EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 7
84-96
Year: 2022

COMPARISON OF REGULATORY REQUIREMENTS FOR CLINICAL TRIAL IN USA, EUROPE, INDIA

M. Suresh Babu*, Abdul Mannan, Mohd Moin, Salman Abdul Majeed, Mohammad Mujju and Mohd Ameenuddin Khan

Deccan School of Pharmacy, Dar-us-salam, Aghapura, Hyderabad. Telangana.

***Corresponding Author: M. Suresh Babu**
Associate Professor M pharm PhD Deccan School of Pharmacy, Dar-us-salam, Aghapura, Hyderabad. Telangana

Article Received on 30/04/2022 **Article Revised on 20/05/2022** **Article Accepted on 10/06/2022**

ABSTRACT
The person is responsible for knowing the regulatory requirements for getting new products approved. They know what commitments the company has made to the regulatory agencies where the product has been approved. Clinical trials (CTs) are conducted to explore new methods of intervention that are better thanthe existing ones and can also be easily tolerated by patients. CTs are conducted in accordance with the regulatory guidelines recommended for the same by the drug regulatory authority of the country where they have to be conducted. In USA, CTs are regulated by USFDA as per their 21 code of federal regulations part 312 (CFR) of Federal Food, Drug, and Cosmetic act. In EU, they are regulated by European Commission and EMA as per their CT directive 2001/20/EC of the European Parliament and of the council of 4 April 2001 and GCP directive 2005/28/EC of 8 April 2005. In India, they are regulated by CDSCO (Schedule Y of the Drugand Cosmetics Rules, 1945) and ICMR (Ethical Guidelines for Biomedical Research on Human Subjects), respectively. The role of these authorities is to ensure the quality, safety, and effectiveness of all medicines in their respectivecountries. In this work, clinical trial regulations in USA, EU and India were compared on the basis of parameters such as regulatory bodies involved, regulations for CTs, clinical trial application format, application fee, approval time, the various forms required, role and responsibilities of IRB/IEC, record retention time, and GCP guidelines. The success rate of CTs in USA and Europe is higher in comparison to India which may be dueto well-trained investigators, fast regulatory approval process and volunteer participation by the subjects. Some case studies related to the clinical trials conducted in these countries have also been incorporated.

KEYWORDS: Clinical Trails, Regulatory requirements, USA, EUROPE, INDIA.

INTRODUCTION
Drug discovery and development can be divided into two subparts 1) drug discovery and 2) drug development. Drug discovery is the sequence of processes in which the first step is identification of disease target followed by its validation. Next is the discovery and development of a chemical compound which can interact with the target and bring the desired therapeutic effect. This interaction process can involve blocking, promoting or modification of the activity of the target. In drug development all requirements of safety and efficacy have to be met before a new compound can be considered suitable for testing in human subjects for the very first time. Drug testing is conducted during preclinical and CTs Clinical trials involve the testing of intervention in human subjects with the aim of evaluating safety and efficacy of the intervention in humans. Interventions can include drugs, medical devices, procedures and vaccines. Since CTs involves the participation of patients and healthy volunteers as the subjects of the study, so they are highly regulated in all the countries.

The objectives of this work are as follows to study the regulatory guidelines for conducting CTs in regulated and semi-regulatedcountries. Comparison of clinical trial regulations in these countries. Regulated countries chosen for this work were USA and EU and india

Research methodology
Pharmaceuticals industries are the highly regulated industries in the world. Each country has its own regulatory authority, which is responsible to draft, impose and ensure compliance with the rules, regulations and guidelines for regulating drug development process, licensing, registration, manufacturing, marketing and labelling of pharmaceutical products. In United States, United States Food and Drug Administration (USFDA), Europe- European Medicine Agency (EMA) and European Commission (EC), India- Central Drugs Standard Control Organization (CDSCO) these are the regulatory agenciesestablished in the respective countries to regulate the drug regulations. In this work, to study and compare the drug regulations in regulated and semi-

regulated countries following steps were conducted.

1. CTs guidelines given by ICH and USFDA were studied.
2. Guidelines for conducting CTs in the European Union were studied.
3. CTs guidelines of India given by CDSCO and Indian Council of Medical Research (ICMR)were studied.
4. Guidelines for the regulated and semi-regulated countries, USA, EU and India respectively, were compared with respect to:-

- Registration process
- Approval timeline
- Regulatory bodies involved
- Applications fees
- Compensation
- GCP guidelines
- Forms required
- Adverse event reporting

5. CT case studies conducted in the USA, EU and India were discussed.

Expected outcomes

This study involves a thorough study and comparison of the CT regulations in USA, EU and India. Some examples of CT case studies that have conducted in the above-mentioned countries will also be discussed. Comparison of guidelines and case studies will help in suggesting to the semi- regulated countries on improvement and compliance with their CT regulations.

