurrence of the SAE. Earlier there was no provision for sending report of SAE to Expert Committee by Sponsor, but now as per Appendix XII, there is p rovision for sending report to the Expert Committee. There was no clear mentioning about payment / compensation given by Sponsor to subject in case of injury / death, but now it is clearly mentioned that in case of any type of injury / death, the sponsor will be responsible for making payment as per Appendix XII.

C) Recent Amendment in the Regard Responsibilities of the Investigator(s)[6]

Prior to amendment the Investigator should send report of all unexpected SAE to Sponsor within 24 hours and to the Ethics Committee that accorded approval to the study protocol within7 working days their occurrence. But now investigator has to send this report to both Sponsor and Ethics Committee within 24 hours. Prior to amendment there was no such provision that Investigators have responsibility to inform the subject or his / her nominee of their rights to claim compensation in case of clinical trial related injury or death. Recent amendments include the responsibility of investigator to inform to the subject about the compensation money and other records and notices.

D) Recent Amendment in the Regard of Responsibilities of the Ethics Committee

Prior to amendment there was no such provision that Ethics Committee have to send the report of SAE to Licensing Authority within 21 calendar days. Earlier the decision about compensation was taken by Ethics Committee but now the

Ethics Committee can only give its opinion about compensation to the Licensing Authority. The Licensing Authority decides the amount of compensation after analyzing report of Ethics Committee and Expert Committee.

E) Recent Amendment in Inform Consent

In Informed Consent process, a new point have included that an audio-video recording of inform consent process of individual subject, including the procedure of providing information to the subject and his understanding on such consent shall be maintained by investigator for record.

F) Recent Amendment in Appendix V

In informed consent's Essential documents of this Appendix, few new statements has been inserted to inform subjects that in clinical trials, there may be possibility of failure of investigational product to provide the intended therapeutic effect and in the case of placebo controlled trial, the placebo administered to the subjects shall not have therapeutic effect. In new amendment version, the following statements describing about the financial compensation and medical management has been included in the Informed consent:

(a) In the event of an injury occurring to the clinical trial subject, such subject shall be provided free medical management as long as required.

(b) In the event of trial related injury or death, the Sponsor or his represent, whosoever has obtained permission from the Licensing Authority for conduct of clinical trial, shall provide financial compensation for the injury or death

(c) In format of Informed Consent Form, the following new points has been inserted

Date of Birth / Age……

Address of the Subject……

Qualification…….

Occupation: Student / Self-Employed / Service / Housewife / Others

Annual Income of the subject……

Name and address of the nominee(s) and his relation to the subject…..

Name of the witness…..

The following shall be inserted:-

- Copy of the Patient Information Sheet and duly filled Informed Consent Form shall be handed over to the subject or his / her attendant

G) Recent Amendment in Appendix VIII [7]

Prior to amendments in Appendix VII, there was no mention regarding the information required for registration of Ethics Committee, but now these are required. Earlier in Appendix VII, there were mentioned only about composition of Ethics Committee and format for approval of Ethics Committee, but in recent amendments some new requirements and guidelines have included like information required for registration of Ethics Committee, maintenance of record and inspection of Ethics Committee by the officers authorized by CDSCO.

H) Addition of Appendix XII [8]

Appendix XII: Compensation in case of injury or death during clinical trial in new amendment version, a new Appendix XII has added, which is related to compensation to be provided to subject in case of injury or death occurring during Clinical Trial. In this Appendix the complete process are described about that how reporting of injury or SAEs or death to the Licensing Authority and what is the process of analyzing SAEs or cause of death and the timeline for reporting SAEs, providing compensation also have amended as compared to prior version.

