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RECENT ADVANCEMENT IN REGULATORY GUIDELINES FOR CLINICAL TRIALS IN USA AND INDIA

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ABSTRACT

Clinical trials (CTs) are conducted to discover new methods of interventions that are better than the existing ones. They are conducted as per the guidelines suggested by the drug regulatory authority of the country where they are being conducted. In United State (U.S.), CTs are regulated by U.S. Food and Drug Administration (USFDA) as per 21 Code of Federal Regulations (CFR) Part 312 and 812 of Federal Food, Drug, and Cosmetic Act. On the other hand In India; CTs are regulated by Central Drugs Standard Control Organisation (CDSCO) in consultation with Indian Council of Medical Research (ICMR) as per the schedule Y of the Drug and Cosmetics Rules, 1945 and Ethical Guidelines for Biomedical Research on Human subjects. To initiate trials in USA, an Investigational New Drug Application (INDA) has to be submitted by the company to USFDA regulatory body. But In India applicant has to be submit, Form 44 along with other documents mentioned in Form 44 checklist. Approval time for INDA in USA is 30days, but in India this will take approximately 16-18 weeks. In USA, the INDA should be submitted in USFDA recommended format or common technical document (CTD) format, whereas, CTD format is still not enforced in India for INDA. In this review article, CTs regulations in India and USA were discussed on the basis of different parameters such as CTs Application Format, Approval Time, Compensation, and Other regulations. The success rate of CTs in USA is higher, which may be due to well-trained investigators, fast regulatory approval process and volunteer participation by the subjects. In

contrast, there is decline in CTs in India because of violation of ethical guidelines and regulations are not being adopted strictly. Hence, by this review, we intend to present a comprehensive view of overall transition and modernization of the drug discovery process and its impacts on the scientific community.

KEYWORDS: Clinical Trails, CDSCO, USFDA, CTD.

INTRODUCTION

The procedure of introducing a new pharmaceutical drug to the market, after a lead compound has been recognized during the process of drug discovery, is called drug development process. In this process, pre-clinical studies are conducted on microorganisms/animals and CTs conducted on humans (Fig.1). Further, for marketing the drug, approval from regulatory bodies has to be obtained. This process is highly regulated and complicated which requires the continuous involvement of research institutions, pharmaceutical industries, and drug regulatory agencies.[1]