Experimental work

Clinical trials in the united states

The United States Food and Drug Administration (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 centers, divisions, and offices situated both centrallyin the Washington metropolitan area as well as several regional offices in the United States. Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) are the two departments of USFDA that regulate the CTs, involving humans, in USA.[1]

Investigational new drug application

In United States, IND application has to be submitted by pharmaceutical companies for conducting CTs. Form 1571(coversheet), 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 form 1571 as cover sheet which is consecutively numbered after the initial submission. USFDA accepts IND applications in both format, U.S.format or the Common Technical Document (CTD) format. The 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 discussed in Figure 1.

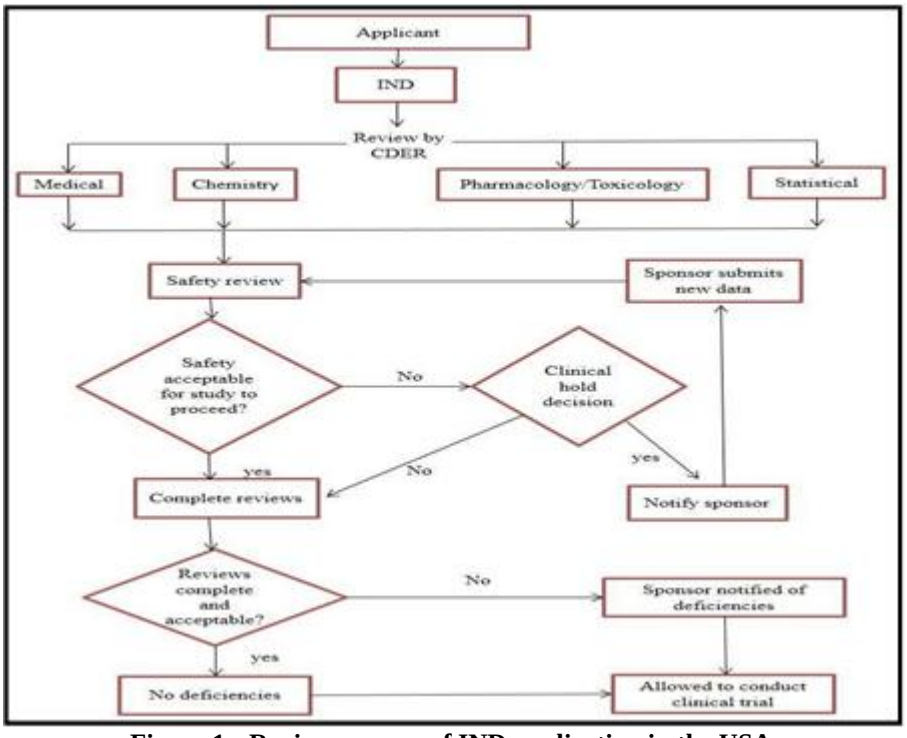

Figure 1: Review process of IND application in the USA.

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 CT. The quality of protocol during Phase II and Phase III of the CT 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.[2]

Regulations for conducting clinical trials in the USA

In USA, CTs are regulated by U.S. Food and Drug Administration (USFDA) as per 21 Code of federal regulations (CFR) Part 312 of Federal Food, Drug, and Cosmetics Act. Table 1 lists the applicable regulations that govern the conduct of CTs in the U.S.[3]

Table 1: Federal Regulations that apply to the IND application process.

21 CFR Part 312	Investigational New Drug
	Sec. 312.2 Applicability
	Sec. 312.23 IND content and format
	Sec. 312.30 Protocol amendments
	Sec. 312.31 Information amendments
	Sec. 312.32 IND safety reports
	Sec. 312.33 Annual reports
	Sec. 312.38 Withdrawal of an IND
	Sec. 312.42 Clinical holds and requests for modification
	Sec. 312.44 Termination
	Sec. 312.45 Inactive status
	Sec. 312.50 Responsibilities of sponsors
	Sec. 312.60 General responsibilities of Investigators
	Sec. 312.61 Control of the Investigational drug
	Sec. 312.62 Investigator record keeping
	Sec. 312.64 Investigator reports
	Sec. 312.66 Assurance of IRB review
	Sec. 312.68 Inspection of investigator's records and reports
	Sec. 312.69 Handling of controlled substances
	Sec. 312.70 Disqualification of a clinical investigator
21 CFR Part 314	IND and NDA applications for FDA approval to market a new drug
21 CFR Part 316	Orphan drugs
21 CFR Part 50	Protection of human subjects
21 CFR Part 56	IRBs
21 CFR Part 201	Drug labelling
21 CFR Part 54	Financial disclosure by clinical investigators

Some regulations are equivalent to those of the EU since both these regulations are based on the principles of ICH GCP.

