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REVIEW ARTICLE ON REGULATORY REQUIREMENTS FOR CLINICAL TRAILS ON VACCINES – AGLOBAL SCENARIO

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ABSTRACT

The studies provide with the guidance to National Regulatory Authorities (NARES) and vaccine manufacturers on the clinical evaluation of vaccines by outlining international regulatory expectations during the different stages of vaccine development and for marketing approval. In this respect, the guidance in this document could also be useful for clinical researchers and investigators. The text is written in the form of guidelines instead of recommendations in view the fact that vaccines represent a heterogeneous class of agents, and the preclinical and clinical testing programmes will need to be adapted for the product in question. Guidelines allow greaterflexibility than Recommendations with respect to specific issues related to particular vaccines. Aseparate WHO document is under development to provide more detailed guidance on preclinical and laboratory evaluation of vaccines. The section of this document that discusses preclinical and laboratory evaluation consequently provides general guidance but does not define international regulatory expectations in this area. Clinical trials (CTs) are conducted to explore new methods of intervention that are better than the 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 this work, clinical trial regulations in USA, EU, India,and Singapore 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.

KEYWORDS: Clinical Trails, USA, EU, India, Singapore, Regulations, GCP.

INTRODUCTION

The procedure of introducing a new pharmaceutical drug to the market, after a lead compound hasbeen recognized during the process of drug discovery, is called drug development process. In thisprocess, pre-clinical studies are conducted on microorganisms/animals and clinical trials (CTs) conducted on humans. 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] The steps are summarized in Figure 1. Time taken to bring a new drug to the market takes almost12-15 years.[2] Given in Figure 1.

Drug Discovery and Development Process

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.[3]

PRECLINICAL RESEARCH

Prior to testing the drug in human being's 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. In these studies, comprehensive doses are used to obtain 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]

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

The objectives of CTs are listed below:

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

PHASES OF CLINICAL TRIALS

CTs are usually divided into four different phases. These includes: -

- Phase 0 trials
- Phase I trials
- Phase II trials
- Phase III trials
- Phase IV trails

Steps involved in clinical trials are given in Table 1.
Comparison of clinical trial guidelines in USA, EU and INDIA are given in Table 2.

TYPES OF CLINICAL TRIALS PREVENTION TRIALS

In these trials, tests are conducted to find new treatments so as to prevent a particular medical condition or to prevent its reoccurrence. The focus of these trials can be on medicines, vitamins and minerals or lifestyle changes.[7]

TREATMENT TRIALS

The best-known clinical studies are those that are meant to test new medications. Before another medication or treatment can be endorsed by drug regulatory authorities of a country, it needs to experience three-phase of CTs. A clinical trial is intended to compare a new treatment and the best-known existing treatment. When there is no existing treatment to use as a reference in these trials, scientists are Liable to compare new medication and a placebo.

DIAGNOSTIC TRIALS

These trials conducted to find new methods for diagnosing a specific disease or condition. The investigator will select one medication that he going to test on subjects. Then the examiner decides whether to compare it with a current treatment or a placebo, and check what type of patient might benefit from the new medication or device.

SCREENING TRIALS

Screening trials are done for early detection of diseases and health condition. The methods of detecting disease, often called screening tests, can include:

- Laboratory tests conducted to check blood, urine, and other body fluids and tissues.
- Genetic tests are done to identify inherited genetic markers of the disease.

QUALITY OF LIFE

These are supportive care trials. These trials are conducted to find out new methods to increase the comfort and satisfaction level of patients suffering from chronic disease.[7]

RANDOMIZED CONTROLLED TRIAL

Randomized controlled trials are a type of investigative analysis. These trials considered as "gold standard" in clinical research, useful for testing the efficacy or effectiveness of healthcare services such as medicine, different therapies or interventions. In these trials, participants are assigned randomly in groups that compare the different treatments. These are viewed as the most reliable scientific evidence in healthcare services as they eliminate confusion and bias.[8]