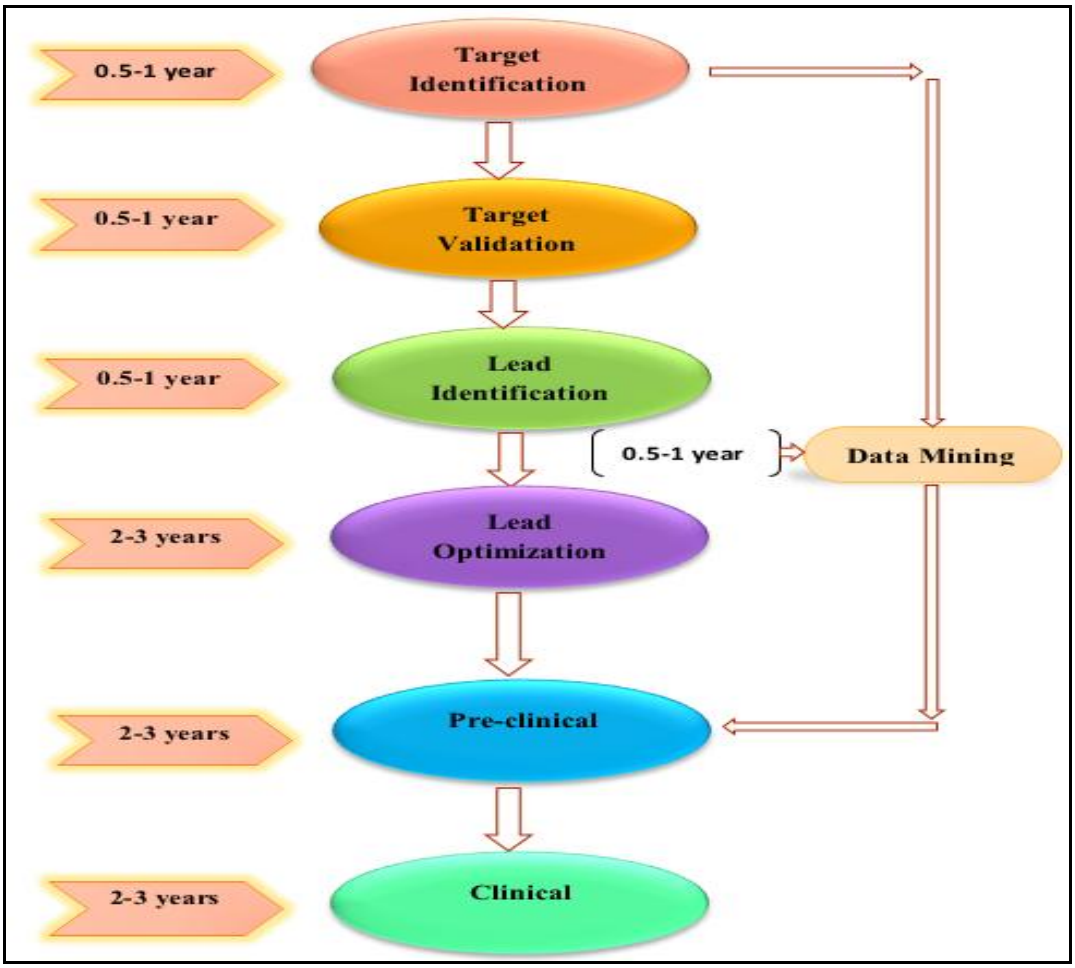

Fig. 1: Steps Involved In Bringing a New Drug in Market.

Time taken to bring a new drug to the market takes almost 12-15 years.[2]

Preclinical research

Prior to testing the drug in human beings researchers must assess whether the drug has the potential of causing serious harm i.e. it is important to evaluate the toxicity of drug. So, this would involve testing of drug in-vitro, which can be in a test tube or in cell culture as well as in-vivo studies using animals and this would be called as preclinical studies.[3] In these studies, comprehensive doses are used to preliminary information regarding the efficacy, toxicity, and pharmacokinetics aspects of the compounds under consideration. In this phase, researchers identify the germs, viruses, or bacteria responsible for causing a specific disease.

In most cases researchers use computer models to study the different test compounds but, computers cannot provide the final answers. So, these compounds are introduced into a living biological system to investigate their therapeutic effect in-vitro conditions. After success in the in-vitro testing (test tubes and cell cultures), researchers then test these compounds in living animals. But, it is not compulsory that an approach that works well in the laboratory or animals will always work well in human being as well. The complete process of preclinical research takes around three and a half years. [4] The process of bringing a new drug to market starting from pre-clinical studies is shown in Table 1.

Table 1: Phases of CTs and Steps Involve to Bringing a Drug Laboratory to Market

Parameters	Preclinical research	Phase I	Phase II	Phase III	FDA	Total Time	Phase IV
Years	3-3.5	1	2	3	2-2.5	12	Post-Marketing
Test population	Laboratory and animal studies	20-100 healthy volunteers	100-300 patient volunteers	1000-3000 patient volunteers	Review process/ approval		
Purpose	Access safety and biologic activity	Determine safety and dosage	Evaluate effectiveness and look for side effects	Verify effectiveness and monitor adverse drug reaction from long term use			
Success rate	5000 compounds evaluated	5 enter trials				1 drug approved	

Clinical Trials

"CTs are research studies in which new treatments, interventions or tests are tested on human in order to find out as a better means of preventing, detecting, treating or manage various diseases or medical conditions. This helps to evaluate if a new intervention works well, if it is safe, and if it is better than the interventions that are already available."[5]

Objectives of CTs

The objectives of CTs are listed below:

a) To evaluate if the new medicinal products are safe and effective for the proposed use.
b) To discover more effective ways to treat and prevent the disease.
c) To discover treatments with fewer side effects.
d) To discover new treatments which can be easily tolerated by patients.[6]