21 CFR Part 11 Electronic records and electronic signature

This rule is applicable to CTs related documents that are required to be maintained and but are not required to submitted to the regulatory agencies. These records should be maintained in electronic form and are considered equivalent to paper records. Electronic records can consist of combination of text, data, audio, pictorial information, which are characterized in digital form with the help of computerized systems. Information and signature of every personnel involved in CT should also be recorded electronically as per this rule.[4]

21 CFR Part 50 Informed consent of human subjects

As per this rule says that investigator can not involve any subject in the trial until he has obtained legal informed consent from the subject. All information present in informed consent must be in the simple and understandable language. The investigator has to explain all these information to subject or his/her representative, if they are unable to understand.[5]

21 CFR Part 56 Institutional review board

Institutional review boards (IRB) play a vital role in the conduct of CTs. The board reviews applications like IND, NDA applications to get approval for the start of the CTs and market the new drug respectively, license for biologics, data related to bioavailability and bioequivalence. After reviewing the applications, it is the responsibility of the board to send a report to FDA regarding final review and approval of the, afore mentioned applications.[6]

21 CFR Part 56.106 Institutional review board registration rules

This is the amendment rule of 21 CFR 56. According to this, all the studies that are regulated by FDA (IND and Investigational device exemptions) studies have to be registered with FDA,irrespective of the fact whether IRB is involved in the conduct of these studies or not.[7]

21 CFR Part 54 Financial disclosure by clinical investigators

According to this rule FDA will take steps to ensure bias in CTs. Major source of bias in CTs is the finicial issues, specifically compensation part. Compensation has to be provided to the subjects if any injury occurrs to the subjects during the CT. The compensation part should be made clear as well as documented. FDA Forms (3454) "Certification of Financial Interests and Arrangements of Clinical Investigators" or (3455) (Annexure 3) "Disclosure Financial Interest and Arrangements of Clinical Investigators" are used for this purpose.[8]

Food and Drug administration amendments act

According to the Food and Drug Administration Amendments Act (FDAAA) section, 801 it is mandatory for sponsors and principle investigator to submit CTs result with ClinicalTrials.gov. Further, the responsible parties will be penalized if they are failed to submit result within the given time limit. ClinicalTrials.gov has launched one Protocol Registration System (PRS) to avoid duplicate registration of the CTs. Clinical trial studies must be registered only by sponsor or principle investigator in order to avoid duplicate registration.[9]

U.S.FDA guidelines for conducting clinical trials

In United States, 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:

1. Information for Clinical Investigators-Drugs (CDER)
2. Information for Clinical Investigators-Biologic (CBER)

Center for Drug Evaluation and Research (CDER)

USFDA is composed of various centers, 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.[45] 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.[11]

The Center for Biologics Evaluation and Research (CBER)

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 PublicHealth 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.[12]

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 FDA-1571 and FDA-1572 for drugs and biologicals respectively, then a communication link is created between them. 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 a exhaustive policy on compensation to be given to the subjects' of theCTs. 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.[13]

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 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.

Clinical trials in europe

The European Union (EU) is responsible for constituting and implementing laws related to pharmaceuticals in all the member states (MS) of EU. European commission (EC), European council, European Parliament are the responsible bodies in EU. EC is an executive branch which supports in drafting of statutory proposals. EC represents the community, and it includes the Heads of State or Ministers, which represent all the MS of the EU. European parliament consists of elected officials which represents the public. In EU, not a single medicinal product can be placed on the market unless an authorization has been issued by either the competent authorities (CA) of that m MS or by the European Medicines Agency (EMA). The European Parliament and Council has allowed a centralized procedure for the authorization of medicinalproducts for human use. In this procedure, the applicant has to submit only a single applicationto market the drug in all MS of the EU. CAs in all member states will review the Investigational Medicinal Product Dossier (IMPD) application. Some MS have separate CAs for human and veterinary medicines such as UK, France and Hungary whereas others have a single CA for human and veterinary medicines (e.g. Netherlands and Ireland. In certain MS, like Germany, they have separate CAs for small molecule-based medicines and biologically based medicines.In EU, IMPD applications has to be submitted in the CTD format.[14,15]

Investigational medicinal product dossier

An IMPD application has to be submitted to the CA for getting approval to start a CT in EU. The IMPD application must include:

- Summaries of the quality, manufacture and control of the investigational medicinalproduct (IMP)
- Complete preclinical and clinical studies data
- Data indicating the an overall risk-benefit of the IMP
- Critical analysis of the preclinical and clinical data, with respect to the potential risks and benefits associated with the proposed study, have to be a part of the IMPD.[16]

The IMPD application review procedure in EU is discussed in Figure 2.