PLACEBO-CONTROLLED TRIALS

Placebos have been used in CTs for a long time and they have contributed significantly in the development of many medical treatments. In these trials, there are two groups and placebo are given to one group and to second group study medication is given. Placebo means an inactive substance, this used in the double-blind CT. Patient who are suffering from chronic disease and have poor chances of survival without proper medical treatment, to them placebo is not given.[9]

CONTROLLED CLINICAL TRIALS

In this type of CTs, the effectiveness of one drug or treatment is compared to the effectiveness ofanother drug or treatment. In numerous controlled trials, the other treatment is a placebo (inactivesubstance) and is viewed as the "control".[9]

MULTICENTRES TRIALS

In multicentre CTs, new medications are evaluated more

efficiently. But in some situations, it is difficult to get required subjects and conduct a trial within the time limit. Trials conducted in different-different centres with a small number of subjects to find new treatments for rare diseases.These trials are conducted under the observation of multi-investigators. Sometimes same clinical trial is conducted in different countries to compare the results on the basis of a different environment. Protocols for conduct of the CTs are kept simple and same for all the centres.[10]

VACCINES

Vaccines have a long history of excellent safety and a highly positive benefit/risk profile. Even so, the lack of specific guidance from regulatory agencies specifically relating to the first application of a new experimental vaccine in humans has hampered product development. Most of the regulatory guidance documents for manufacturers are too broad and sometimes only vague where vaccines are concerned. As regulators deeply involved both in the development of the European Medicines Agency's (EMA; London) new regulatory framework on risk identification and mitigation, and in assessment and authorization of clinical trial applications for biotechnological and biological products (especially vaccines), we have been repeatedly approached by companies and vaccine developers regarding regulatory issues for first-in-human clinical trials. Here, we discuss these considerations as they relate to vaccines within the context of the current EMA guideline for risk identification and mitigation for first-in-human clinical trials based on the apparently considerable uncertainty among developers. We describe how regulatorsapply the guideline and where we see the limitations or the need to take alternative approaches. The discussion primarily focuses on prophylactic and therapeutic vaccines against infectious diseases as this classic field of products is associated with particular uncertainty.

OVERALL REGULATORY FRAMEWORK FOR VACCINES

In the United States, all vaccines, including those in the SIP, are regulated as biologics by the Centre for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA). A single set of basic regulatory approval criteria apply to all human vaccines, regardless of the technology used to produce them. CBER's current legal authority for the regulation of vaccines derives primarily from Section 351 of the Public Health Service (PHS) Act and from certain sections of the Federal Food, Drug and Cosmetic (FD&C) Act. The PHS Act is implemented through regulations codified in Title 21 of the Code of Federal Regulations (CFR), Parts 600 through 680, which contain regulations specifically applicable to vaccines and other biologics. In addition, because a "vaccine" meets the legal definition of a "drug" under the FD&C Act, sponsors must also comply with current Good Manufacturing Practice (cGMP) regulations in 21 CFR Parts 210 and 211, and, for all human testing prior to licensure, the Investigational NewDrug (IND) regulations in 21 CFR Part 312. Most of the vaccines included in the SIP are directedagainst pathogens that are now identified as Select Agents (42 CFR Part 72; 42 CFR Part 73; 7 CFR Part 331; 9 CFR Part 121), which can cause life-threatening and/or fatal illness in exposed laboratory workers., the SIP presently consists of eight U.S. licensed vaccines, seven that are administered under active INDs held by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), and one administered under an active IND held by the Centres for Disease Control and Prevention (CDC). Given the large expansion in laboratory research for Select Agents and other existing or emerging pathogens during the past decade, the number of vaccines that might be included in the SIP is expected to grow.

Given this overall regulatory framework, the current objectives of the SIP, and the potential expansion of the program to provide immunization against additional pathogens, this chapter focuses on four major questions:

- How can the SIP best ensure continuous and convenient availability of appropriate vaccines for prevention of severe disease caused by Select Agents and other high-risk pathogens to which laboratory workers may be exposed?
- What regulatory pathways are available to obtain FDA approval for as many SIP vaccinesas possible, both now and in the future?
- How can the evaluation of investigational SIP vaccines administered under IND be improved and extended?
- What are the most expeditious and cost-effective means of bringing additional vaccines into the program?

