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Current Research and Regulatory Steps for Further Development of Clinical Trials in India

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A B S T R A C T

In drug development, two partly overlapping phases can be differentiated, namely the preclinical and clinical phase. During the first part of drug development necessary requirements for first use in man are met be performing preclinical pharmacological, toxicological, and pharmacokinetic investigations in the animal and in-vitro testing. The Central Drugs Standard Control Organization (CDSCO) is the National Regulatory Authority in India. Its equivalent counterparts elsewhere include United States Food and Drug Administration (US FDA), Health Canada (HC) and the, European Medicines Agency (EMA). The Drugs Controller General of India (DCGI), an official of the CDSCO, is the final regulatory authority for the approval of clinical trials in the country. DCGI office is also responsible for inspections of trial sites, sponsors of clinical research and manufacturing facilities in the country. In case of noncompliance, study may be rejected or discontinued; suspend or cancel the clinical trial permission, or debar the investigator(s), sponsor including his representative to conduct any clinical trial in future by DCGI. In future steps, the CDSCO office may start working on filling some of gaps in areas of Subject Expert Committee (SEC) and post-trial access guidance document. Finally, there could be difficulty in implementing these rules and it will be interesting to watch how the CDSCO office takes on the challenging task of meeting the objectives laid out by these rules. The review concludes that the clinical trial industry in India has great potential to become the most favourable destination in the world because of low cost of doing business, the availability of skilled professionals, and, the availability of a large and diverse patient pool. Many global CROs relocate their research units to India for drug development activities. Though the CT industry has been taking advantage of the huge financial gains, technological transformation for development of NCE is not happening. Also, the Indian public health industry only partially benefits from CTs. The Government of India needs to establish a policy framework for the Indian CT industry to provide for easy access to affordable drugs developed through adaptive clinical trials in India. There is also a need to create a regulatory environment capable of ensuring the conduct of clinical trials without violation of humanitarian ethics and other social norms.

Keywords: CIOMS, CDSCO, GCP, ICMR, DCGI, USFDA

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

- A medical device can be any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other related article, intended by the manufacturer to be used, alone or in combination for a medical purpose.
- Medical devices are used in many diverse settings, for example, by laypersons at home, by

paramedical staff and clinicians in remote clinics, by opticians and dentists and by health-care professionals in advanced medical facilities, for prevention and screening and in palliative care. Such health technologies are used to diagnose illness, to monitor treatments, to assist disabled people and to intervene and treat illnesses, both acute and chronic.

- The Global Harmonization Task Force (GHTF) is proposing a harmonized scheme for medical device classification
- People rely on these devices every day and expect them to be safe and incorporate the latest progress in science and innovation. The current rules on the safety and performance of medical devices in the EU were harmonized in the 1990s.
- To reflect the substantial technological and scientific progress in this sector over the last 20 years, the Commission proposed to update the rules to improve the safety of medical devices for EU citizens, create the conditions to modernize the sector and to consolidate its role as a global leader.
- Activities related to medical devices in the People's Republic of China (PRC), including their manufacturing, marketing, distribution, and sale, are mainly regulated by the Regulations on Supervision and Administration of Medical Devices (the Regulations) promulgated by the State Council and most recently amended in May 2017. The National Medical Products Administration (NMPA) is the governmental authority principally responsible for the supervision and administration of medical devices in the PRC.

2. Materials and Methods

Clinical trial

Clinical trial in relation to a new drug or investigational new drug means, any systematic study of such new drug or investigational new drug in human subjects to generate data for discovering or verifying its,

- Clinical or;
- pharmacological, including pharmacodynamics, pharmacokinetics or;
- adverse effects, with the objective of determining the safety, efficacy or tolerance of such new drug or investigational new drug;

Orphan Drug

Orphan drug means a drug intended to treat a condition which affects not more than five lakh persons in India;

Post-trial Access

"Post-trial access" means making a new drug or investigational new drug available to a trial subject after completion of clinical trial through which the said drug has been found beneficial to a trial subject during clinical trial, for such period as considered necessary by the investigator and the Ethics Committee.

New Drug

- A drug, including active pharmaceutical ingredient or phytopharmaceutical drug, which has not been used in the country to any significant extent, except in accordance with the provisions of the Act and the rules made there under, as per conditions specified in the labelling thereof and has not been approved as safe and efficacious by the Central Licensing Authority with respect to its claims; or
- A drug approved by the Central Licensing Authority for certain claims and proposed to be marketed with modified or new claims including indication, route of administration, dosage and dosage form.