Clinical Trials Regulations in the United States

USFDA is the agency of the U.S Department of Health and Human Services (DHHS), whose main role is to assure the safety, efficacy, and quality of human as well as veterinary drugs. This agency is also responsible for facilitating advances in healthcare system of USA. It is a large and somewhat complex federal agency with a number of centres, divisions, and offices situated both centrally in the Washington metropolitan area as well as several regional offices in the United States. Centre for Drug Evaluation and Research (CDER), and the Centre for Biologics Evaluation and Research (CBER) are the two departments of USFDA that regulate the CTs in USA.[7]

Investigational New Drug Application

In United States, INDA application has to be submitted by pharmaceutical companies for conducting CTs. Form 1571 also has to be submitted with the application which is numbered as 000 for initial submission. The subsequent communications for the same application should contain the USFDA form 1571 as cover sheet which is consecutively numbered after the initial submission. USFDA accepts IND applications in either format, U.S. format or the Common Technical Document (CTD) format. The USFDA form 1572 contains all information related to educational qualification and experience of the investigator. This form involves a formal declaration by the investigator that the conduct of the CT is in accordance with GCP and related regulations. Review process of IND application in the USA indicated in (Fig. 2).

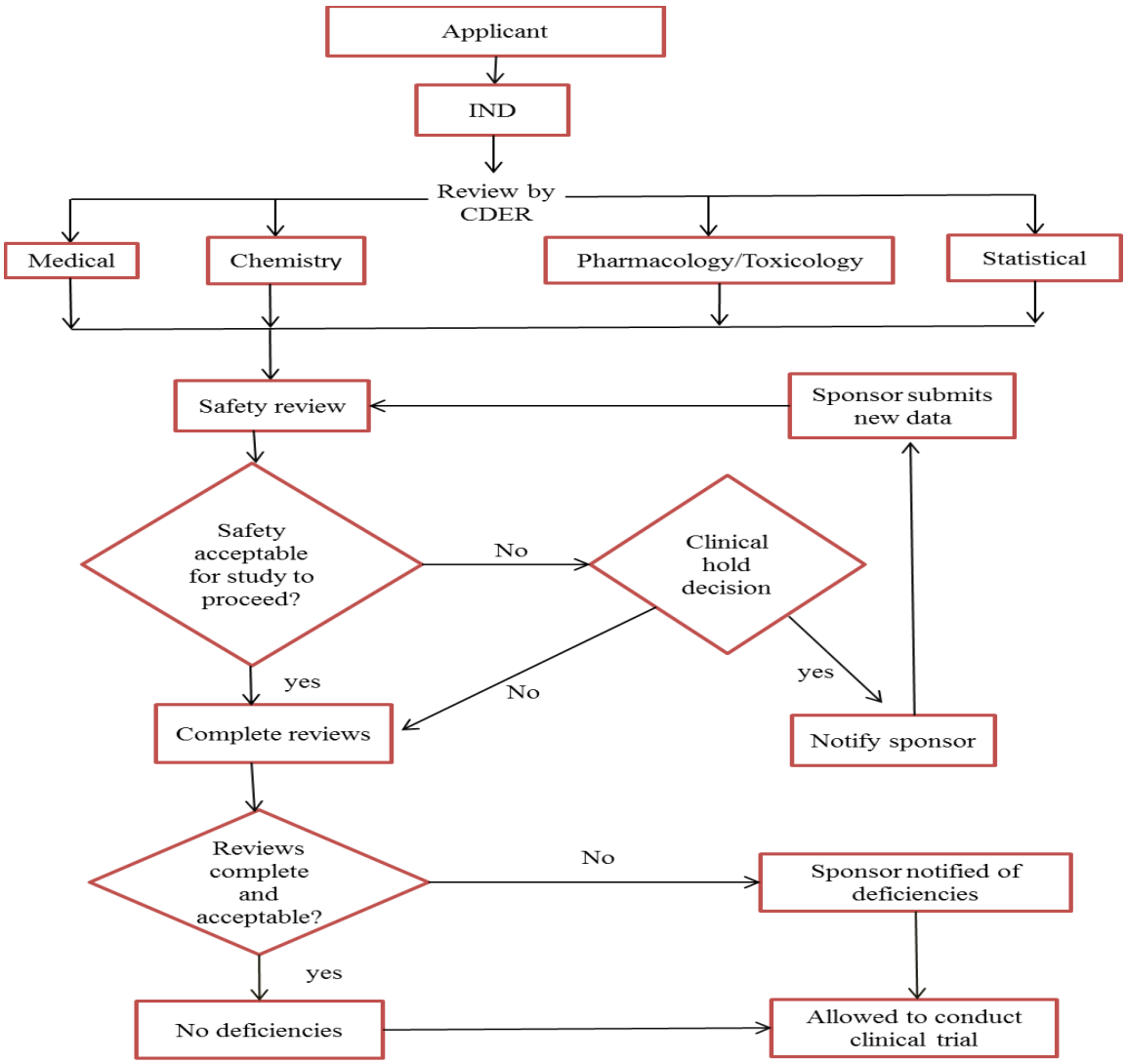

Fig. 2: Review process of IND application in the USA.

FDA allots a unique reference number to IND application and appropriate review committees of the CDER or (CBER) reviews the application. The experts assess the study protocol and ensure that the safety of subjects will not be compromised during the conduct of CTs. The quality of protocol during Phase II and Phase III of the CTs is also reviewed. The entire review process takes 30 days, after which the study can be started. In USA, IND application should be submitted in national format or the CTD format. From 2018, onwards IND application has to be submitted in electronic common technical document (eCTD) format.[8]

Regulations for conducting clinical trials in the USA

In USA, CTs are regulated by USFDA as per 21CFR Part 312 of Federal Food, Drug, and Cosmetics Act.[9] In USA, the USFDA GCP program coordinates FDA policies, provides leadership, and direction, plans and conducts training, and also contributes to ICH-GCP

harmonization activities. It also acts as a link between the Office of Human Research Protection (OHRP) and other federal agencies that are involved in the protection of subjects of CTs.[10] The following are some of the departments of USFDA that provide guidance on the conduct of clinical research:

- Information for Clinical Investigators-Drugs.
- Information for Clinical Investigators-Biologic.

Centre for Drug Evaluation and Research

USFDA is composed of various centres, divisions, and departments. CDER is the department of USFDA which deals with pharmaceutical products and CTs. Its main function is to ensure the safety and effectiveness of drugs that are available to the U.S population. Over-the counter (OTC) and prescribed medications, including biologics and generic drugs are also controlled by CDER.[11] According to the current law, every single new medication needs verification of being effective and safe for US population. After verification only, they will get approval for marketing. Though, it would not be wrong to say that there is always some risk of an adverse reaction due to a medication. So, while evaluating the safety aspects of the medication it is important to ensure that investigational drug has a high benefit-to-risk ratio. Then only it will be considered as safe and will get approval from CDER for its marketing in USA. CDER has the additional responsibility of reviewing the CTA and give their opinion and reports to FDA regarding the same.[12]

Centre for Biologics Evaluation and Research

CBER is the department within FDA which deals with biologics, different therapies, blood-related products, vaccines, sera and gene therapies under relevant federal laws that is the Public Health Service Act and the Federal Food, Drug and Cosmetic Act. CBER's, main function is to promote advancement in biologics to secure and improve the public health by ensuring that they are safe and effective for their use.[13]

Guidance for Institutional Review Boards and Clinical Investigators

The interaction between the sponsor and IRB usually occurs through investigator but the regulations do not restrict the interaction between the sponsor and the IRB. The communication between sponsor, investigator and IRB helps in the proper conduct of CTs properly.

When the sponsor and IRB sign forms USFDA-1571 and USFDA- 1572 for drugs and biological respectively, then a communication link is created between them.[10] This communication can lead to remarkable changes in the study procedure or specific wording in an informed consent document.

Compensation rules for conducting clinical trial in the USA

USFDA does not have exhaustive policy on compensation to be given to the subjects' of the CTs. The current US law, related to the conduct of CTs, does not specifies whether the free medical care or compensation is to be provided to all the research participants. For the participants who suffer greater than minimal risk in research are provided free medical treatment. In a study conducted by the US Department of Health and Human Services (HHS) it was found that many institutions involved in research do not have compensation policies related to injury incurred during the conduct of the CTs.