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 agencies established in the respective countries to regulate the drug regulations.In this work, to study and compare the drug regulations in regulated and semi-regulated countriesfollowing 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 given by Health Sciences Authority (HSA) were studied.
5. Guidelines for the regulated and semi-regulated

countries, USA, EU & India respectively, were compared with respect to: -

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

6. CT case studies conducted in the USA; EU & India are being discussed.

REGULATIONS

INTERNATIONAL CONFERENCE ON HARMONIZATION GUIDELINES

The "International Conference on Harmonization (ICH) of technical requirements for registration of Pharmaceuticals for Human Use" is a joint effort of regulatory authorities of Europe, Japan and the United States as well as experts from the pharmaceutical industries in the three regions to discuss the scientific and technical aspects related to registration of pharmaceutical products. Theobjectives of ICH are to improve efficiency of new drug development and registration process, to promote public health, to prevent duplication of CTs in humans and minimize the use of animal testing without comprising on the procedure for evaluation of the safety and effectiveness of pharmaceuticals.

ICH gave guidelines for conducting the CTs. These guidelines are globally accepted and were drafted in consultation with USA, Japan, and EU, the three ICH regions. These guidelines were finalized by ICH working group committees and expert committees. ICH GCP guidelines have originated from the Declaration of Helsinki.[11]

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

The "World Medical Association (WMA) set up the Declaration of Helsinki as a statement of Ethical principles for medical research involving human subjects" in 1964. According to Declaration of Helsinki:

- It is the duty of the practitioner to promote and protect the public health.
- The health of the patient shall be the first priority of the practitioner.
- Safety of the research subjects must take preference over all other interests.
- Some research needs special populations and for them special protection is required.
- According to this declaration neither national nor international ethical, legal or regulatory requirement can reduce or eliminate any of the protections for research subjects.

PRINCIPLES FOR ALL MEDICAL RESEARCH

- Generally accepted scientific principles must be followed in medical research involving human subjects.
- The design and procedures of each research study involving human subjects must be described well in a research protocol.
- The protocol should include information regarding funding, sponsors, investigator, institutional affiliations details and compensation for subjects who are harmed in the research study.
- The research protocol should be submitted to ethics committee to get approval for the startof the CT.
- Every CTs should be registered in a publicly available database before registration of the first subject.
- Medical research involving human subjects can only be conducted if the benefit is more than risk. (12)

ICH HARMONIZED TRIPARTITE GUIDELINES FOR GOOD CLINICAL PRACTICEICH E6 (R1)

ICH E6 (R1) Good Clinical Practice (GCP) guidelines describe suitable quality standards for CTs design, conduct, monitor, audit, record, and reporting.[13] The main aim of GCP is to ensure safetyand protect the rights of subjects. GCP gives the guarantee that the data and results reported are reliable and correct. GCP came into force in 1997 but was not implemented by law. In 2005, EU implement GCP directive and it changed the world's prospective for GCP. Now all the CTs beingconducted in the United Kingdom and Europe follow the GCP directive regulations. GCP guidelines vary from country to country so, ICH issued the E6 guidelines for GCP. These guidelines were approved on 17 July 1996 and came into force on 17 January 1997. These guidelines were made in consultation with The United States, EU, Japan, Australia, the Nordic countries, Canada and WHO.

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 5 lists the applicable regulations that govern the conduct of CTs in the U.S.[14]

21 CFR Part 50 Informed consent of human subjects

As per this rule says that investigator cannot 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.[15]

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.[16]

21 CFR Part 55.106 Institutional review board registration rules

This is the amendment rule of 21 CFR 55. 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.[17]

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 financial issues, specifically compensation part. Compensation has to be provided to the subjects if any injury occurs 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.[18]

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.[19] 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)

THE CENTRE 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 Public Health Service Act and the Federal Food, Drug and Cosmetic Act. CBER's, main function is to promoteadvancement in biologics to secure and improve the public health by ensuring that they are safe and effective for their use.[20]