I) Submission of Reports

- The reports of SAEs of deaths should be prepared and submitted in red cover
- The reports of SAE of injury other than deaths should be prepared and submitted in blue cover
- The SAE report other than that mentioned at (a) & (b) above is to be prepared and submitted in white cover

Amendments in ICF

The Format of ICF have been amended to include-

- address
- qualification
- occupation
- annual income of the subject and
- Name & address of his nominee.
- It is mandatory for Investigator to hand over a copy of duly filled ICD to the subject or his/her attendant

Expansion of Responsibility of Investigators

- Investigator shall report SAE to the DCG (I), Sponsor and Ethics Committee within 24 hr.
- The report of SAE of death, after due analysis shall be forwarded within ten calendar days to: Chairman of the EC, Chairman of the independent Expert Committee with a copy to DCG(I) , Head of the Institution where the trial has been conducted

The Investigator shall provide information through informed consent process to the subject about

- Essential elements of the clinical trial as per Appendix-V
- Right to claim compensation in case of trial related injury or death.
- Right to contact the applicant for the purpose of making claims in the case of trial related injury or death

Introduction of Rule 122DAC (Second Amendment)[9]

- This rule specifies various conditions for conduct and inspection of clinical trials. It specifies the prerequisites required for a clinical trial to be considered as adequate ,in order for the Licensing Authority to grant permission for conduct of the trial on humans
- Clinical trial shall be conducted in compliance with the approved protocols, requirements of Schedule Y, Good Clinical Practice Guidelines for conduct of clinical trials in India and other applicable regulations
- Approval of the Ethics Committee shall be obtained before initiation of the study;
- Clinical trials should be registered in clinical trial registry of India before enrolling the first patient of the study.
- Any report of SAE should be forwarded within 10 days of its occurrence in compliance with the procedure mentioned In schedule Y
- Authority of CDSCO for inspection of clinical trial sites of Sponsor & Investigator.
- In case of non-compliance by the sponsor, Investigator s and clinical trial sites licensing Authority can take following actions:
  - ✓ Suspend or cancel the clinical trial permission
  - ✓ Debar the Investigator(s), Sponsor including his representative to conduct any clinical trial in future.

Insertion of Rule 122 DD (Third Amendment):

It deals with mandatory registration of the Ethics Committee and specifies that no Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration with the Licensing Authority as defined in clause (b) of rule 21 and describes the procedure of such registration to be made by filling an application directed to the Licensing Authority as per the requirements specified in the Appendix VIII of Schedule Y of the Rule and the procedure there of

- CDSCO can inspect the facilities, records, documents etc. of Ethics Committees.
- The registration of an Ethics Committees shall be valid for a period of three years.

Audio-Visual Recording of Consent[10]

The central government together with Drugs Technical Advisory Board (DTAB) proposed the Gazette of India notification dated 7th June 2013 to make draft rule that audio-video (AV) recording of the informed consent process of individual participant by an investigator including procedure of providing information to the subject and his understanding on such consent shall be maintained by the investigator for record while conducting clinical trials in India.[11] This step has now become mandatory. The AV recording will safeguard the rights of the subjects and stakeholders involved in the trial. Voluntary participation of patients who understand their role in the study and adhere to the study protocol is assured resulting in quality data generation. The AV recording increases the transparency and the conduct of the consent process. The customs and traditions still prevalent in many parts of India could make convincing people to appear on camera, especially women, a tough job for the site management staff. This also impacts recruitment severely. A single recording of such a long duration is difficult to achieve. In case of sexually transmitted disorders and immunodeficiency syndromes, discussing the ailment over the camera is uncomfortable for the patients and they refuse to do so. Also, a lot more costs are incurred for the equipment required.

Fast-tracking approval timelines: In September 2009, the CDSCO revised timelines for various regulatory processes. If the application is complete, first response from the DCGI office can now be expected within 30 days for Test license and 45 days for approval of clinical trial applications. Moreover, applicants can check the status of their application since the approval letters sent out by the DCGI office are displayed on the CDSCO website under 'Daily Dispatch' section.[12]

Single-window clearance for export No Objection Certificate (NOC): Indian regulators have recently introduced a single-window approval process through the DCGI for trial-related biological sample export NOC. Earlier, after obtaining permission from the DCGI for conducting a trial, an applicant had to apply separately to the Directorate General of Foreign Trade (DGFT) for an export NOC. This process has now been simplified and fast-tracked, so that an applicant can apply simultaneously for trial permission as well as export NOC to DCGI, without the need for a separate application to DGFT.