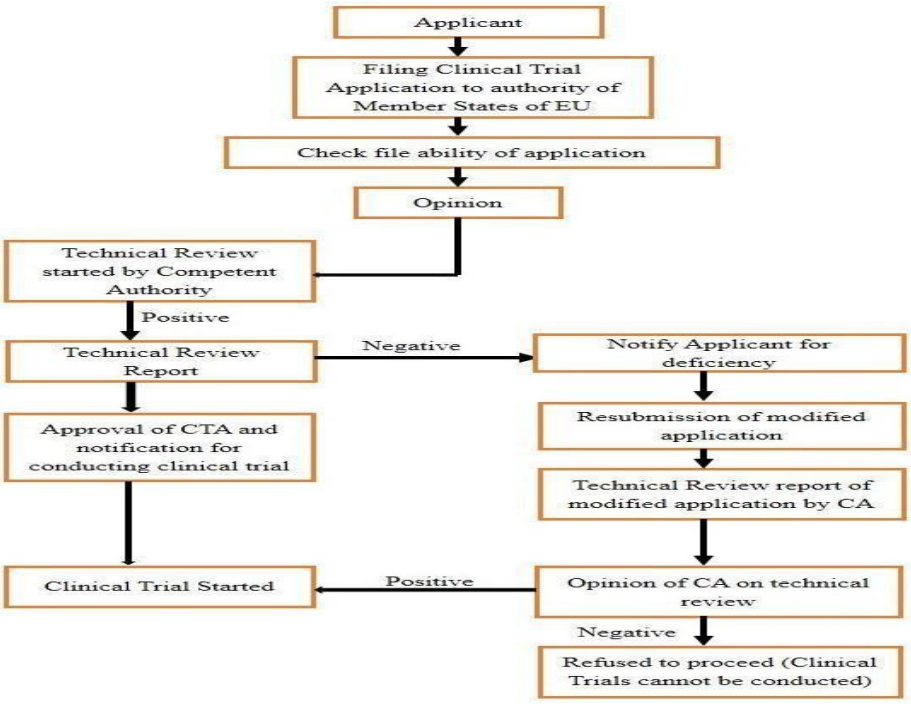

Figure 2: IMPD review process.

To ensure the implementation of GCP in the MS of EU Clinical Trial Directive came into forcein April 2001. The MS were asked to modify the requirements as per directive, into their respective national laws before May 2004. The Directive declared a harmonized procedure for obtaining approval to conduct clinical research in any of the EU Member States. All documentation has to be submitted to the IEC to obtain its approval. IMPD has to be submitted to the CA of the concerned member state (CMS) for review and approval. After the completion of the trial, the sponsor of CT is required to submit full CT related data in marketing authorisation application (MAA) which should be prepared in the CTD format. It is compulsory in EU to submit the application in CTD format. After the full review of this application, conducted for evaluating the safety and effectiveness of the IMP, the CA's of the CMS will provide approval for the marketing the drug.

Regulations for conducting clinical trials in europe

Clinical trial regulations in EU aim to provide a conducive environment for conducting CTs and to ensure the highest standards of patient care and safety in all the EU Member States. Thenew Regulation EU No 536/2014 was adopted on 16 April 2014. Its main aim is to make it simpler to conduct trials in CMS of the EU. It will be applicable after May 2016, two years after its publication. The modifications made in the new regulations includes; EU portal and database to maintain record of all the CTs to be conducted in Europe, a single approval system for all CTs i.e. centralized procedure and additionally, prudent transparency for CTs data.

It is required that CTs should be conducted as per the CTs Directive until the new regulations (EU No 536/2014) come into force. This Directive will be withdrawn after the entry of the newCT regulations.