COMPENSATION RULES FOR CONDUCTING CLINICAL TRIAL IN THE USA

USFDA does not have an 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 specify 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 is 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 dollars 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.[21]

Some Government federal agencies also provide treatment or compensation for injuries resulted during research. These include the US Department of Défense (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 provide 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;

1. Researcher owed a duty to the participant;
2. Researcher failed to satisfy ethical, legal, or moral obligations
3. Violation of law which caused patient's injury;
4. 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.[21]

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 medicinal products for human use. Inthis procedure, the applicant has to submit only a single application to 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 besubmitted in the CTD format.[22,23]

INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER

An IMPD application (Annexure 4) 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 medicinal product(IMP)
- Complete preclinical and clinical studies data
- Data indicating 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.[24]

The IMPD application review procedure in EU is discussed in Figure 4.

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. The new Regulation EU No 536/2014 was adopted on 16 April 2014. Its main aim is to make it simpler toconduct trials in CMS of the EU. It will be applicable after May 2016, two years after its publication.[49] 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 new CT regulations.

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 is required to give its opinion to the applicant and the CA of the CMS within 60 days of the receipt of 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 xenogeneic cell therapy application by the IEC.[25]

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 hasalso been discussed.

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 to India. Directorate General of Health Services (DGHS) which comes under Ministry of Health and Family Welfare (Mo HFW), 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 [26]. The protocol for CTs is examined by the office of DCGI before the permission for their conduct are granted (Figure 6). DCGI and IEC has the major role in controlling the CTs in India.

Regulatory Authorities involved in Clinical Trials are given in Figure 6.

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.[26] CTD format is still not enforced in India.[27] The IND application review process

in India is depicted inFigure7.

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 are also being accepted till this system is not fully adopted in India.[26]

IND application review process are given in Figure 7.

THE RECENT AMENDMENTS IN SCHEDULE Y

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

1. GSR 53 E; 30th Jan. 2013: Serious adverse event (SAE) reporting and compensation for study-related injury.
2. GSR 63E; 1st Feb. 2013: Conditions to be fulfilled by Sponsor to conduct a clinical trial in India.
3. GSR 611E; 19th Nov. 2013: Audio visual 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. (28)
6. GSR 11E; 6th January 2016 is in draft stage for amendments in schedule Y.[29]

VACCINE DEVELOPMENT, TESTING, AND REGULATION

Vaccine development is a long, complex process, often lasting 10-15 years and involving acombination of public and private involvement.

The current system for developing, testing, and regulating vaccines developed during the 20thcentury as the groups involved standardized their procedures and regulations.

STAGES OF VACCINE DEVELOPMENT AND TESTING

In the United States, vaccine development and testing follow a standard set of steps. The first stages are exploratory in nature. Regulation and oversight increase as the candidate vaccine makes its way through the process.

FIRST STEPS: LABORATORY AND ANIMAL STUDIESEXPLORATORY STAGE

This stage involves basic laboratory research and often lasts 2-4 years. Federally funded academic and governmental scientists identify natural or synthetic antigens that might help prevent or treat a disease. These antigens could include virus-like particles, weakened viruses or bacteria, weakened bacterial toxins, or other substances derived from pathogens.

PRE-CLINICAL STAGE

Pre-clinical studies use tissue-culture or cell-culture systems and animal testing to assess the safety of the candidate vaccine and its immunogenicity, or ability to provoke an immune response. Animal subjects may include mice and monkeys. These studies give researchers an idea of the cellular responses they might expect in humans. They may also suggest a safe starting dose for the next phase of research as well as a safe method of administering the vaccine.

Researchers may adapt the candidate vaccine during the pre-clinical state to try to make it more effective. They may also do challenge studies with the animals, meaning that they vaccinate theanimals and then try to infect them with the target pathogen.

Many candidate vaccines never progress beyond this stage because they fail to produce the desired immune response. The pre-clinical stages often lasts 1-2 years and usually involves researchers in private industry.

