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COMPARATIVE ANALYSIS OF REGULATIONS AND REQUIREMENTS TO CONDUCT CLINICAL TRIALS IN A MODEL COUNTRY FROM ASIA, AMERICA AND MIDEAST

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ABSTRACT

Clinical trials (CTs) are research studies that investigate whether a medical strategy, treatment, or devices is safe and effective for humans. These researches may also reveal which medical treatments are most effective for specific disorders or groups of people. Clinical trials are designed to conduct research, thus they follow strict scientific guidelines. These guidelines protect patients while also helping in the production of reliable study results. Clinical trials are carried out in compliance with the regulatory guidelines set forward by the drug regulatory authority in the country in which they are to be carried out. In India, CTs are regulated by Central Drugs Standard Control Organization (CDSCO) (Schedule Y of the Drug and Cosmetics Rules, 1945) and Indian Council on Medical Research (ICMR) (Ethical guidelines for Biomedical Research on Human subjects) respectively. In USA they are regulated by USFDA as per their 21 Code of federal regulations part 312(CFR) of federal food and Drug cosmetic act. In Saudi Arabia CTs are regulated by Saudi Food and Drug Authority. This review paper contains Comparative Analysis of Regulations and Requirements to conduct clinical trials in a model country from Asia, America and Mideast, viz, India, USA and Saudi Arabia respectively, in order to determine safety and efficacy of pharmaceutical products like drug, biologic and medical device and to confirm the clinical trials studies follows strict scientific standards.

KEYWORDS: Clinical trials, CDSCO, USFDA, SFDA, Regulatory framework.

INTRODUCTION

Pharmaceutical companies throughout the world are progressing in order to become more competitive, which has resulted in regulatory authorities in many countries around the world establishing new rules and standards. Effective drug regulation is essential to assure the safety, efficacy, and quality of pharmaceuticals, as well as the accuracy and appropriateness of drug information available to the public, and is the responsibility of regulatory authorities and organizations. Regulatory organizations give strategic, tactical, and operational guidance and support for working within regulations in order to accelerate the development and delivery of safe and effective healthcare products to people all over the world.[1]

1. Clinical trials in india

The Central Drugs Standard Control Organization (CDSCO) under Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare (MHFW), Government of India is the National Regulatory Authority (NRA) of India, having it's headquarter located in New Delhi.

The Drugs and Cosmetics Act, 1940 and Rules 1945 have entrusted various responsibilities to central and state regulators for regulations of drugs and cosmetics. CDSCO is constantly thriving upon to bring out transparency, accountability, and uniformity in its services in order to ensure safety, efficacy, and quality of the medical products manufactured, imported and distributed in the country.

In exercise of the powers conferred by section 12 and section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government, after consultation with the Drugs Technical Advisory Board, hereby makes the following rules, namely: —

New Drugs and Clinical trials rules 2019- These rules shall apply to all new drugs, investigational new drugs for human use, clinical trial, bioequivalence study, bioavailability study and Ethics Committee.

1.2 Definitions

Clinical trial- Any systematic study of new drug or investigational new drug to generate data for discovering clinical or pharmacological including pharmacodynamics, pharmacokinetics or adverse effects with the aim of determining the safety, efficacy, or tolerance of such new drug or investigational new drug.

Investigational new drug- Investigational new drug means a new chemical or biological entity or substance that has not been approved for marketing as a drug in any country.

New drug- 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; or a fixed dose combination of two or more drugs, approved separately for certain claims and proposed to be combined for the first time in a fixed ratio, or a modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licensing Authority.

1.3 Central licensing authority—The Drugs Controller, India appointed by the Central Government in the Ministry of Health and Family Welfare.

1.4 Ethics committee- Whoever intends to conduct clinical trial or bioavailability study or bioequivalence study shall be required to have approval of an Ethics Committee

1.5 Constitution of ethics committee for clinical trial—The Ethics Committee shall have a minimum of seven members from medical, non-medical, scientific and non-scientific areas with at least,

(1) One lay person
(2) One woman member
(3) One legal expert
(4) One independent member from any other related field such as social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian.

Every Ethics Committee shall make an application for grant of registration to the Central Licensing Authority in Form CT-01

The Central Licensing Authority shall scrutinize the information and documents furnished with the application and make such further enquiry, if any, considered necessary and after being satisfied, that the requirements of these rules have been complied with, may grant registration to Ethics Committee in Form CT-02

1.6 Proceedings of ethics committee for clinical trial— An Ethics Committee may not review a clinical trial, bioavailability, or bioequivalence protocol, or related documentation, unless at least five of the members listed below are present.