Impact of Recent Regulatory Changes on Conducting Clinical Trials in India[13]

A) Reduced speed of clinical trial completion

The speed of clinical trial depend on taking long time for regulatory approval and recruitment of patient, number of investigator only registered in Ethics committee (EC) approved clinical trial protocol.

B) Increased cost

The site cost per patient will increase as the investigator has to spend more time per recruited patient. The investigator has to devote time and effort to become aware of new regulatory compliance processes. Maintaining records and ready for inspection available for long monitoring and audit visit from sponsor team.

C) The sponsor

The sponsor, in addition to the above, the cost of medical management, and compensation for clinical trial related SAE, and exhaustive monitoring and audit will have a big impact on the trial budget.

D) Ensuring quality and compliance

The regulatory inspections conducted to check Good clinical practice (GCP) compliance have highlighted areas of deficiencies in quality. These regulatory inspection findings suggest that there are deficiencies in compliance to regulatory requirements for human protection and data integrity Post 2013, the EC's role has become crucial in ensuring rights, safety and wellbeing of the clinical trial participants EC should devote time and efforts in re-learning ethical issues - human protection, independence in decision making, handling conflict of interest, reviewing safety reports and compensation and effective oversight of clinical trial conduct during the trial conduct.

Report of the Prof. Ranjit Roy Chaudhary expert committee[14]

This report put forward in July 2013 by the Expert Committee constituted by the Ministry of Health and Family Welfare enlists practices that would be conducive for the growth of clinical trial industry in India while meeting the regulatory standards. It formulated policy and guidelines for approval of new drugs, clinical trials and banning of drugs. The actions taken by the Ministry based on the recommendations included

- Clinical trials should be conducted in accredited sites by an accredited Investigator with the oversight of accredited Ethics Committees (ECs). The Accreditation would be provided by a Quality Council of India
- As discussed above with Rule 122 DD, Registration of Ethics Committee is made mandatory but the proposed accreditation required a special procedure which calls for amendments in Drugs and Cosmetics Act.
- Regarding the procedure for review and application of new drugs, New Drug Advisory Committees are renamed as Subject Expert Committees. Applications for new drugs will initially be evaluated by these followed by review from the Technical Review Committee (TRC). CDSCO will take the final decision based on recommendations from the TRC.
- A computerized database of experts in each area will be generated which will be updated every year based on specific selection criteria.
- If India takes part in a global clinical trial for a new drug, approval should be sought from the CDSCO before marketing the drug.
- The CDSCO will review applications for approval of clinical trials within six months and ultimately bring down the timeline to one month.
- An investigator cannot take part in over three trials at a time. All details about payment of the investigator by the Sponsor should be made available to the DCGI.
- Use of information technology shall be used at all points in the clinical trial to ensure total transparency.

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CONCLUSION

As India is approaching towards globalization in the recent developments in the Pharmaceutical sector, based on its comparatively low cost and high skill base, India portrays to be a prospective hub for many big foreign Pharmaceutical Companies for drug innovation. So as to exploit this opportunity for the betterment of the country, it is pertinent that introduction of any drug innovation in the market should be preceded by a successful clinical trial which should be both methodologically and ethically valid. In spite of the appreciable steps taken so far, our law makers further need to put efforts to raise the standard for a more rigid and stricter vigilance mechanism on the Pharmaceutical Companies who conduct such clinical trial at the cost of the lives of some vulnerable and poor individuals who are not even aware that, there is existence of “right” to lead a safe and healthy life that the Supreme law of the land-the Constitution guarantees to each and every one irrespective of their economic conditions, race or any other difference.

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