IND APPLICATION

A sponsor, usually a private company, submits an application for an Investigational New Drug (IND) to the U.S. Food and Drug Administration. The sponsor describes the manufacturing and testing processes, summarizes the laboratory reports, and describes the proposed study. An institutional review board, representing an institution where the clinical trial will be conducted, must approve the clinical protocol. The FDA has 30 days to approve the application.

Once the IND application has been approved, the vaccine is subject to three phases of testing.

NEXT STEPS: CLINICAL STUDIES WITH HUMAN SUBJECTSPHASE I VACCINE TRIALS

This first attempt to assess the candidate vaccine in humans involves a small group of adults, usually between 20-80 subjects. If the vaccine is intended for children, researchers will first test adults, and then gradually step down the age of the test subjects until they reach their target. PhaseI trials may be non-blinded (also known as open-label in that the researchers and perhaps subjectsknow whether a vaccine or placebo is used).

The goals of Phase 1 testing are to assess the safety of the candidate vaccine and to determine thetype and extent of immune response that the vaccine provokes. In a small minority of Phase 1 vaccine trials, researchers may use the challenge model, attempting to infect participants with thepathogen after the experimental group has been vaccinated. The participants in these studies are carefully monitored and conditions are carefully controlled. In some cases, an attenuated, or modified, version of the pathogen is used for the challenge.

A promising Phase 1 trial will progress to the next stage.

PHASE II VACCINE TRIALS

A larger group of several hundred individuals participates in Phase II testing. Some of the individuals may belong to groups at risk of acquiring the disease. These trials are randomized and well controlled, and include a placebo group.

The goals of Phase II testing are to study the candidate vaccine's safety, immunogenicity, proposed doses, schedule of immunizations, and method of delivery.

PHASE III VACCINE TRIALS

Successful Phase II candidate vaccines move on to larger trials, involving thousands to tens of thousands of people. These Phase III tests are randomized and double blind and involve the experimental vaccine being tested against a placebo (the placebo may be a saline solution, a vaccine for another disease, or some other substance).

One Phase III goal is to assess vaccine safety in a large group of people. Certain rare side effects might not surface in the smaller groups of subjects tested in earlier phases. For example, suppose that an adverse event related to a candidate vaccine might occur in 1 of every 10,000 people. To detect a significant difference for a low-frequency event, the trial would have to include 60,000 subjects, half of them in the control, or no vaccine, group (Plotkin SA et al. *Vaccines*, 5th ed. Philadelphia: Saunders, 2008).

Vaccine efficacy is tested as well. These factors might include 1) Does the candidate vaccine prevent disease? 2) Does it prevent infection with the pathogen? 3) Does it lead to production of antibodies or other types of immune responses related to the pathogen?

NEXT STEPS: APPROVAL AND LICENSURE

The U.S. Food and Drug Administration's (FDA's) Centre for Biologics Evaluation and Research external icon (CBER) is responsible for regulating vaccines in the United States.

The sponsor of a new vaccine product follows a multi-step approval process, which typically includes

- An Investigational New Drug application
- Pre-licensure vaccine clinical trials
- A Biologics License Application (BLA)
- Inspection of the manufacturing facility
- Presentation of findings to FDA's Vaccines and Related Biological Products Advisory Committee external icon (VRBPAC)
- Usability testing of product labelling

After approving a vaccine, FDA continues to oversee its production to ensure continuing safety.

Monitoring of the vaccine and of production activities, including periodic facility inspections, must continue as long as the manufacturer holds a license for the vaccine product.

FDA can require a manufacturer submit the results of their own tests for potency, safety, and purity for each vaccine lot. FDA can require each manufacturer submit samples of each vaccine lot for testing.

After a successful Phase III trial, the vaccine developer will submit a Biologics License Application to the FDA. Then the FDA will inspect the factory where the vaccine will be made and approve the labelling of the vaccine.

After licensure, the FDA will continue to monitor the production of the vaccine, including inspecting facilities and reviewing the manufacturer's tests of lots of vaccines for potency, safety and purity. The FDA has the right to conduct its own testing of manufacturers' vaccines.