The national regulatory body

The Drugs Controller General of India (DCGI) is an official of the CDSCO who is the final regulatory authority for the approval of clinical trials in the country. His ambit, in addition, also extends to inspections of trial sites, inspections of sponsors of clinical research and manufacturing facilities in the country, oversight of the Central Drugs Testing Laboratory (Mumbai) and the Regional Drugs Testing Laboratory as also heading the Indian Pharmacopeia Commission among various other roles, responsibilities and functions.

Schedule – Y: [See rules 122A, 122B, 122D, 122DA, 122DAA and 122E]: Requirements and Guidelines for Permission to Import And / Or Manufacture of New Drugs for Sale or to Undertake Clinical Trials

1. Application for permission

- Application for permission to import or manufacture new drugs for sale or to undertake clinical trials shall be made in Form 44 accompanied with following data in accordance with the appendices.
- If the study drug is intended to be imported for the purposes of examination, test or analysis, the application for import of small quantities of drugs for such purpose should also be made in Form 12.

2. Approval for clinical trial

Clinical trial on a new drug shall be initiated only after the permission has been granted by the Licensing Authority under rule 21 (b), and the approval obtained from the respective ethics committee(s). The trial site(s) may accept the approval granted to the protocol by the ethics committee of another trial site or the approval granted by an independent ethics committee (constituted as per Appendix VIII), provided that the approving ethics committee(s) is/are willing to accept their responsibilities for the study at such trial site(s) and the trial site(s) is/are willing to accept such an arrangement and that the protocol version is same at all trial sites.

3. Responsibilities of Sponsor

The clinical trial Sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the clinical trial is conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practice (GCP) Guidelines issued by the Central Drugs Standard Control Organization, Directorate General of Health Services, Government of India as well as with all applicable statutory provisions. Standard operating

procedures should be documented to ensure compliance with GCP and applicable regulations.

4. Responsibilities of the Investigator(s)

The Investigator(s) shall be responsible for the conduct of the trial according to the protocol and the GCP Guidelines and also for compliance as per the undertaking given in Appendix VII. Standard operating procedures are required to be documented by the investigators for the tasks performed by them.

5. Informed Consent:

In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject. The Subject's consent must be obtained in writing using an 'Informed Consent Form'.

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3. Results and Discussion

1 Regulatory Requirements for clinical trials in India

Good research contributes to evidence-based medicine and thus better and improved patient care with the ultimate goal of promoting health. Research, however, is a laborious, time and laborintensive task that can take months or even years to reach fruition. Drug development research, in particular, is long and arduous and bringing a single new drug costs on an average USD 1.78 billion and takes approximately 13.5 years from discovery to the market. Drug development research is primarily funded by the pharmaceutical industry including the process of human testing (Phase I-IV studies). These studies (called clinical trials or regulatory studies) are conducted with the academician as the principal investigator largely in academic centers. The pharmaceutical industry funds or 'sponsors' the studies and ensures compliance with the country's regulatory requirements. Academicians, however, also carry out their own research and these studies are called as 'Investigator initiated studies' (IISs). Here, the academician raises funds for the study through his efforts from various sources including possibly the pharmaceutical industry. In these IISs, he dons the dual mantle of an investigator and 'sponsor' and thus directly becomes responsible for ensuring regulatory compliance.

2 The national regulatory body (CDSCO)

The Central Drugs Standard Control Organization (CDSCO) is the National Regulatory Authority in India. Its equivalent counterparts elsewhere include the United States Food and Drug Administration (US FDA), Health Canada and the European Medicines Agency.

3 Department of health research and the Indian council of medical research

The Indian Council of Medical Research (ICMR) is the apex body that is responsible for the formulation, coordination and promotion of biomedical research. It receives funding from the Ministry of Health and Family Welfare and the Department of Health Research, Government of India.