The clinical trial directive

Before the implementation of this Directive, rules for carrying out CTs differed significantly amongst the different MS in the EU. This Directive was implemented in 2004. The main objective of this Directive is to protect the health and provide safety to participants of theCT.[17]

Good clinical practice directive

This directive provides guidelines for the conduct of the CTs according to GCP. The GCP guidelines have to be followed for the design, conduct, record, and reporting of CTs. The Directive lists the requirements for the authorization, manufacturing or importation of medicinal product for human use. It discusses the

1. Roles and responsibilities of the IEC, sponsor, investigator, IB
2. Regulations for manufacturing or import authorization
3. The trial master file and archiving
4. Inspectors and Inspection procedures.[18]

Independent ethics committee

A positive judgment of the IEC is required before a trial can start in the CMS. The IEC shall consider the following points while preparing its opinion:

- Significance of the CT and the CT design
- Protocol
- Appropriateness of the investigator and the supporting staff to be include in CTs
- Investigator's brochure
- Quality of the facilities
- Compensation

After the receipt of IMPD application for the conduct of a CT, IEC starts reviewing it. IEC isrequired to give its opinion to the applicant and the CA of the CMS within 60 days of the receiptof IMPD application. During the review of the application, IEC may request for supplementary information other than the information that has been already submitted by the applicant. Only in the cases, where CTs involve the use of medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms, additional 30 days' time limit is allowed for review of application by IEC. Further extension of 90 days period can be given for these products for the purpose of discussion in a group or a committee according to the regulations and procedures of the CMS. There is no time limit defined for the review and authorization of xenogenic cell therapy application by the IEC.

Sponsors

Sponsor may be an institution, an individual, a company or an organization. The main responsibility of sponsor is to ensure that the trial is conducted and the data generated is in accordance with Directive 2001/20/EC.

Manufacture or import authorization

Authorization should be required for both complete and incomplete manufacture of IMPs. If the products are manufactured for export or the products are imported from third countries into member states then also authorization is required. Within 90 days after receipt of a valid application, CA is required to give its opinion regarding the application for authorization. If the holder of the authorization is unable to fulfil the appropriate requirements, then the CA should suspend or cancel the authorization.

The trial master File and Archiving

The trial master file consists of important documents related to the CT. The trial master file contains all data related to each phase of CT which helps in evaluation of the conduct of trial and the quality of data obtained in a CT. These documents are referred to in Article 15(5) of Directive 2001/20/EC. These documents provide evidence that the CTs was conducted following the principles and guidelines of GCP. The trial master file contains all data, so, it isuseful to the independent auditor of sponsor for auditing. It is also useful during an

inspectionby the CA.

Inspectors

The inspectors are appointed by the CMS for the conduct of CTs inspection. They are appointed according to regulations Article 15(1) of Directive 2001/20/EC. The inspectors should have finished education at university level and have involvement in medicine, pharmacy, toxicology, pharmacology or other relevant fields. It is the duty of member states to give training to them for continuous improvement in their skills.

Inspection procedures

Inspection is done during CTs to check that the procedure established by EC No 726/2004 is being followed. These inspections are requested by the EMA. GCP inspections may take place, prior, during or after completion of the CT.

The european union guidelines for clinical trials

In EU, CTs are conducted according to the guidelines given by following regulatory bodies which are listed below. The guidelines given by the respective regulatory bodies for the CT conduct has also been discussed.

European Commission

Guidelines given by EC are published in Volume 10 of "EudraLex. These guidelines state thatapplication dossier should be submitted to the CA of the member states and the IEC for the initiation of CTs. The conditions under which the application is made should be clearly indicated by the applicant for applications submitted according to Article 8 and Article 9 of Directive 2001/20/EC. The Volume 10 of "EudraLex describes the detailed Guidance for the request for approval of CTs, collection, verification and presentation of adverse event reports arising from CTs on a medicinal product for human use, quality of the IMP, conduct and preparation of GCP inspections.[19]

European medicines agency

Volume 3 of the EudraLex "The rules governing medicinal products in the European Union" describes scientific guidelines drafted by the Committee for Medicinal Products for Human Use (CHMP) in consultation with the CA's of the EU member states. This document is beneficial for the applicants to prepare MA applications for medicinal products for human use. MA for a medicinal product for human use will be given by EMA. The main function is to protect and promote human and animal health. Heads of medicines agencies have set up a CTs facilitation group (CTFG) to discuss ongoing technical issues regarding CTs. EC and EMA are the observers for this group.[20]

ICH Efficacy and GCP guidelines also used in EU for conducting the CTs. These guidelines have been discussed in the earlier part of the work (6.1.1 and 6.1.2).