POST-LICENSURE MONITORING OF VACCINES

A variety of systems monitor vaccines after they have been approved. They include Phase IV trials, the Vaccine Adverse Event Reporting System, and the Vaccine Safety Datalink.

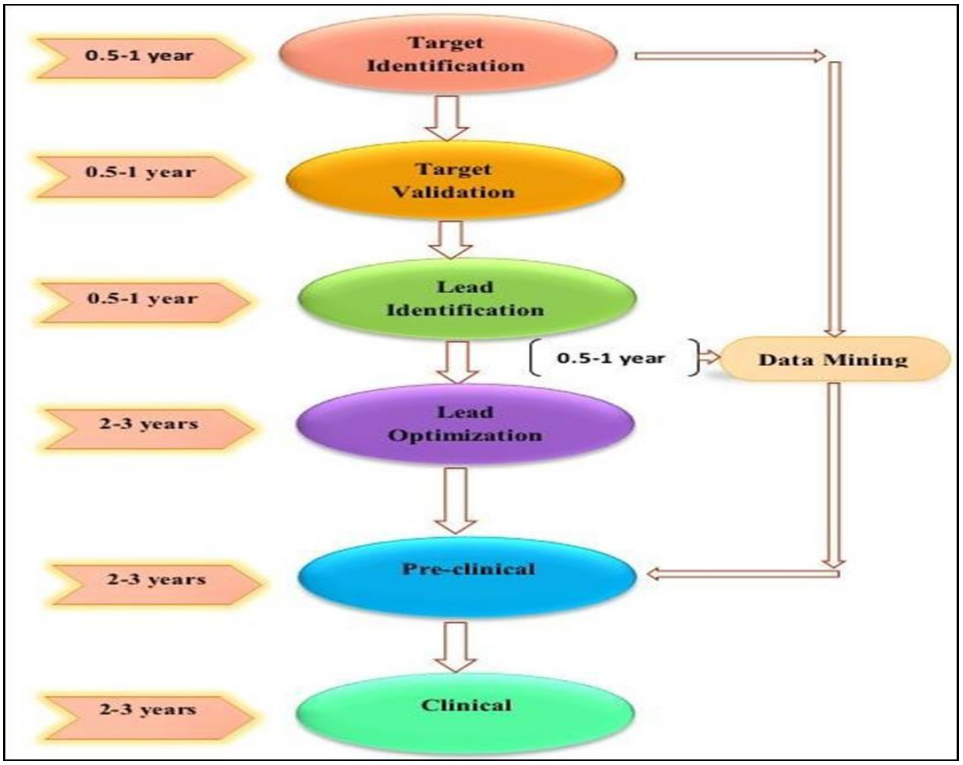

Figure 1: Steps involved in bringing a new drug in market.

Table 1: Steps involved in the Clinical Trails.

Parameters	Pre-Clinical 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 & Animal studies	20-100 Healthy Volunteers	100 – 300 Patient Volunteers	1000-3000 Patient Volunteers	Review Process/ Approved		
Purpose	Access safetyand biologic activity	Determinesafety anddosage	Evaluate effectiveness and look for side effects	Verify effectiveness and monitor ADRs forlong term use			
Success Rate	5000 Compoundsevaluated	5 Enter Trails				1 Drug Approved	

Table 2: Comparison of Clinical Trial Guidelines in USA, EU and INDIA.

Parameters	United States	Europe	India
Regulatory bodies	USFDA	Clinical trialdirective 2001/20/EC	CDSCO
Clinical trialapplication	Investigation newdrug application (IND)	Investigational medical product dossier (IMPD)	Form 44 is an application made for getting approval to start clinical trial
Application fee	NO fee	Minor fees, variesfrom one member state to another	Fees is required in phase I, II, III. e.50000,25000,25000respectively
Application submission format	Common technicaldocument (CTD) formats, USA format	CTD format	Form 44 have to besubmitted according to national format
Approval Timeline	30days	60days	16-18weeks
Institutional review board/Independent Ethical committee	Institutional reviewboard and center for drug evaluation and research (CDER) approval required	Ethics Committee approval requiredECs appointed or authorized by the CMS	DCGI and ethicscommittee approval required
Forms required	FDA forms 1571,1572, 3454, 3455 required	Annexure 1 clinical Trial applicationform	Form44
Records Storage	2 years record	Patient identification codeshave	3 years recordretention time after