Out of 129 reviewed policies, 84% did not at all provide free medical care or treatment to injured patients while none of this provided compensation for lost salary, pain and suffering. Some academic institutions, for example, University of Washington, provided funds up to 10,000 dollar as compensation for research-related injuries. It has been observed that most of the research institutes, where CTs are being conducted, receive one or two claims every year for the CTs related injuries.[14] Some Government federal agencies also provide treatment or compensation for injuries resulted during research. These include the US Department of Defence (DOD) and the US Department of Veterans' Affairs (DVA). DVA regulations provide treatment for injuries that result from research, including the injuries that occurred in minimal risk research. Similarly, DOD also provides medical treatment to individuals suffering from injuries that occurred due to research, but does not provides other expenses. The National Institute of Health (NIH) also gives short term medical treatment or insurance to subjects injured during CTs but does not provide long-term treatment. People who participated in CTs in an institution that does not provide compensation can avail compensation by bringing a lawsuit. But it is important that participants can prove that injury occurred due to the negligence of the investigator. In order to claim the compensation by law, the participants have to prove the following;

a) researcher owed a duty to the participant;
b) researcher failed to satisfy ethical, legal, or moral obligations.
c) violation of law which caused patient's injury;

d) the researcher does not have a legal justification to the injury;

A major hurdle observed in these types of cases is that proving the above mentioned circumstances will be difficult for participants because the injury might have occurred in the absence of investigator.[14]

Clinical Trial Regulations in India

In India, CDSCO is the regulatory and licensing authority which approves any New Chemical Entity (NCE) which is to be imported to India. Directorate General of Health Services (DGHS) which comes under Ministry of Health and Family Welfare (MoHFW), governs CDSCO. In India, Drug Control General of India (DCGI) heads CDSCO and gives final approval for the start of CTs. Under DCGI, there are two committees, such as Drugs Technical Advisory Board (DTAB) and the Drugs Consultative Committee (DCC). These two committees work with DCGI to regulate CTs in India. It is the responsibility of the DCGI to establish the standards for drugs, approval of new drugs, and regulate CTs in the country.[15]

The protocol for CTs are examined by the office of DCGI before the permission for conduct the CTs shown in (Fig.3). DCGI and IEC has the major role in controlling the CTs in India.

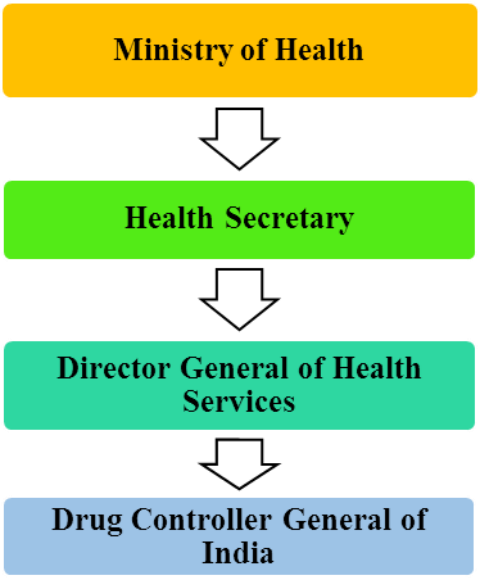

Fig. 3: Regulatory authorities involved in clinical trials in India.

In India Form 44 has to submit by applicant to get approval for the start of CTs in India. All the data as per form 44 checklist has to submit to DCGI. After the full review of the

application form by the CDSCO regulatory authorities, final approval will come from DCGI for the start of the CTs. [15] Till date In India physical applications only submitted by applicants, CTD format is still not enforced in India. [16]. The IND application review process in India is depicted in (Fig. 4).