Compensation rule for clinical trials in europe

In the last 10 years, most of the countries that are extensively involved in research, including thirty-one European countries and few non-European countries, have ordered to pay for examination related damage. In Europe, a common legal framework for the protection of subjects taking part in CTs has been set up as per the EU Directive 2001/20/EC. According tothe Directive, a CT may be undertaken only if provision has been made for indemnity to coverthe liability of the investigator and the sponsor, As per the directive 2001/20/EC, before giving the decision on compensation, it has to be check that if the CTs were approved by Research Ethics Committee (REC) or not. Compensation to be provided to the subjects is that mentionedin the informed consent.[21]

Clinical trials in India

In India, Central Drugs Standard Control Organization (CDSCO) is the regulatory and licensing authority which approves any new chemical entity (NCE) which is to be imported toIndia. 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.[22] The protocol for CTs are examined by the office of DCGI before the permission for their conduct are granted (Figure 3). DCGI and IEC has the major role in controlling the CTs in India.

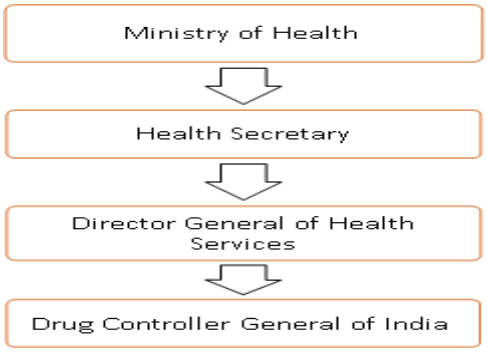

Figure 3: Regulatory authorities involved in clinical trials.

Investigational new drug application

IND application Form44 is submitted to get approval for the start of CTs in India. DCGI gives the final approval for the start of the CT. CTD format is still not enforced in India.[59] The IND application review process in India is depicted inFigure4.

In September 2015, CDSCO issued new guidelines for the submission of clinical trial application (CTA). As per these guidelines applicants can submit CTA online. Hard copies arealso being accepted till this system is not fully adopted in India.

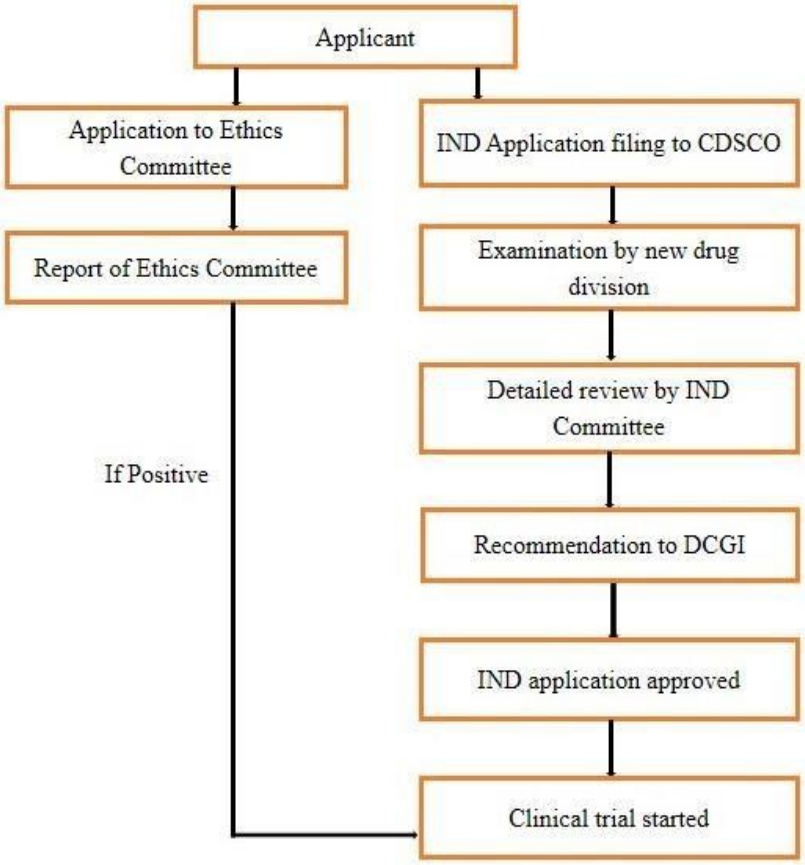

Figure 4: IND application review process.