(1) Medical scientist (Preferably a pharmacologist)

(2) Clinician

(3) Legal expert

(4) Social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian or a similar person

(5) Lay person.

1.7 Maintenance of records by ethics committee for clinical trial— this section should document that the study was carried out in accordance with the ethical principles of Declaration of Helsinki. The Ethics Committee shall maintain data, record, registers and other documents related to the functioning and review of clinical trial or bioavailability study or bioequivalence study, as the case may be for a period of five years after completion of such clinical trial.

1.8 Prerequisites for conducting clinical trials in india

- Permission from the Drugs Controller General, India (DCGI).
- Approval from respective Ethics Committee where the study is planned.
- Mandatory registration on the web portal of ICMR i.e., www.ctri.in.

The process in respect of above-mentioned is as follows

1. Any person, institution, or organization intending to conduct a clinical trial of a new drug or an investigational new drug must submit a completed Form CT-04 to the Central Licensing Authority.
2. The DCGI has 90 calendar days to evaluate the application for drugs developed outside India and 30 days for drugs discovered, researched, and manufactured in India. If the DCGI does not respond within 30 days to applications for drugs developed in India, the sponsor (applicant) may conclude that permission to conduct the trial has been granted.
3. The permission granted for specific applications remain valid for two years from the date of its issue, unless extended by DCGI.

1.9 Permission to conduct a clinical trial is subject to the following conditions

- The clinical trial protocol and other related documents must be approved by the Ethics Committee of each site before the trial to start.
- The Central Licensing Authority must be informed of the Ethics Committee's approval within fifteen working days of it being granted.
- Before enrolling the first subject for the trial, the clinical trial must be registered with the Clinical Trial Registry of India, which is maintained by the Indian Council of Medical Research.
- Clinical trials must be carried out in compliance with the approved clinical trial protocol and other related documentation, as well as the requirements of the Good Clinical Practices Guidelines and these rules.
- Each clinical study must submit a six-month status report to the Central Licensing Authority via the SUGAM portal, indicating whether it is ongoing, finished, or cancelled.

- **Review process focus on following evaluations**
- Risk vs. benefit
- Innovation vs. existing therapy
- Unmet medical need
- Ethical aspects for patient safety
- India specific concerns.[2-6]

2. 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, and quality of human as well as veterinary drugs.

USFDA plays an important role in reviewing and authorizing investigational new drug applications (INDs) to conduct clinical trials using investigational drug or biological products in humans.

2.1 Several centers are responsible for Pharmaceutical and Biological product regulations are

- **Center for drug Evaluation and Research (CDER) -** Ensures that safe and effective drugs are available to improve the health of the people in the United States.

- **Center for biologics Evaluation and Research (CBER)** - Regulates biological products for human use under applicable federal laws.
- **FDA's office of good clinical practice (OGCP)** - Is responsible for overseeing good clinical practice and human subject protection issues arising from clinical research.
- **HHS office for human research protections (OHRP) -** Guides the agency's efforts to safeguard the rights, welfare, and well-being of human research subjects for studies conducted or supported by HHS. OHRP also provides oversight to all federal agencies engaged in human subject research.

2.2 Definitions

IND means an investigational new drug application

Investigational new drug - means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes.

Institutional ethics committee (IEC) -means a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection. An institutional review board (IRB), is one type of IEC

Institutional review board - means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research.

2.3. Registration of IRB

Each IRB in the United States that reviews clinical investigations regulated by FDA under the act must register at a site maintained by the Department of Health and Human Services (HHS).

Each IRB must renew its registration every 3 years.

2.4. Constitution of IRB

A. Each IRB must contain at least five members with diverse backgrounds, including race, gender, cultural backgrounds, and sensitivity considerations.

B. Each IRB must have at least the following members:

- One primarily focused on scientific issues
- One focused on nonscientific issues

- One unaffiliated with the institution, and not part of the immediate family of a person affiliated with the institution

2.5. Process of approval of clinical trials

- Institutional Review Board (IRB) review of clinical investigation may be conducted in parallel with the Food & Drug Administration's (FDA) review of the investigational new drug application (IND). However, EC approval must be obtained prior to the sponsor being permitted to initiate the clinical trial.
- Drug developer/Sponsor must submit Investigational New Drug Application to FDA before beginning of clinical research. IND contains Animal study data and toxicity, Manufacturing information, Clinical protocols, Information about the investigator, etc.
- IND submissions may be submitted in either paper or electronic format.
- Based on information provided in 21CFR Part312, for paper IND submissions, the sponsor must submit an original and two copies, including the original submission and all amendments and reports.
- The FDA IND review team has 30 days to review the original IND submission. The process protects volunteers who participate in clinical trials from unreasonable and significant risk in clinical trials.
- Upon review of IND, FDA may give approval to begin clinical trials.
- All clinical trials conducted to secure FDA marketing authorization must adhere to 21 C.F.R. Parts 50 and 56 which are regulations designed to protect the rights of human subjects.[7-11]