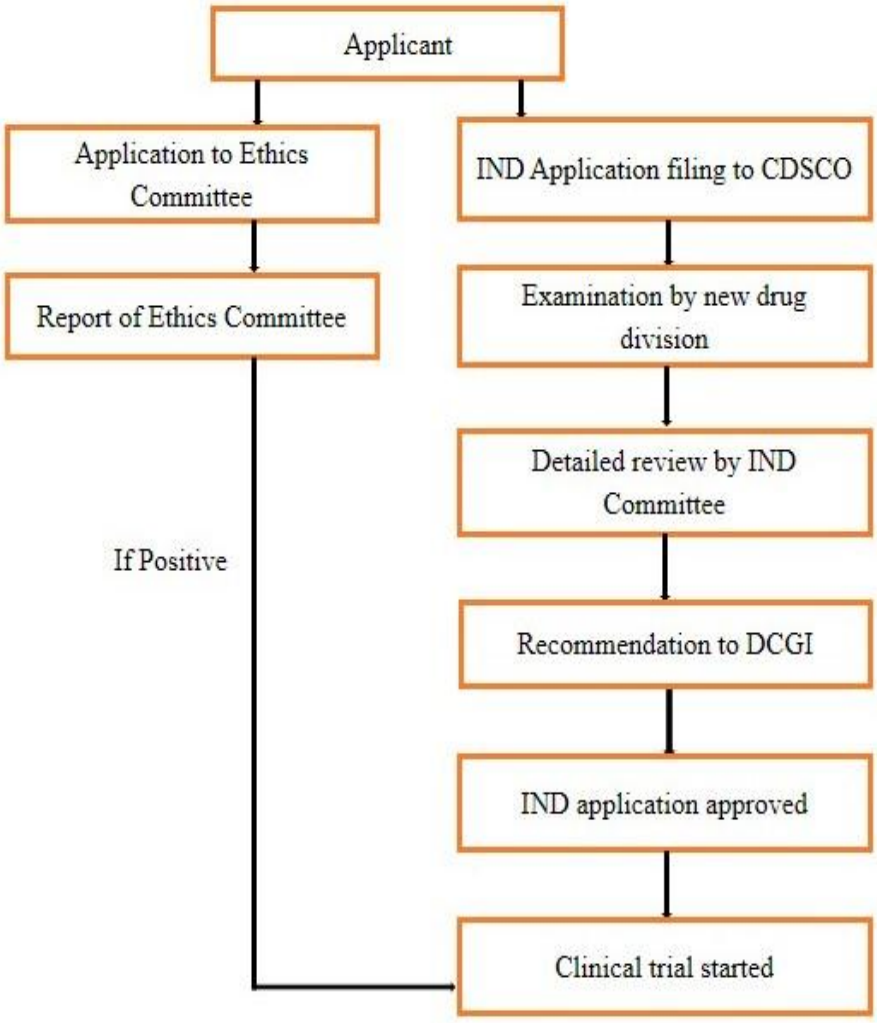

Fig. 4: IND application review process in India.

In September 2015, CDSCO issued new guidelines for the submission of CTA. As per these guidelines applicants can submit CTA online. Hard copies are also being accepted till this system is not fully adopted in India.[17]

IND application contains the details regarding

a) Clinical protocol and investigator information, where and who will conduct the CTs.

b) Information regarding the manufacturing of the compound.

c) Animal pharmacology and toxicology studies data which will indicate how the drug is expected to work in the body and any toxic effects found in the animal studies/preclinical studies.

In India CTD format has been adopted for the submission of New Drug approval (NDA) applications in which the entire CTs data has to be documented. By adopting the CTD format, CDSCO hopes to improve the review procedure and approval times for the importation, manufacture and marketing of new drugs. In addition, this should also simplify the exchange of regulatory information between CDSCO and regulatory authorities of other countries. Appendix I, IA and VI of Schedule Y, also describes the information required for approval of an application to import or manufacture of new drug for marketing in India.

For performing CTs in India, there are several laws, regulations, and rules to examine and look at trials in a practical and ethical way. Indian regulations for the conduct clinical research are issued by CDSCO.

The Drugs and Cosmetics Act, 1940

The framework of this act consists of powers for regulating and ensuring quality, safety and efficacy of drugs. This act also includes necessary rules, procedures and guidelines related to CTs.[18] Rules for conducting CTs in India are listed below:

a) Permission to conduct the clinical trial (Rule 122 DA)
b) Definition of CTs (Rule 122 DAA)
c) Compensation in case of trial related injury or death (Rule 122 DAB)
d) Conditions of clinical trial permission & inspection (Rule 122 DAC)
e) Registration of IEC (Rule 122 DD)
f) Definitions of new drugs (Rule 122 E)[19]
g) General statutory rule (GSR) 1011(E) is in draft stage for amendments in rule 122 DA, it was announced on 29th December 2015. It is related to increase in the fees for Phase I, II, and III of the CT.