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 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.[23]

The Drugs and Cosmetics Act, 1940

The framework of this act consists of powers for regulating and ensuring quality, safety and efficacy of drugs (60). This act also includes necessary rules, procedures and guidelines related to CTs.[61] 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).[62]
g) General statutory rule (GSR) 1011(E) is in draft stage for amendments in rule 122DA, 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

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 revisedin 2005, to bring the Indian regulations for CTs at par with internationally accepted standards., 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.[24]

The recent amendments in schedule Y are

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

New regulations announced by CDSCO:

1) GSR 53 E; 30th Jan. 2013: Serious adverse event (SAE) reporting and compensation forstudy-related injury.
2) GSR 63E; 1st Feb. 2013: Conditions to be fulfilled by Sponsor to conduct a clinical trial inIndia.
3) GSR 611E; 19th Nov. 2013: Audiovisual recording of the informed consent process.
4) Expert committees have been constituted for examination of serious adverse events other than death related to CTs.
5) GSR 889E; 12th Dec. 2014: Notification about specific provisions in respect of compensation for ineffectiveness and placebo-controlled trials (25).
6) GSR 11E; 6th January 2016 is in draft stage for amendments in schedule Y.[26]

Fundamentals of conducting a clinical trial in India

1. Permission from the Drug Controller General of India

In order to conduct CTs in India, the applicant has to be take permission from the DCGI, as well as from the institute where the CTs will be conducted. DCGI will give final approval for the commencement of CTs, approval of a license for a specific category of drugs such as blood,sera, vaccines, blood products etc. DCGI is the governing body which comes under the Health Ministry. Applicant has to submit total information about chemical and pharmaceutical data, generic and chemical name, dosage form, composition, animal toxicology and pharmacology data to the DCGI. After primary approval, the applicant has to send safety reports with the annual report.[27]

2. Independent Ethics Committee/Institutional Review Board

The review of CT application by IRB has to be conducted in parallel with the DCGI review. This will help to start the CT as soon as possible. Each IRB is expected to have their written standard operating procedures (SOP), curriculum vitae (CV) of all IRB members, copies of all CTs documents that have been received for review, complete correspondence between IRB and investigator, detailed minutes of IRB meetings and final report of each study. After granting the approval for carrying out CTs, it is the responsibility of IRB, to keep a check on all serious adverse events and adverse drug reactions happening at the trial sites, review and approval of amendments in the protocol or informed consent documents. The frequency of these reviews may vary from one institute to another, as specified in the respective IRB charters or SOPs, butis usually once in 4-8 weeks. The usual time for approval by the IEC is6-8 weeks.[28]

3. Mandatory registration with CTs Registry India

The National Clinical Trial Registry was established by National Institute of Medical Statistics (NIMS) in July 2011. It is mandatory for all new CTs being conducted in India to be registered with the Clinical Trial Registry of India (CTRI). CTRI has made available all the necessary information that is accountable and is required for maintaining transparency in the conduct ofCTs.

Indian guidelines for clinical trials

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. The Drug Technical Advisory Board (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. 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.[29,30]

Indian council of medical research guidelines

The Indian council of medical research (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 violateany globally valid ethical standards. ICMR has also given guidelines concerning the compensation to be given to the subjects.

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.[72]

The amendments states that the subject is allowed for compensationdue 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 theinvestigator;
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) statesthat 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 a injury or death is tobe calculated by IEC and Expert Committee appointed by DCGI .

Clinical trial data

The data of number of CTs approved in India by DCGI was obtained from website of regulatory authority i.e. Central Drugs Standard Control Organization (CDSCO). Trials approved by DCGI from 2017 till April 2021 were noted for analysis (Table 2). The data of 2021 has been excluded from analysis as it is not the complete data. It has been shown for informationonly.

Table 2: CTs approved by Drug Controller General of India (DCGI).

Year	Approved Trials
2017	71
2018	76
2019	95
2020	87
2021	100
Total	429

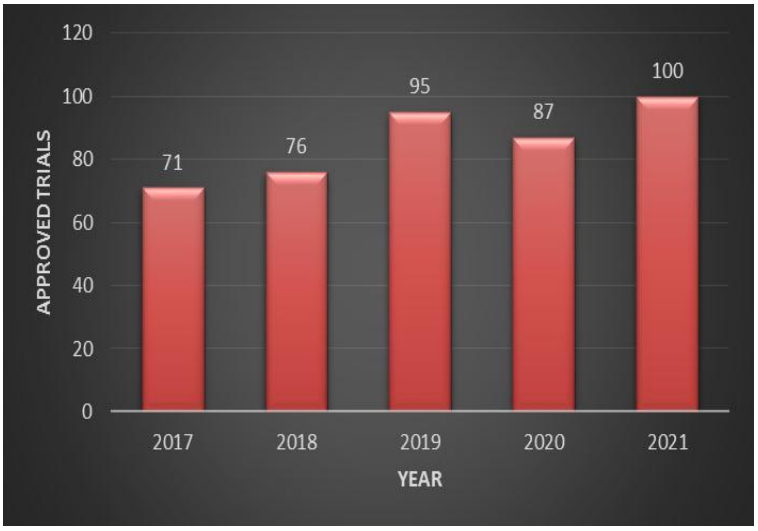

Figure 5: CTs approved by Drug Controller General of India (DCGI).