3. Clinical trials in the saudi arabia

Having the largest economy in the Gulf Cooperation Council (GCC), by population and gross domestic product (GDP), Saudi Arabia has the region's largest pharmaceuticals market, despite having a low local production of branded drugs compared to generic products. The Saudi pharmaceutical sector depends heavily on imported drugs from the US, Europe, China, and India. Because of the low production of pharmaceuticals, the government has focused its efforts on encouraging pharmaceutical investment.

The pharmaceutical market in Saudi Arabia is controlled by the government and private sectors; and is regulated mainly by the Saudi Food and Drug Authority (SFDA) in collaboration with the Ministry of Health (MoH). The SFDA, established in 2003, regulates

the medicine supply chain, registration, sale, and pricing of any drug product, in addition to licensing, inspecting, and suspending of manufacturers that do not meet the country's licensing requirements.

3.1 Clinical trial administration

The Clinical Trial Administration was founded in 2009 as part of the licensing division of the drug sector of the SFDA with the goal of promoting clinical research by increasing the regulatory body's capacity, regulatory control, and regulation of clinical trials.

All prospective trials must be approved by an ethics committee before they can begin.

The SFDA has a direct role in the review of the trial's scientific data, which consists mainly of the study protocol, informed consent form, investigator brochure (IB), and IRB/EC approval, in order to issue "approval" for the proposed trial.

The Clinical Trial administration has three departments: Clinical Trials Evaluation department, Saudi Clinical Trials Registry department (SCTR), and the Good Clinical Practice (GCP) department.

- **The clinical trials evaluation department-** This department's responsibilities include reviewing and assessing all forms of clinical trial applications, amendments, and medical evaluations of cases of adverse events resulting from clinical trials.
- **The saudi national clinical trials registry department-** the Saudi Clinical Trials Registry (SCTR) is an online database for clinical trials in Saudi Arabia. The SCTR's role is to ensure that every clinical trial conducted in Saudi Arabia is prospectively registered "before the first participant enrolls" and that all trial data and information is fully disclosed throughout the registry system.
- **GCP department-** GCP department has the responsibility of two main tasks: a) Clinical Research Organization (CRO) accreditation and b) the clinical trial inspection process. The main objective of this department is to ensure that all clinical trial stakeholders (e.g., sites, CROs, principal investigators, etc.) are following good clinical practice (GCP) and good laboratory practice (GLP).

3.2 Types of clinical trial application- The application processes of any clinical trial review divided into two categories:

I. Registered drug in Saudi Arabia

II. Unregistered drug in Saudi Arabia with further sub-grouping of the unregistered drug into

- Registered drug with FDA (Food and Drug Administration) and/or EMA (European Medicine Agency)
- Unregistered drug with FDA and/or EMA.

3.3. Ethical committee- The National Committee of Medical & Bioethics is the main ethics committee in Saudi Arabia. It was approved by the Royal Decree on 18/5/1422H, and directly handled by the King Abdulaziz City for Science and Technology (KACST) in Riyadh. KACST is an independent scientific organization administratively reporting to the Prime Minister.

3.4. Constitution- The National Committee of Bioethics (NCBE) at KACST consists of sixteen different members from various places in the kingdom. KACST, the National Guard, the Ministry of Defense and Aviation, the Ministry of Interior, the General Presidency of Religious Research and Ifta', the Ministry of Higher Education (Universities), the Ministry of Health, the Ministry of Education, the Ministry of Agriculture, the Saudi Wildlife Commission, the Saudi Food and Drug Authority, the King Faisal Specialist Hospital and Research Center, the Human Rights Commission, the Director of Research Ethics Monitoring Office, and a member from the private sector are among the members.