	retention time	to bemaintained till 15years after the completion of the	completion
		CT	
GCP Guidelines	ICHGCP	ICHGCP	India GCP
Adverse EventReporting	Life-threateningadverse reactionreported to FDA within 7 days	Serious adverse reactions are reported by sponsorwithin 7-15days	Any injury or death related to a clinical trial; sponsors have to be informed to theDCGI within 24hours
Regulations	Code of federal regulations 21CFRPart312,50,54,56 have to be followed	Clinical TrialDirective (2001/20/EC)	Drug and cosmetic act 1940, and schedule Y of the Drug and cosmetics act and rule 1945
Compensation	Compensation according to informed consent21CFR Part 50 and financial disclosureby the clinical	Requires separate"certificate of patient insurance"Discussed in protocol and in informed consent also	According to 122DABrule

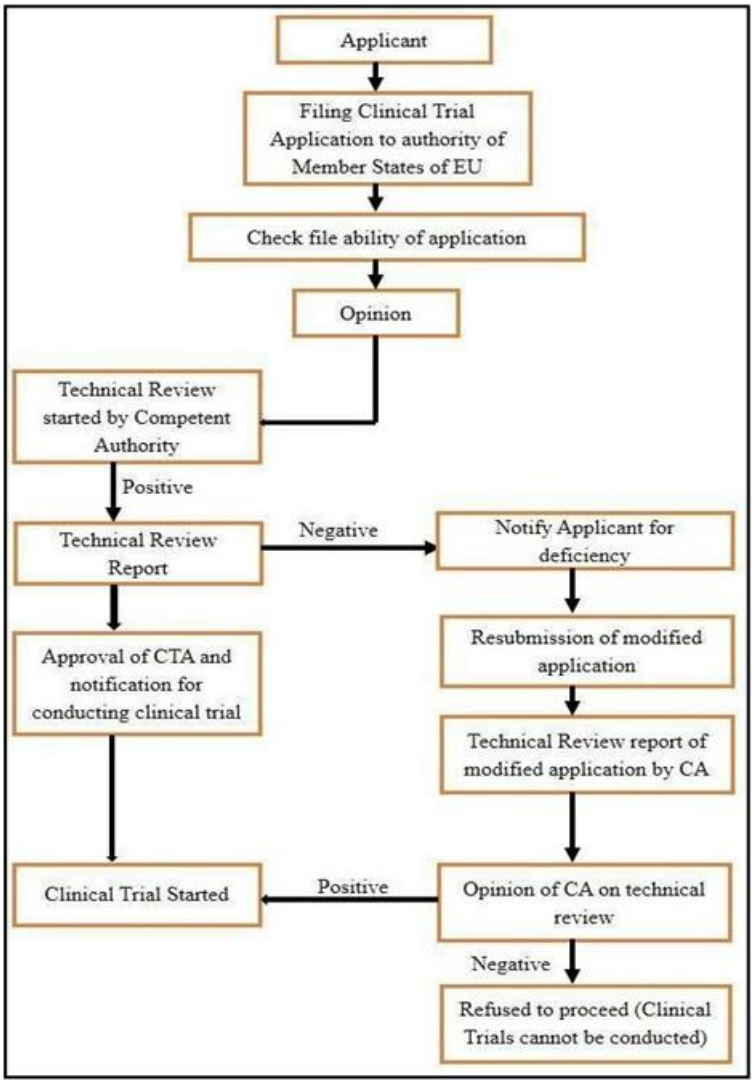

Figure 4: IMPD review process.