The proposed revised fees for the different phases of CTs are:-

Phase I: Fifty thousand rupees to two lakh fifty thousand rupees

Phase II: Twenty-five thousand rupees to two lakh fifty thousand rupees.

Phase III: Twenty-five thousand rupees to two lakh fifty thousand rupees[20]

Current regulations in India

Presently CTs are conducted according to Schedule Y of the Drug and Cosmetics Rules, 1945. This schedule provides the information about the fundamentals and guidelines for permission to Import or manufacturing of new drugs for sale or to undertake CTs. Schedule Y was revised in 2005, to bring the Indian regulations for CTs at par with internationally accepted standards. After January 2013, CDSCO has amended a number of guidelines to ensure the compliance with CTs regulations by the investigator or sponsor and the entire clinical trial team. Additionally, Schedule Y1 is being drafted which will provide guidelines for registration of clinical research organization (CROs). However, it is still in the draft stage due to change in the expert panel of CDSCO.[21]

The recent amendments in schedule Y are

Recent amendments in Schedule Y are strategies taken for further strengthening of clinical trial regulations to ensure the protection of rights, safety, and wellbeing of clinical trial subjects and for creating authentic biomedical data.

New regulations announced by CDSCO:

- GSR 53 E; 30th Jan. 2013: Serious adverse event (SAE) reporting and compensation for study-related injury.
- GSR 63E; 1st Feb. 2013: Conditions to be fulfilled by Sponsor to conduct a clinical trial in India.
- GSR 611E; 19th Nov. 2013: Audio-visual recording of the informed consent process.
- Expert committees have been constituted for examination of serious adverse events other than death related to CTs.
- GSR 889E; 12th Dec. 2014: Notification about specific provisions in respect of compensation for ineffectiveness and placebo-controlled trials[22]
- GSR 11E; 6th January 2016 is in draft stage for amendments in schedule Y[23]

Indian GCP guidelines

Clinical research is the way to find out new diagnostic methods to introduce new drugs for treatment. According to GCP guidelines CTs have to be designed appropriately to ensure the efficient conduct and recorded as per the requirements of the regulatory agency. These guidelines were developed to make sure that quality CTs conducted in India. CDSCO has set up an expert committee which will issue GCP guidelines for the production of clinical data on drugs. DTAB, is the highest technical body which has approved these guidelines for the

conduct of CTs. These guidelines have established two basic principles; protection of the rights of subjects and accurate data generation during CTs. These guidelines were drafted in consultation with World Health Organization (WHO), ICH, United States and European GCP guidelines. The Indian GCP have incorporated certain guidelines that are different than ICH GCP and are also difficult to comply with, for example, in Indian.

GCP guidelines both investigator and sponsor should sign the SOPs, whereas, in ICH-GCP only investigator have to sign SOPs.[24] In case of Indian GCP, monitors have the duty to inform ethics committee or sponsor for any violation from the protocol but in case of ICH GCP monitoring of SOPs is done by monitors and auditors.[25]

Before there is no such guidelines for conducting CTs on herbal medicines in India, but in March 2013 Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) published new GCP guidelines for CTs on ASU drugs.[26]

Indian council of medical research guidelines

ICMR has given 'Ethical guidelines for biomedical research on human subjects'. With growth in science and technology it has become necessary to update these guidelines regularly. Human participants involved in research should not violate any globally valid ethical standards. ICMR has also given guidelines concerning the compensation to be given to the subjects.[27]

Compensation for Participation

Compensation must be paid to subjects for the inconvenience caused and time dedicated by them. Free medical services should be provided but not too extensive. Sponsor and investigator should not force subjects to participate in CTs against their interest. All payments and medical services to be provided to participants must be approved by the IEC. If the subject withdraws from the trial for a medical reason related to the study, then the sponsor and the investigator have to provide the same facilities/benefits as those provided for full participation.

Compensation for Accidental Injury

If a participant gets physically injured (temporary or permanent injury) during the CT then the sponsor/investigator is expected to provide the subjects financial and other required

support. In case of death of a subject, compensation should be provided to the family of the subject.