The above data of approved CTs (Figure 5) compares the number of CTs approved from 2017to 2021 by DCGI. From the data, we can observe that amongst all the years, it was in 2017 thatvery few CTs were approved i.e., only 21 CTs while in the year 2021 maximum number of trials were approved i.e. 100 CTs. The number of CTs approved in 2018, 2019, and 2020 were 76, 95, and 87, respectively. There is quite high variations in number of trials registered. The main reason behind the failure of CTs was the violation of protocol. Regulations are not strict and not adopted properly, so lots of deaths occur which also affects CTs enrolment rate in India.

Comparison of the clinical trial regulations in the USA, Europe and India

The clinical trial regulations of USA, Europe and India were compared on various aspects like legal framework, CT application, application fee, application submission format, approval time, IRB/IEC, forms required, regulations, compensation, record storage time, GCP guidelines, adverse event reporting. The comparison is shown in Table 3.

Table 3: Comparison of clinical trial guidelines in USA, EU and India.

Parameters	United States	Europe	India
Regulatory bodies	USFDA	Clinical trial directive 2001/20/EC	CDSCO
Clinical trial application	Investigational new drug application (IND)	Investigational medicinal product dossier (IMPD)	Form 44 is an application made for getting approval to start clinical trial
Application fee	No Fee	Minor fees, varies from one member state to another	Fees is required in Phase I,II,III i.e.
Application submission format	Common technical document(CTD) formats, U.S. format	CTD format	Form 44 have to be submitted according to national format
Approval Timeline	30 days	60 days	16-18 weeks
Institutional review board/Independent Ethics committee	Institutional review board and center for drug evaluation and research(CDER) approval required	Ethics Committee approval required. ECs appointed or authorized by the CMS	DCGI and ethics committee approval required
Forms required	FDA forms 1571, 1572, 3454 and 3455 required	Annexure 1 clinical trial application form	Form 44
Regulations	Code of federal regulations 21 CFR Part 312,50,54,56	Clinical Trial Directive(2001/2 0/EC)	Drug and cosmetic act 1940, and Schedule Y of the Drug and cosmetics act and rule 1945
	have to be followed	Good Clinical Practice Directive(2005/2 8/EC)	

Compensation	Compensation according to informed consent 21 CFR Part 50	Requires separate "certificate of patient insurance"	According to 122 DAB rule
	and Financial disclosure by the clinical investigator	Discussed in protocol and in informed consent also	
Records storage	2 years record retention time	Patient identification codes have to be maintained till 15 years after the completion of the CT	3 years record retention time after completion
GCP Guidelines	ICH GCP	ICH GCP	Indian GCP
Adverse Event Reporting	Life-threatening adverse reaction reported to FDA within 7 days	Serious adverse reactions are reported by sponsor within 7-15 days	Any injury or death related to a clinical trial, sponsors have to be informed to the DCGI within 24 hours

SUMMARY AND CONCLUSION

Suggestions

It is often observed that same CTs are conducted in different countries. It is suggested that there should be a Common International Clinical Trial Organization where every CT should be registered. This will reduce the duplicacy in the conduct of CTs, as well as save time, effort, money and discomfort to the patient of different countries.

Some of the drawbacks

1. Lack of harmonization in the IND application format. There should be common application/process for all the countries so that IND can be submitted and approved at the faster pace and without any confusion and duplication.
2. After completion of the CT phase III, NDA application takes near about 6 months to 2 years for getting approval from the regulatory authorities. There is a scope for all regulatory authorities USA, EU and India to speed up NDA review and approval at the earliest through effective planning of their resources.
3. No compensation provided by companies to subjects. There should be a penalty or imprisonment if sponsor or investigator is not compensating subjects for injuries occurred during or after the end of the CT.

CONCLUSION

It can be concluded that regulated countries such as USA and EU have better established guidelines in comparison to semi-regulated countries like India. In USA, 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 Europe, CTs are regulated byEMA and EC. There, it is mandatory to submit IMPD application and other CT related data inCTD and eCTD format respectively. In USA and Europe, ICH-GCP guidelines are followed for conduct the CTs. In case of semi-regulated countries such as India neither are their guidelines for CTs fully developed and nor do they follow internationally accepted standards, till now. In both countries, CTD format is yet not adopted for submission of clinical trial applications, which leads to delay for getting approval for start the CTs. In these countries, CTs are conducted according to national guidelines. The ICH-GCP guidelines are also not fully adopted for conduct the CTs. Due to these reasons the success rate of clinical trials in EU ismore than India.

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