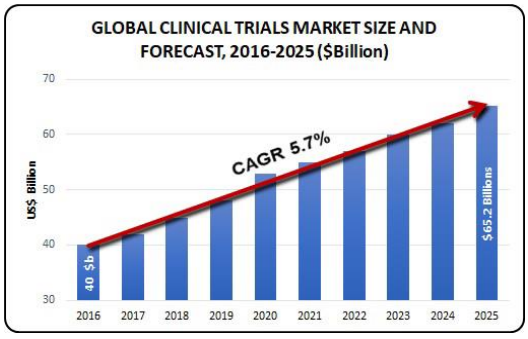

Fig.1

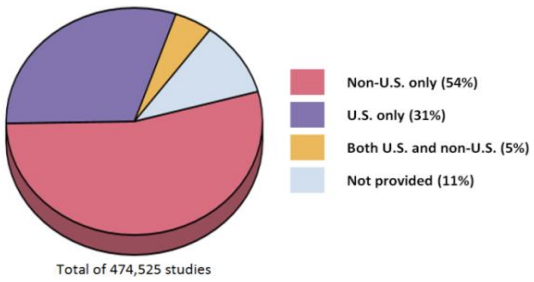

Fig.2

Stage of Development	Phase 1	Phase 2	Phase 3	Phase 4
End Point	Safety	Efficacy	Efficacy	Efficacy
Specific End Point	Safety Profile	Cardiac Output	Reduction in Mortality Rate	Reduction in Mortality Rate
Types of Studies	Different Indications; Single or Multiple Dose	Placebo Controlled; Dose Escalation	Placebo Controlled; Long Term Follow Up	Comparative; New Indications

Fig.3

Fig.4

4. Key documents in clinical research

(Drugs and Cosmetics Act (1940) and Drugs and Cosmetics Rules (1945). This act first came into being in 1940 and regulates the import, manufacture and distribution of drugs in the country to ensure that drugs and cosmetics sold in the country are safe, effective and conform to essential quality standards.

- It has Chapters, Rules and Schedules[6,7] and is amended at regular intervals to ensure greater safety, efficacy and drug quality.
- The Schedule Y along with rules 122A, 122B, 122D, 122DA, 122DAC and 122E (see below) is the key document that governs clinical research in the country. Per law, it is mandatory that all clinical research that falls under the ambit of Schedule Y complies with the necessary requirements.

5. Ethical guidelines on clinical research in India

The revised ICMR guidelines released in 2006 is called the 'Ethical Guidelines for Biomedical Research on Human Participants' and remains valid as of today, and a revised version is expected in 2017. This guideline covers two broad aspects of clinical research – the general principles that need to be followed and guidance regarding special areas of research (e.g., research in children or herbal research). Researchers are expected to be familiar with both these documents and abide by the requirements in the former and the guidance in the latter.

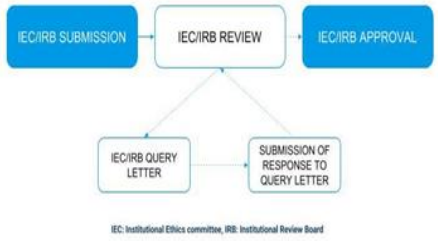

Fig.5

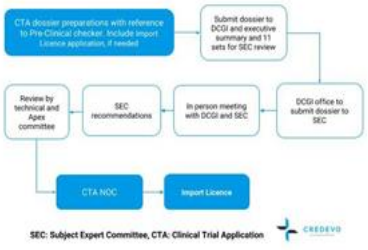

Fig.6

4. Conclusion

In drug development, two partly overlapping phases can be differentiated, namely the preclinical and clinical phase. During the first part of drug development necessary requirements for first use in man are met be performing preclinical pharmacological, toxicological, pharmacokinetic investigations in the animal and in in-vitro testing. These investigations are playing a central part for the benefit/risk evaluation of new drugs. Only if the risks connected to the clinical study are medically justifiable in relation to the likely therapeutic benefit of the compound, the clinical trial may basically take place under consideration of the legal requirements of the country in which the study is carried out. In drug research, clinical pharmacology is the connecting link between preclinical and clinical research. Clinical pharmacology produces the necessary basis for the clinical trial of a new substance in the patient with the target indication. After a first clinical-pharmacological profile of the new substance has been established during phase I on the basis of which a decision for the continuation of the clinical trial and the probable effective dose range and dosing interval is made, the aim of phase II-IV is to answer the important questions of the therapeutic efficacy and tolerability in a large number of patients with the target indication. Only with a very careful drug investigation during phase I-IV it is really possible to register the therapeutic risk and benefit of a new drug and to control resulting serious problems. The below given advantages, global players view India as a favored destination for conducting clinical trials. They are as follows. The Central Drugs Standard Control Organization (CDSCO) is the National Regulatory Authority in India. Its equivalent counterparts elsewhere include

- United States Food and Drug Administration (US FDA),
- Health Canada (HC) and the
- European Medicines Agency (EMA).

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- The submission process was made easier for early
- Approval process was made easier
- Timeline Approximately 4-5 months**.**

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