Obligation of the sponsor to pay

Before the start of the CT, the sponsor should discuss compensation with participant through an agreement for any injury incurred during the CTs, whether physical or psychological. A committee can be set up by the institution to decide on the issue of compensation. This committee is expected to solve compensation issues in larger trials, compensation for additional care, for an unrelated illness and free treatment. Committee will check whether these conditions were present in a prior agreement or not and on the basis of documented facts the committee will give their decision regarding the compensation to be provided to the subjects of the CT.

Compensation rule for clinical trials in India

CDSCO introduced a new rule GSR 53(E) dated 30th January 122DAB and a new Appendix – XII in Schedule 'Y'. Under 122DAB three amendments have been published, addressing compensation to trial subjects due to any injury or death during the CTs. Compensation for injuries or death during CTs has been discussed in the first amendment while the second amendment has discussed the conduct of CTs. The third one mainly concentrates on registration of IEC.[28] The amendments states that the subject is allowed for compensation due to injury or death when;

a) Any adverse effect is produced due to IMP;
b) Exploitation of the approved protocol, scientific misconduct by the sponsor or the investigator;
c) If the IP is unable to produce expected therapeutic effect;
d) Use of placebo in a placebo-controlled trial;
e) Any injury cause in utero because of the involvement of parent in the trial, Clause (b) states that any injury or death occurred due to violation of protocol or scientific misconduct or negligence by sponsor, compensation should be paid by the sponsor only instead of investigator, who must be blamed for any misconduct.

According to Rule 122 DAB 5(c), compensation should be given to subjects in case of injury or death caused, due to the failure of IP But at the time of start of trial it is not known whether the IP will work better than the standard drug. It should also be noted that the amendment did not mention compensation to any injury or death due to standard drug. Rule 122 DAB also

states that the amount of compensation to be paid to a subject in case of injury or death is to be calculated by IEC and Expert Committee appointed by DCGI.

DISCUSSION

In this review we discussed the regulatory guidelines in USA and India. In case of India regulatory authorities has to take strict action against violation of the regulations. CTD and eCTD format they have to enforce for fast approval process. In USA, there is strict regulations enforce by USFDA, which leads number of CTs success in USA. There must be a Common International Clinical Trial Organization where every CT should be registered. This will reduce the duplicity in the conduct of CTs, as well as save time, effort, money and discomfort to the patient of different countries. Some other parameters also discussed those shown in Table.2.

Table 2: Different Parameters of Clinical trial guidelines in USA and India.

Parameters	United States	India
Regulatory bodies	USFDA	CDSCO
Clinical trial application	Investigational New Drug Application (IND)	Form 44
Application fee	No Fee	Fees is required in Phase I,II,III i.e. 50000,25000,250000 respectively
Application submission format	Common technical document(CTD) formats, U.S. format	Form 44 have to be submitted according to National format
Approval Timeline	30 days	16-18 weeks
Institutional review board/Independent Ethics committee	Institutional Review Board and Center for Drug Evaluation and Research(CDER) approval required	DCGI and ethics committee approval required
Forms required	FDA forms 1571, 1572, 3454 and 3455 required	Form 44 along with documents mentioned in Form 44 checklist
Regulations	Code of federal regulations 21 CFR Part 312,50,54,56 have to be followed	Drug and cosmetic act 1940, and Schedule Y of the Drug and cosmetics act and rule 1945
Compensation	Compensation according to informed consent 21 CFR Part 50 and Financial disclosure by the clinical investigator	According to 122 DAB rule
Records storage	2 years record retention time	3 years record retention time after completion
GCP Guidelines	ICH GCP	Indian GCP
Adverse Event Reporting	Life-threatening adverse reaction reported to FDA within 7 days	Any injury or death related to a clinical trial, sponsors have to be informed to the DCGI within 24 hours

CONCLUSION

From this review, we concluded that USA has better established guidelines. CTs are highly regulated through their federal agencies. Data related to CTs also is recorded electronically and soon in USA they are going to enforce eCTD format for submission of IND application, which will eventually speed up approval process. In case of India neither is their guidelines for CTs fully developed and nor do it follow internationally accepted standards, till now. In India, CTD format is yet not adopted for submission of clinical trial applications, which leads to delay for getting approval for start the CTs.

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