Investigational New Drug Application

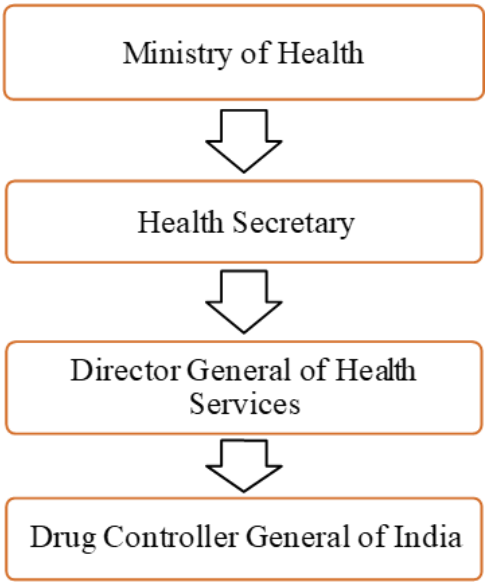

Figure 6: Regulatory authorities involved in clinical trials.

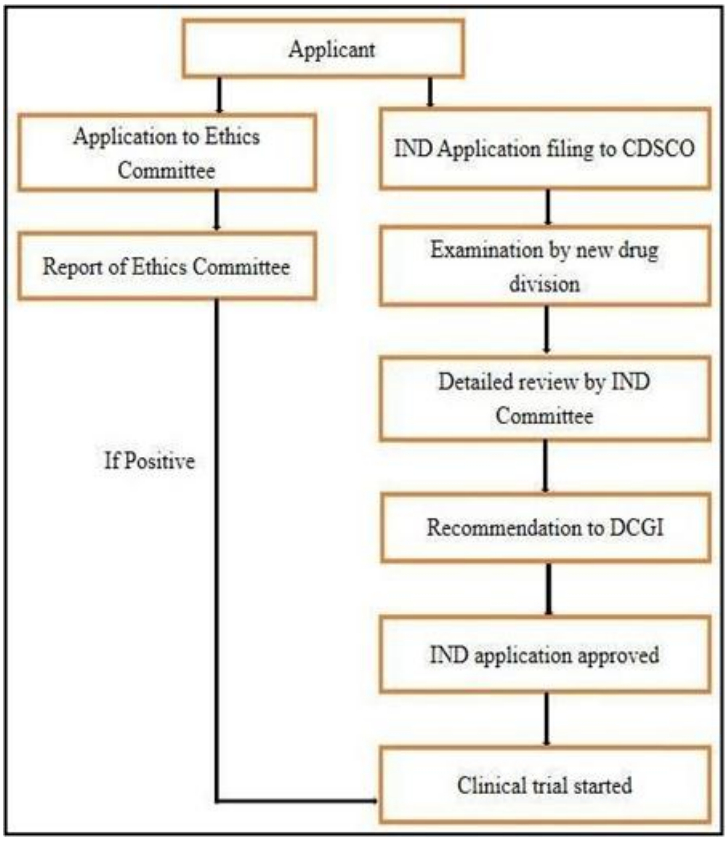

Figure 7: IND application review process.

CONCLUSION

Vaccines are developed, tested, and regulated in a very similar manner to other drugs. In general, vaccines are even more thoroughly tested than non-vaccine drugs because the number of human subjects in vaccine clinical trials is usually greater. In addition, post-licensure monitoring of vaccines is closely examined by the Centres for Disease Control and the FDA.

It can be concluded that regulated countries such as USA and EU have better established guidelines in comparison to semi-regulated countries like India and Singapore. In USA, CTs are highly regulated through their federal agencies. Data related to CTs also is recorded electronicallyand soon in USA they are going to enforce CTD format for submission of IND application, which will eventually speed up approval process. In Europe, CTs are regulated by EMA and EC. There, it is

mandatory to submit IMPD application and other CT related data in CTD and e-CTD format respectively. In USA and Europe, ICH-GCP guidelines are followed for conduct the CTs. In caseof semi-regulated countries such as India and Singapore 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 nationalguidelines. The ICH-GCP guidelines are also not fully adopted for conduct the CTs. Due to thesereasons the success rate of clinical trials in EU is more than India.

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