3.5. Institutional Review Board (IRB) - Several local ethics committees across the kingdom make to the National Committee of Medical and Bioethics. Those local ethics panels are known as Institutional Review Boards (IRBs) and serve as independent ethics committees. It oversees the essential review, monitoring, and modification requests, as well as the approval or disapproval of any medical study involving human participants. The principle of the IRB review is to ensure that the research is conducted in a manner that protects the rights and welfare of human research subjects, both in advance and through periodic evaluation.[12-14]

4. Comparative Analysis of Regulations and Requirements to conduct Clinical trials in India, USA and Saudi Arabia.[13-16]

Sr. No	Features	India	United States (US)	Saudi Arabia
1	Clinical Trial Definitions	As per CDSCO, Clinical trial means a systemic study of any new drug in human subject to generate data for discovering and verifying the clinical, pharmacological (Including pharmacodynamic and pharmacokinetic) and adverse effects with the objective of determining safety and efficacy of the new drug.	According to the National Institutes of Health (NIH) A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.	As per SFDA Each research (study) with collecting and analyzing information, which related to volunteers and patients to reach general knowledge that, could be applied on other patients according to the mechanism of disease occurrence, diagnosis, its spreading or treatment.
2	Clinical trial or study application language in all respective countries	English	English	English, Arabic
4	Regulatory Authority	CDSCO	USFDA	SFDA
5	Submission of essential documents for protocol approval	• Dossiers, • Case Record Form (CRF), • Informed Consent Documents (ICD), • Investigators Brochure (IB), • Trial Master File (TMF), • Laboratory Related Documents. • Diagrammatic	• Dossiers, • Case Record Form (CRF), • Informed Consent Documents (ICD), • Investigators Brochure (IB), • Trial Master File (TMF), • Laboratory Related Documents. • Diagrammatic flow chart for protocol.	• Arabic-Headed letter to SFDA Drug Trial Department Including SCTR registration Number • IRB approval • Informed Consent Form (Arabic and English) • Trial protocol according to GCP • Investigator Brochure

		flow chart for protocol.		• Case Report Form • Clinical Trial Agreement • Certificate Of Analysis For the Study Drug • Subjects Insurance • GMP certificate of research team • Statement of Investigator • Any Supportive Document if Available
6	Authority for clinical trial registration in respective countries	CTRI	NHMRC (USA)	SCTR
7	Access for registration of trial in respective countries	http://ctri.nic.in	https://clinicaltrials.gov	http://sctr.sfda.gov.sa/
8	Payment methods for clinical trial registration	There is no payment required for registering CTs	There is no payment required for registering CTS	
9	Governing Law for clinical trial regulation	• Drugs and Cosmetics Act 1940 (Schedule Y) • Drugs and Cosmetics Act (II Amendments) Rules, 2005 • ICMR guidelines • CDSCO guidelines • GCP guidelines	• The Federal Food Drug and Cosmetic Act(FD&C) • Title 21 is the portion of Code of Federal Regulation (CFR) that governs Food and Drug within the United States for the Food and Drug Administration • 21 CFR Part 50-Protection of Human Subject (Informed Consent) • 21 CFR Part 54-Financial	• Saudi Food and Drug Authority (SFDA) • Royal Decree No M/59 Law of Practicing Healthcare Professions • Law of Bioethical Research on Living Creatures. • IRB Regulations • ICH guidelines for Good Clinical Practices E6(R2)

			disclosure by Clinical Investigators • 21 CFR Part 56-Investigational Review Board • 21 CFR Part 58-GLP for Nonclinical Laboratory Study • 21 CFR Part 312-Investigational New Drug Application	
Regulatory authority fees for respective countries according to clinical trial phases				
10	Phase I	3,00,000	The Food & Drug Administration (FDA) does not charge any fee to review investigational new drug (IND) submissions	15,000 Saudi Riyals for each submitted trial as an evaluation fee for the clinical trial, excluding phase IV from such fees.
	Phase II	2,00,000		
	Phase III	2,00,000		
	Phase IV There must be no fee payable for the conduct of a clinical trial by a person of an institution or organization that is completely or partially sponsored by the central government or a state government.	2,00,000		
11	Regulatory Authority and Ethics Committee reviews conducted at same time of trial submission in all respective countries	Both reviews conducted in same time	Both reviews conducted in same time	Both reviews conducted in same time
Clinical trial application regulatory approval timeliness				
12	Regulatory review	45 days	Within 30 calendar days of receipt of	• 10 working days

	timelines of clinical trial protocol in respective countries		original IND	for clinical trials on drug registered at the SFDA • 30 working days for clinical trials on unregistered drug at the SFDA while they are registered by FDA and EMA • 180 working days for clinical trials on unregistered drug at SFDA, FDA and EMA.

5. CONCLUSION

It is concluded that clinical trials in Saudi Arabia are less regulated in comparison to USA and India. The comparison of clinical trial regulations assists sponsors in determining the most straightforward path to clinical trial approval in any country. Clinical trials are carried out in many countries under various regulations and under the supervision of various regulatory authorities. The clinical trial regulations of India, US and Saudi Arabia were compared on various aspects like legal framework, clinical trial definition, clinical trial application, application fee, application submission format, approval time, regulatory authority, forms required, and regulations.

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